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Environmental Evidence

SYSTEMATIC REVIEW

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What is the effect of phasing out long-chain per- and polyfluoroalkyl substances on the concentrations of perfluoroalkyl acids and their precursors in the environment? A systematic review

Magnus Land[1*], Cynthia A. de Wit[2], Anders Bignert[3], Ian T. Cousins[2], Dorte Herzke[4], Jana H. Johansson[2] and Jonathan W. Martin[2,5]

Abstract

Background: There is a concern that continued emissions of man-made per- and polyfluoroalkyl substances (PFASs) may cause environmental and human health effects. Now widespread in human populations and in the environment, several PFASs are also present in remote regions of the world, but the environmental transport and fate of PFASs are not well understood. Phasing out the manufacture of some types of PFASs started in 2000 and further regulatory and voluntary actions have followed. The objective of this review is to understand the effects of these actions on global scale PFAS concentrations.

Methods: Searches for primary research studies reporting on temporal variations of PFAS concentrations were performed in bibliographic databases, on the internet, through stakeholder contacts and in review bibliographies. No time, document type, language or geographical constraints were applied in the searches. Relevant subjects included human and environmental samples. Two authors screened all retrieved articles. Dual screening of 10% of the articles was performed at title/abstract and full-text levels by all authors. Kappa tests were used to test consistency. Relevant articles were critically appraised by four reviewers, with double checking of 20% of the articles by a second reviewer. Meta-analysis of included temporal trends was considered but judged to not be appropriate. The trends were therefore discussed in a narrative synthesis.

Results: Available evidence suggests that human concentrations of perfluorooctane sulfonate (PFOS), perfluorodecane sulfonate (PFDS), and perfluorooctanoic acid (PFOA) generally are declining, while previously increasing concentrations of perfluorohexane sulfonate (PFHxS) have begun to level off. Rapid declines for PFOS-precursors (e.g. perfluorooctane sulfonamide, FOSA) have also been consistently observed in human studies. In contrast, limited data indicate that human concentrations of PFOS and PFOA are increasing in China where the production of these substances has increased. Human concentrations of longer-chained perfluoroalkyl carboxylic acids (PFCAs) with 9–14 carbon atoms are generally increasing or show insignificant trends with too low power to detect a trend. For abiotic and biological environmental samples there are no clear patterns of declining trends. Most substances show mixed results, and a majority of the trends are insignificant with low power to detect a trend.

*Correspondence: magnus.land@eviem.se
[1] Mistra EviEM, Stockholm Environment Institute, Box 24218, 104 51 Stockholm, Sweden
Full list of author information is available at the end of the article

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Conclusions: For electrochemically derived PFASs, including PFOS and PFOA, most human studies in North America and Europe show consistent statistically significant declines. This contrasts with findings in wildlife and in abiotic environmental samples, suggesting that declining PFOS, PFOS-precursor and PFOA concentrations in humans likely resulted from removal of certain PFASs from commercial products including paper and board used in food packaging. Increasing concentrations of long-chain PFCAs in most matrices, and in most regions, is likely due to increased use of alternative PFASs. Continued temporal trend monitoring in the environment with well-designed studies with high statistical power are necessary to evaluate the effectiveness of past and continuing regulatory mitigation measures. For humans, more temporal trend studies are needed in regions where manufacturing is most intense, as the one human study available in China is much different than in North America or Europe.

Keywords: Perfluoroalkane acids, PFOA, PFOS, Temporal trends, Phase-out, Source, Emission, Environmental fate, Regulation, Concentration

Background

PFASs are a broad class of man-made substances that have been produced and used in water-, soil-, and stain-resistant coatings for clothing, leather, upholstery, and carpets; oil-resistant coatings for food contact paper; aviation hydraulic fluids; fire-fighting foams; paints, adhesives, waxes, polishes, and other products; and industrially as surfactants, emulsifiers, wetting agents, additives, and coatings [1–6]. The perfluoroalkyl moiety (C_nF_{2n+1}–) of PFAS molecules is both hydrophobic and lipophobic [1]. The extreme strength and stability of the C-F bond [7] renders perfluorinated carbon chains resistant to environmental degradation processes. Owing to the wide diversity of PFASs (i.e. chain-lengths, molecular weight, degree and pattern of fluorination, presence of polar functional groups), it is difficult to generalize their properties, environmental fate, and production histories [8]. In this study, we have focused on two groups of perfluoroalkyl acids (PFAAs):

1. Perfluoroalkyl carboxylic acids (PFCAs) and their precursors.
2. Perfluoroalkane sulfonic acids (PFSAs) and their precursors.

The terminology used in this review is that recommended by Buck et al. [8]. A list of abbreviations used in this review is provided in Additional file 1: List of abbreviations. A more detailed review of PFASs can be found in the protocol for this study [9].

Perfluoroalkyl carboxylic acids (PFCAs) and their precursors

PFCAs in water are relatively bioavailable and have been detected in various living organisms [10–14], including humans [15, 16]. Perfluorooctanoic acid (PFOA) was the PFCA manufactured in the largest quantity. It was produced mainly by electrochemical fluorination (ECF) by the 3M Co. until 2002 (3M dominated the global market) and was primarily used as a processing aid (emulsifier) in the manufacture of polytetrafluoroethylene (PTFE). The ECF manufacturing process produces a mixture of linear (approx. 70%) and branched (approx. 30%) isomers [17]. After the 3M phase-out of PFOA in 2002, other companies continued to manufacture PFOA mainly through the telomerization process which produces a pure isomer product, typically the linear isomer [17]. PFCAs are completely dissociated anions in environmental media and are present mainly in the dissolved phase in surface waters. PFCAs can thus be transported long distances by rivers and ocean currents and now occur in the open marine environment, even in the remote Northern Atlantic, Pacific, and Arctic Oceans [18, 19]. PFCAs are also detected at low concentrations in the ambient atmosphere, where they may be directly emitted [20], and/or formed indirectly by atmospheric oxidation of semivolatile PFCA-precursors such as the fluorotelomer alcohols (FTOHs) [21].

Overall, the direct and indirect sources (i.e. precursor degradation) of PFCAs to the environment are various, and the relative importance of each source is temporally variable, specific to each substance and not well quantified. The relative importance of atmospheric versus marine transport of PFCAs, or of direct atmospheric emission versus atmospheric oxidation of PFCA-precursors is the subject of much recent and ongoing research.

Bioaccumulation and trophic magnification have been shown to occur in mammals and birds, and increase with perfluoroalkyl chain length [22]. Trophic biomagnification is highest for PFCAs and PFSAs with a perfluoroalkyl chain length containing 8 or more perfluorinated carbon atoms in the terrestrial and freshwater ecosystems studied. Some short-chain alternatives (e.g. perfluorobutyl- or hexyl-based) are also persistent, but do not bioaccumulate to the same extent, as they are excreted rapidly from the organisms studied [23].

In 2000, 3M announced a global phase-out by 2002 of its production of products based on perfluoroalkyl chains

containing 6, 8 and 10 carbon atoms, including PFOA [24]. In 2006, eight major PFCA, fluoropolymer and fluorotelomer manufacturers joined the US EPA 2010/15 Stewardship Program to work towards the elimination of long-chain PFCAs and their precursors from emissions and products by 2015 [25]. PFOA, its ammonium salt ammonium perfluorooctanoate (APFO), and C9–C14 PFCAs were included in the Candidate list of substances of very high concern and under the European chemicals regulation, REACH [26]. Although long-chain PFCAs are being incrementally phased out by the major manufacturers and to some extent are regulated in Japan, Western Europe and the United States (US) [24, 25, 27], new manufacturers (largely in continental Asia) have begun to produce long-chain PFCAs and their precursors [28, 29]. As a result of the phase-outs of many long-chain PFASs in recent years, many alternative fluorinated products have been introduced [30] and these new, alternative industrial processes and products have resulted in new sources of PFCAs and other fluorinated substances.

Perfluoroalkane sulfonic acids (PFSAs) and their precursors

Similar to PFCAs, sources of PFSAs include release during manufacture and use, as well as from the degradation of various precursor substances [5, 31]. Commercial scale manufacture of perfluorooctane sulfonyl fluoride (POSF)-based products began by 3M in the late 1950s with product lines based on *N*-methyl perfluorooctane sulfonamidoethanols (MeFOSEs) used in surface treatment applications (e.g., carpets, upholstery and textiles). In the late 1960s product lines based on *N*-ethyl perfluorooctane sulfonamidoethanols (EtFOSEs) were introduced for use in paper and board packaging applications. PFOS and various salts were manufactured for direct use in a variety of products {e.g. aqueous film-forming foams (AFFFs) for firefighting and mist suppressants in acid baths used for metal plating (see Paul et al. [5])}. Commercial use of PFOS and its salts started around 1970 [5] and estimated uses and emissions of PFSAs and their precursors steadily rose to the end of the tweentienth century [5]. PFSAs and their precursors have been manufactured almost exclusively by ECF which produced a mixture of linear (70%) and many branched (total 30%) isomers [32]. For more thorough reviews see Paul et al. [5] and Armitage et al. [33].

PFOS and other PFSAs are widely distributed in the global environment [34–38], biota [39–44] and humans [15, 45–52]. Due to the dominance of POSF-based products historically, PFOS is usually the most abundant PFSA found. Although properties vary with chain-length, the environmental fate and bioaccumulation behavior of PFSAs is broadly similar to that of PFCAs. PFSAs are fully dissociated anions in environmental media [53] and tend to accumulate in surface waters [31], they are persistent, bind weakly to organic phases [54] compared to other persistent organic substances, bioaccumulate in laboratory studies [55, 56] and biomagnify in food webs [57, 58]. In 2000 the major manufacturer of PFOS in the US (3M) announced they would cease the production of C6, C8 and C10 perfluoroalkane sulfonyl fluoride (PASF)-based products and completed the phase out in 2002 [59]. In 2006 the EU adopted a Marketing and Use Directive (2006/122/EC) that banned the use of PFOS in semi-finished products (maximum content of PFOS: 0.005% by weight) as of summer 2008. In 2009, PFOS, and related substances derived from POSF, were listed under Annex B (restriction of production and use) of the Stockholm Convention on Persistent Organic Pollutants. However, China now manufactures PFOS, and according to Zhang et al. [60] the production volume of PFOS increased from 30 tonnes in 2002 to 247 tonnes in 2006. Since then, production volumes of PFOS in China declined to about 100 tonnes/year in 2008 as a consequence of international legislation to restrict or eliminate PFOS production.

Stakeholder engagement

There is a high level of concern in Sweden that continued emissions of PFASs may cause environmental as well as human health effects [61]. At a stakeholder meeting arranged by Mistra EviEM in 2012 the Swedish Chemicals Agency (KEMI) highlighted the need for a systematic review on PFASs in the environment. In later discussions KEMI raised concerns about increasing concentrations of short-chain substances such as PFBS [62]. They needed more information on whether this is a local or global trend and whether similar trends have been observed for other PFASs with recently increased production volumes. Mistra EviEM discussed potential review questions for this topic also with representatives from other government agencies, including the Swedish Agency for Marine and Water Management (SWAM) and the Swedish National Food Agency, as well as with scientists working in this field. When the review question had been agreed upon, EviEM arranged a meeting with a broader group of stakeholders, including e.g. governmental agencies, municipal drinking water producers, environmental consultants and NGOs, to set the scope of the review and discuss inclusion criteria etc. Before drafting a review protocol, EviEM also discussed the review with the Fluorocouncil, which is a global organization representing a range of different fluoro-technology companies.

Objective of the review

The objective of this systematic review is to investigate whether concentrations of PFASs in the environment are changing significantly, and whether any spatial

differences or changes in temporal concentration trends can be related to implemented phase-outs or regulatory actions. The environment is broadly defined herein, including biological and abiotic samples, as well as human samples and consumer products. To the extent possible, another aim is to collate as much evidence as possible to understand why conflicting temporal trends may be reported.

The primary question in this systematic review is "*What is the effect of phasing out long-chain per- and polyfluoroalkyl substances on the concentrations of perfluoroalkyl acids and their precursors in the environment?*"

The PICO elements, i.e. the population, intervention, comparator, and outcome are summarised as follows:

> Population/subject: Abiotic and biological samples including general human populations.
> Intervention: Legislative or voluntary phase-out of production and use of long-chain PFASs.
> Comparator: Before intervention.
> Outcome: Change of concentrations of the phased-out substances and their precursors and substitutes.

Methods

Searches

Searches for scientific literature were conducted in seven bibliographic databases and using Google Scholar (see Additional file 2). The search string used was adapted to the syntax of each database, but in general it was designed as below, where * is a wildcard that can be any number of characters, and a question mark is exactly one arbitrary character.

(perfluor* OR polyfluor* OR fluorotelomer* OR PF?S OR PF?A OR PFC OR PFT OR PFHxS OR FOSE OR FOSA OR PAPS) AND (((trend OR variation) NEAR (time OR temporal)) OR ((change OR increase OR decrease) NEAR/5 (level or concentration)) OR "time series" OR ((snow OR ice OR sediment) NEAR (core OR column OR cap)) OR archive* OR "specimen bank" OR "long-term monitoring" OR "repeated measurements" OR historic*)

The fields searched were in most cases title, abstract and key words. Detailed information about the searches is given in Additional file 2. No limitations in time, document type, or language were applied in the searches. However, due to limitations in translation resources, articles in other languages than English, French, German, and Scandinavian languages were excluded during the screening process. Grey literature was searched using the Google search engine. Searches were also conducted on specialist websites listed in Additional file 2, where search strings for these searches are also shown. In addition, stakeholders were asked to provide relevant reports. For searches with search engines and on specialist websites the first 100 search results were screened. The comprehensiveness of the searches was tested by cross-checking the obtained records with (1) a list of papers that the review team a priori thought should be found by the searches, and (2) bibliographies in relevant review articles (see Additional file 2).

Article screening and study inclusion criteria

The following inclusion criteria were applied.

- *Relevant subjects* Abiotic and biological samples, including general human populations exposed to ambient loads of PFASs and their precursors. Populations with occupational exposures related to manufacturing of PFASs and populations exposed to distinct local point sources such as contaminated drinking water were excluded, as were populations with deliberate exposures in controlled trials. No geographic limitations were applied.
- *Relevant intervention* All implemented regulations and voluntary phase-outs of manufacturing and use of PFASs, starting in 2000.
- *Relevant comparator* Before intervention.
- *Relevant outcomes* (1) time trends of PFAS concentrations covering at least two years and containing at least three separate time points, or (2) difference in PFAS concentrations between two or more different time points.
- *Relevant study period* At least part of the study period should be after year 2000.
- *Relevant type of study* Recurring measurements at a given location (monitoring) or measurements of samples from environmental archives (e.g. dated sediment cores, ice cores) or from specimen banks (e.g. biota, human diet, human samples).

At the title and abstract level all retrieved articles were screened by two reviewers. In doubtful cases where it could not be decided whether the article should be included or excluded on the title and abstract level, the article passed to full text screening. To check that the screening was consistent and complied with the agreed inclusion/exclusion criteria, 10% of the retrieved articles were double screened by the other reviewers, and Kappa tests were used to evaluate the consistency of the screening. Screening at the full-text level was conducted in the same manner as at the title and abstract level, including double screening and kappa tests. After double screening the disagreements were discussed by all reviewers. At both title/abstract and full text levels, excluded articles were coded with a reason for exclusion. A list of all

Table 1 Description of quality aspects considered in critical appraisal and criteria for high risk of bias

Quality aspect	Description	High risk of bias
Selection bias	Information about samples and what they represent must be sufficient to determine whether samples from different sampling occasions are comparable	Large differences in sample populations or food source between time points. Populations affected by contaminated land or drinking water
Accuracy of dating	In most cases it is known when samples were collected, but samples from environmental archives such as sediment or ice cores are more complicated to date accurately. Dating by means of e.g. isotope techniques that give an absolute age to each individual sample may be regarded as high quality dating. Dating by means of historical markers (e.g. peak concentrations of other contaminants) providing relative ages may be regarded as acceptable dating. Post-depositional perturbations caused by for instance thawing-freezing cycles in snow or bioturbation in sediments should be discussed and assessed	No dating or probable perturbations of deposited material or migration of PFASs
Sample integrity	Samples may deteriorate with time (especially critical to specimen banks with long storage times)	Sample pre-treatment, sample preservation, prevention of contamination or storage methods not suitable for the sample type
Analytical quality	Analytical procedures should be appropriate and consistent throughout the study period. Was there a risk that analytical parameters may have biased the temporal trends?	Internal standards not used, procedural blanks or field blanks not run, limit of detection (LOD) or limit of quantification (LOQ) not reported, significant changes in analytical techniques during the study period
Study design	Was the sampling dedicated to PFAS analyses or were the samples originally taken for other purposes? When was the study period in relation to known phase-outs (i.e. intervention time points)?	Sampling methods not suitable for PFAS analysis or sampling strategy (study period and sampling frequency) cannot be related to known interventions

articles excluded at full text screening, including reasons for exclusion, is provided in Additional file 3.

Study quality assessment

Critical appraisal of relevant studies was carried out by four reviewers. To ensure high consistency between the reviewers, 20% of the included articles after full text screening were double-checked and Kappa tests were used to test the consistency. Articles with conflicting judgements and those for which a reviewer was uncertain during single critical appraisal were discussed by the entire review team before any decision was made. These discussions were helpful in gaining an understanding of how others reasoned and led to more consistency in the critical appraisal.

Prior to critical appraisal the review team designed a critical appraisal tool consisting of a checklist (Additional file 4) and an Excel spreadsheet (Additional file 5). This tool was finalised after publication of the protocol and was therefore not provided in that document. The checklist highlights five aspects of quality directly affecting the internal validity of a temporal PFAS trend study, including (1) selection bias (2) accuracy of dating of samples (3) sample integrity, (4) analytical quality, and (5) study design. For each aspect a number of factors that should be considered during critical appraisal is listed. Brief descriptions of the quality aspects and criteria for high risk of bias are shown in Table 1.

Study length, sampling frequency, and number of individual or pooled samples at each time point were recorded, but these parameters were not in themselves part of the regular critical appraisal. Instead, we evaluated the statistical power according to a method suggested by Nicholson & Fryer [63] to detect a fixed average trend of 10% a year, which the above-mentioned parameters affect, and indicated this for each time trend dataset in the results.

Information important for the assessment of external validity, or how transferable the studies are to the context of the question, were recorded as well. As indicated by the study inclusion criteria, relatively few restrictions regarding populations/subjects were applied.

Studies where the risk of bias was judged to be unclear (inadequate information) or high (see criteria in Table 1) for one or more of the quality aspects were excluded from the review. All other studies were included in a narrative synthesis. Considering the broad range of sample types, locations, and substances included in this review (and the complexity of multiple interventions that may interact), it is difficult to define generic criteria for high risk of bias that are completely unambiguous. A certain degree of expert judgement is inevitable and doubtful cases do occur. In such cases we have chosen to be inclusive, but also to be careful to make a note that the risk of bias potentially is high. The judgements for each quality aspect were entered in the critical appraisal sheet (see Additional file 5) by indicating whether the risk of bias is high (Yes), may be high (Potentially), low (No), or unclear due to lack of information (Unclear). To be able to evaluate the effects of including doubtful cases (where the risk of bias potentially is high) we divided the included studies into two groups. Studies where a majority of the quality aspects were doubtful were categorized as Medium risk of bias, and studies where a majority of the aspects had low risk of bias were categorized as Low risk of bias. These two groups were then compared and qualitatively evaluated for any systematic differences in study results.

Data extraction strategy

Data were extracted and recorded by two of the reviewers. Outcome data and other important study information were extracted from studies with low and medium risk of bias and recorded in pre-designed Excel data sheets. As with the critical appraisal tool, the design of the data sheets were finalised after publication of the protocol and they were therefore not provided in that document. Outcome data included (1) reported time trends (rates of change in concentration), (2) difference in concentration between two or more time points, and (3) raw data (concentrations at each measured time point). Other important study information included geographical location, sample type (air, sediment, water, biological species etc.), matrix (bulk sediment, liver, water, plasma etc.), covariates (age, sex, etc.), sampling strategy (time period covered, number of sampling occasions, number of pooled or individual samples). Data were always recorded as reported in the primary studies, and all necessary transformations and calculations were performed at the analysis stage. In some cases the authors were contacted for complementary information. Repeatability was tested qualitatively. Both reviewers started by extracting data from 10 articles each (in total 20 articles were extracted). The reviewers then checked each other's data extraction and reconciled any disagreements.

Potential effect modifiers and reasons for heterogeneity

In this review the potential effect modifiers and reasons for heterogeneity listed below were considered. In the review protocol [9] also food web changes over time were listed as an effect modifier, but information about that was not reported in any of the included studies so could not be evaluated in this review. Potential effect modifiers and reasons for heterogeneity were evaluated qualitatively by assigning the studies to different categories and assessing whether the results of a particular category deviated from the rest. The list of potential effect modifiers and reasons for heterogeneity were compiled by the review team during preparation of the protocol.

- *Timing of the study relative to the interventions* A study with data from just a few years directly after the intervention is likely to show a smaller effect (or lower power to detect an effect) than a more recent study covering a longer study period after the interventions.
- *Proximity to past and present sources* Since the interventions are not yet implemented globally, it is reasonable to assume that the effect will be smaller in regions close to present sources compared to regions close to past sources where the interventions have been implemented.
- *Geographical differences* In areas where phase-out has been implemented, contaminated areas may still be present and leach the phased-out substances to the surrounding environments. However, if any such area is known to affect the studied population the study should not be included in the review.
- *Mode of predominant transport of PFASs to the studied site* In terrestrial or high-altitude areas where the input of PFASs is dominated by long-range atmospheric transport of volatile precursors, the response to the interventions may be different compared to marine and coastal areas where the PFAS source is dominated by direct long-range transport in the aquatic environment.
- *Type of sample and matrix* Different sample types have different routes of exposure to PFASs, and the partitioning behaviour of PFASs is different for different matrices.
- *Species differences* Route of exposure and metabolism differ among different species.
- *Study design* For human data the results may be different between cross-sectional and prospective studies. For both human and biological data the results may also depend on the studied populations (differences in sex and age etc.).
- *Analytical quality* In the early years standards were not always available for accurate calibration of the analytical instruments. Both accuracy and precision have been improved in recent years, and studies using archived samples and only the latest analytical techniques may be better at detecting trends.
- *Sampling design and quality* Long-term studies with targeted and frequent sampling may be better at detecting trends than short-term studies or studies with less frequent sampling.

Data synthesis and presentation

We have chosen to synthesise time trends based on our own analysis of raw data as well as on the calculations performed in the original research papers. The main reason for this is that a wide range of different statistical methods were used by different authors to calculate the time trends. For example, some authors treated all samples from a particular time point as independent samples whereas others used the average or median. This affects the degrees of freedom and may also influence the chance to detect a statistically significant trend. Furthermore, some authors assumed a log-linear relationship between concentrations and time, whereas others used e.g. linear or polynomial models. Another problem when comparing different time trends is that different authors used different methods for detecting change-points. Most authors did not justify their choice of change-point, but seem to have picked it based on a visual inspection of the data. We deemed it necessary to treat all datasets the same way and use the same objective method for all studies, making various datasets more comparable. Nevertheless, we also investigated whether our objective change-point analyses differed from the original analyses. However, it should be stressed that we only analysed datasets that were checked or corrected for confounding factors, such as differences in age or sex between time points, because we lacked the resources to make complete statistical models or to filter out true temporal trends in large public databases such as the US National Health and Nutrition Examination Survey (NHANES).

In our own analyses, we used median values, geometric means, or arithmetic means (in preferred order) for each particular time point, depending on what was reported, To calculate the time trends we used a log-linear regression model, and the resulting rates of change in concentration are expressed in units of % year^{-1}. To detect a change-point we used a technique similar to that outlined by Sturludottir et al. [64]. The whole time-series was repeatedly divided into two parts with at least 3 years in each part and log-linear regression lines were fitted to each part and the residual variance was recorded for each combination. The combination of regression lines that gained the smallest variance was compared with a log-linear regression line and the mean for the whole time period with an F-test. The degrees of freedoms were down-adjusted to compensate for the less restrained situation with two regression lines compared to a single regression line. A number of choices were made: (1) Only one change-point was searched for because the time-series were generally too short for several change-points; (2) Data from the identified change-point year was included in both pre- and post-time series. This is a conservative approach which reduces the influence of abrupt changes from one year to the next (which may be an artefact) but may also reduce the chance to detect significant trends on either side of the change-point; (3) The two parts may not necessarily point in different directions (increasing- decreasing) and may not show significant slopes separately, but they still show

a significant decrease in residual variance, i.e. they explain significantly more of the variation in PFAS concentration than the mean or a regression line for the whole period; (4) Change-points were searched for in datasets with 7 or more time-points only, and for datasets with fewer time points with a minimum of 4 years, we calculated a log-linear time trend for the whole study period.

In contrast to what was set out in the protocol [9], we chose not to perform meta-analyses. This is because there were too many sources of heterogeneity to allow for any meaningful meta-analysis. These are discussed more thoroughly in "Discussion" section, but in short, the outcome is not only dependent on distance from past and present sources of the PFASs, and from which environmental setting the samples were taken, but also on the timing of the study period in relation to the phase-outs (i.e. interventions). It is reasonable to assume that there is a time lag between the interventions and any measurable effects in the environment. Therefore, studies conducted shortly after a phase-out are less likely to show significant effects compared to studies with long time-series after the intervention. However, in the future when a larger number of comparable studies may be available, it is possible that meta-analyses will be feasible.

The results are presented in horizontal bar charts where each bar represents an individual dataset. The length of the bars shows the study period (years on the x-axis), and colour codes show whether the trends are significantly increasing or decreasing ($p < 0.05$) or insignificant ($p > 0.05$). For insignificant trends only, the statistical power to detect a trend is also categorized as sufficient (Power > 0.8) or low (Power < 0.8). If a significant change-point was detected, the change-point is indicated as a narrow black band on the horizontal bar. It is especially important to note that an insignificant trend does not necessarily mean that there is no 'true' trend. As we shall see, most of the studies showing insignificant trends have low statistical power to detect even quite high rates of change in concentration. Admittedly, the lack of further quantitative synthesis may encourage vote counting, ignoring effect sizes and differences in reliability between studies. However, we tried to avoid this and we strongly advise the reader to do the same.

Results

Review descriptive statistics

Searches in the literature databases resulted in 10,170 unique records (searches were performed in May 2014, and a search update was conducted on 20 October 2015). Based on title and abstract 9602 were excluded (Fig. 1). Four of the articles included based on title and abstract could not be retrieved in full text. The remaining

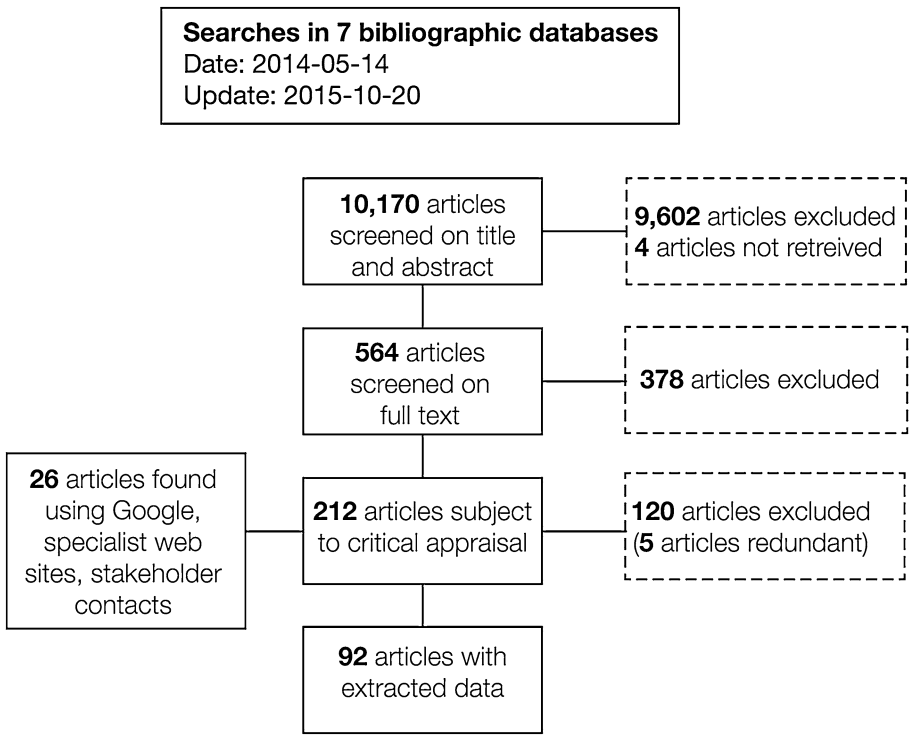

Fig. 1 The searches identified 10,170 unique records. Four of the articles that passed the abstract screening could not be retrieved in full text. Five articles were excluded at critical appraisal because the same data ware published elsewhere

564 articles were screened on full text, and based on this another 378 articles were excluded. These articles are listed in Additional file 3 together with reasons for excluding the articles. In searches for grey literature we found 26 reports that potentially could be useful and where the same data could not be found in the scientific literature. Interestingly, the data in several other reports were also published in scientific journals. Comparing our search results with the articles that were listed a priori as articles that should be captured by the searches, and with articles in bibliographies of review articles, the searches seem to have been comprehensive. Some relevant grey literature studies were not captured, but more recent versions of those were found instead (see Additional file 2, section C). No additional relevant articles (based on title screening) were found in the bibliographies of the review articles (see Additional file 2, section D).

In total, 186 articles and 26 grey literature reports were included based on full text and critically appraised. During this process, which also involved data extraction, it was found that some studies were redundant, i.e. the same data was published in more than one article. In some cases one article had added some data to a previously published time trend, and in such cases we used the study containing the longest study period and/or the study with the most frequent sampling. Redundant studies are listed in Additional file 3, together with a reference to the article that finally was used in this review. After critical appraisal and removal of redundant articles, 92 articles [11, 12, 37, 38, 40, 42, 62, 65–149] remained for full data extraction. More details on the outcome of the critical appraisal are given in the next section.

Among the 92 articles included, a total number of 227 time trend datasets could be extracted. However, not all of these time trends are independent and should not be treated as separate studies. For instance, in one article studying polar bears [134], PFASs were analysed in both kidney and liver. These two datasets are not independent from each other. Other articles have investigated human populations from the same locations but with different age groups and/or sex. Such datasets may also not be independent from each other. Furthermore, in some investigated populations or matrices the concentrations were above the LOQ in too few samples to allow for a time trend analysis. Data for a total number of 42 different PFASs or precursors were extracted (see "Narrative synthesis" section). Many of these were analyzed in a limited number of samples presented in only a few articles and were therefore not further considered here. The more frequently analysed substances that this review focused on included C4, C6, C8, C10 sulfonates (i.e., PFBS, PFHxS, PFOS, PFDS) and the precursor FOSA, as well as C7–C14 carboxylates (i.e., PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, and PFTeDA). Figure 2 shows, for each of these substances, the total number of time trend datasets that were identified.

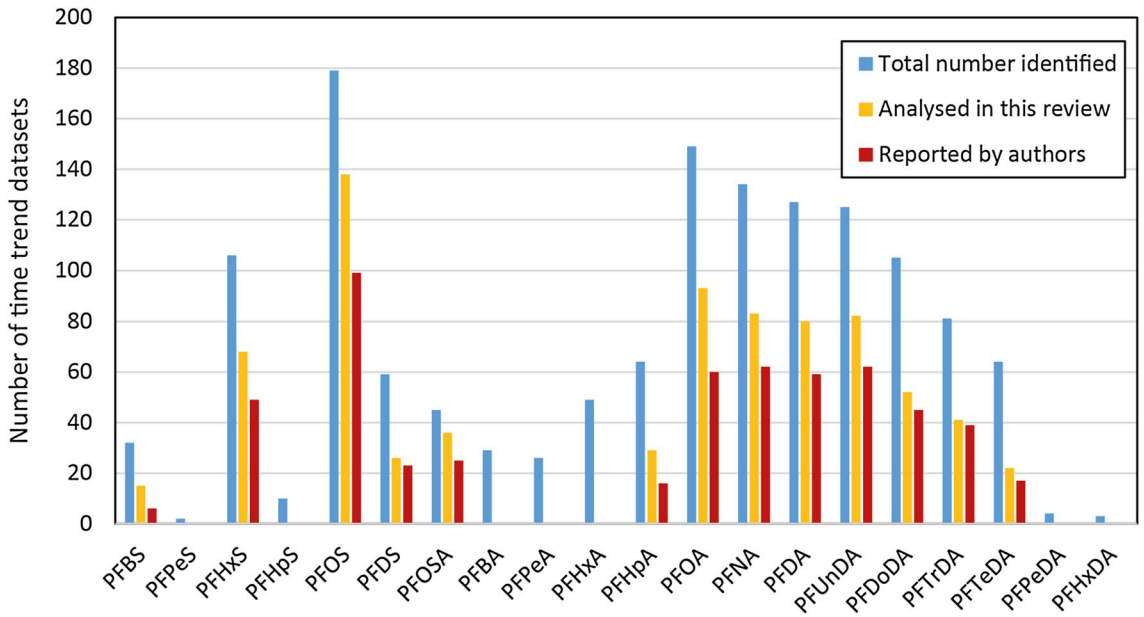

Fig. 2 Total number of time series measured in the included articles (blue bars), number of time trends re-analysed in this review (yellow bars), and number of time trends originally reported by the authors (red bars). Low detection frequency or different focus of the paper were the main reasons authors did not evaluate and report time trends for measured substances. Low detection frequency was the main reason time trends for measured substances were not re-analysed in this review

The same figure also shows the number of datasets that were re-analysed in this review and the number of time trends that originally were reported by the authors of the reviewed articles, respectively. The most frequently analyzed substance is PFOS, followed by PFOA.

Most of the studies were conducted in North America and Europe followed by the Arctic. A small number of additional studies have been conducted in East Asia. From the southern hemisphere only one study, investigating PFASs in human blood serum in an Australian population, was included [138]. Figure 3 shows the distribution between geographical areas.

The total number of time trend datasets on human samples was 84, and for the vast majority of these the studied matrix was blood plasma or serum. Plasma and serum are considered equivalent matrices for monitoring time trends of PFASs. Two other datasets were concentrations in whole blood and in two other datasets the matrix was milk from lactating women (Fig. 4).

Nine datasets involved food samples, and 31 datasets were found for abiotic environmental samples including air, snow/ice, water, and sediment. Man-made matrices, comprising various commercial products and sewage sludge, made up 16 datasets. Biota was the largest category with 86 datasets including mammals, birds, fish, reptiles and invertebrates. Among the environmental samples, most datasets were taken from coastal or marine environments (Table 2). However, for abiotic environmental samples most datasets were taken from inland or high altitude environments where the major source of PFASs is atmospheric deposition.

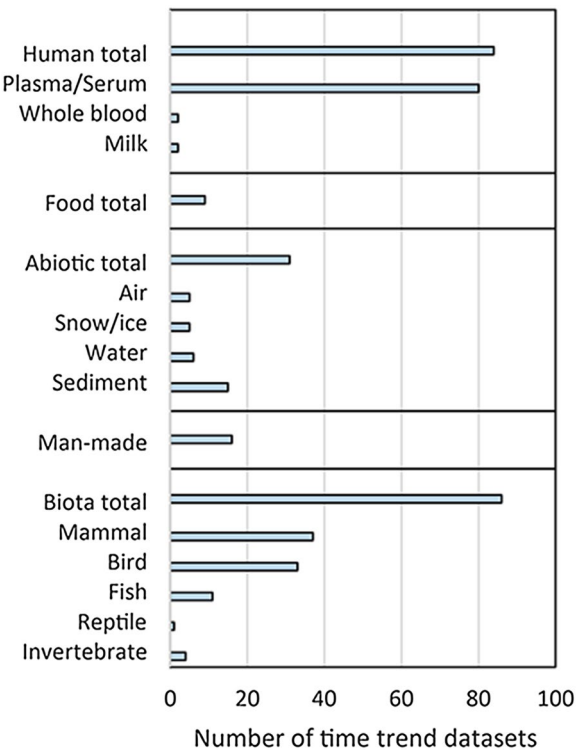

Fig. 4 Number of time trend datasets in different sample categories. Man-made refers to man-made products including digested sewage sludge (biosolids)

The oldest article included in this review was published in 2002, just after the major phase-out by 3M, but most of the articles were published in the period 2011–2015 (Fig. 5).

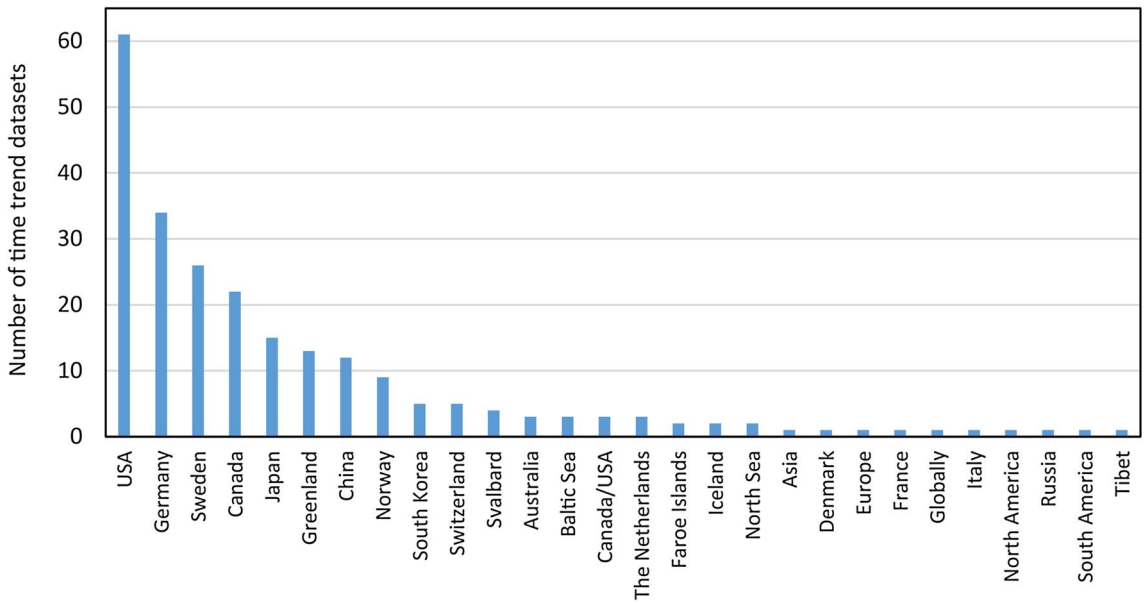

Fig. 3 Geographical distribution of measured time series

Table 2 Number of environmental datasets from different environments

Category	Inland	Coastal/marine
Abiotic samples	19	7
Biota	18	68
Total	40	75

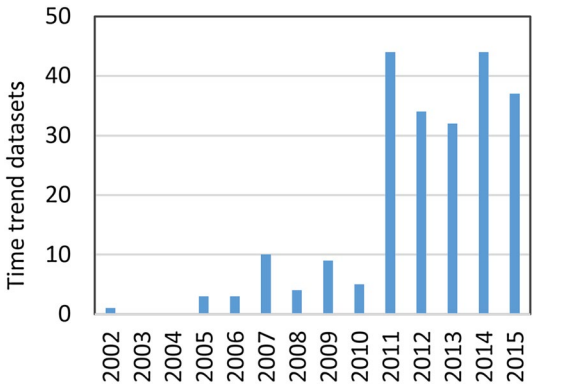

Fig. 5 Distribution of publication year among included articles

Narrative synthesis including study quality assessment

The critical appraisal of studies included after full text screening is shown in Additional file 5, and a narrative synthesis table including articles passing the critical appraisal is shown in Additional file 6. Since there is no quantitative synthesis in this review, a detailed discussion of the findings follows below. All results from the studies included are shown in Additional file 7 (reanalysis of raw data in this review) and Additional file 8 (reported time trends in the original studies).

Human samples

Overall results from the analysis of included human PFAS temporal trend datasets are displayed in Additional file 7. Studies from which included datasets were drawn were largely focused in Europe (Germany, Norway, Sweden), Asia (China and Japan) and the United States. Only one study was included from the southern hemisphere (Australia), and only one study was included from an indigenous northern population (Inuit, Greenland). Most datasets included used cross-sectional sampling of the population in various years, except for one study from Tromso, Norway, where serum from the same male donors was analyzed at 5 sampling times over 28 years (1979–2007), and one study in Gullah African Americans from coastal South Carolina (2003–2013).

PFOS *Change point analysis* For PFOS in human samples, twelve datasets containing at least 7 time points were evaluated by change point analysis (Fig. 6). Eleven of these datasets were for European countries, and one was in New York, USA. Nine of these twelve datasets (75%), all in Europe, had a significant change point and most change points were detected between 1998 and 2003. The earliest change point for PFOS was in 1988 for pooled breast milk samples from primiparous women in Stockholm [137], where the trend went from significantly increasing (pre 1988) to significantly decreasing (post 1988). Visual inspection of the data suggested a levelling off of concentrations between 1988 and 2000 before a stronger decline occurred. This relative trend was similar to what was observed in Norwegian males, where a significant change-point was observed in 1993 [92]. The shape of these two human temporal trends [92, 137] closely mirrors the trend in annual production volumes of PFOS reported by Paul et al. [5] and as plotted in our associated review protocol [9]. Three datasets from Swedish dietary items [99] were also analyzed for change points, but no change points were detected.

General observations With few exceptions, for all studies of PFOS in human samples that were of sufficient statistical power (i.e. > 0.8) a significant decreasing temporal trend was observed, either across the whole study period or after the detected change point (Fig. 6). No significant temporal trends for PFOS were observed in only 6 datasets of human samples [89, 102, 115, 121, 143], and two datasets of dietary items [99, 142], but in each case the power to detect a trend was low. Overall, the declining trends for PFOS generally coincide with the timing of the 3M Co. phase out by 2002.

One obvious exception among all PFOS datasets was for the only study in China [98], where a significantly strong and rapid increase (> 40% annual change) of PFOS concentrations was detected in male and female serum. A statistical evaluation of the change point was not possible because of only 4 time points, but visual observation suggests that concentrations began to increase in the mid 1990s, with much more rapid increases after 1999. Unfortunately, all samples in this study were only from one city and the last samples analyzed were from 2002.

The unique study of PFOS (and other PFAS) temporal trends in Greenland Inuit serum [110] was of particular interest, but data could not be extracted for an independent analysis. While the authors reported some 'age-dependent' statistically significant temporal trends for PFOS, after age-adjustment no significant temporal trends were evident for PFOS, nor for any other PFAS. An evaluation of the statistical power in this study is also not possible.

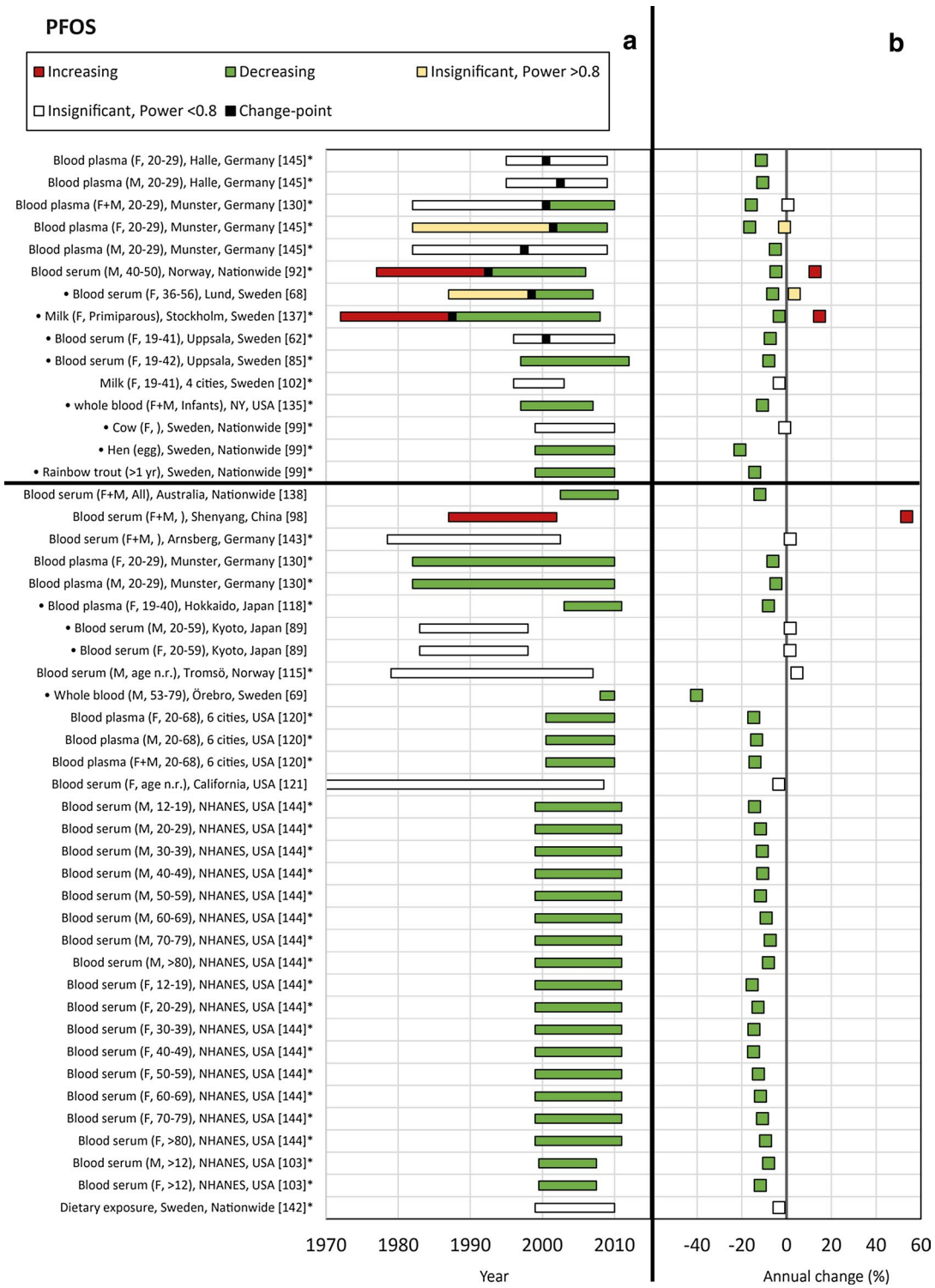

Fig. 6 Calculated time trends for PFOS in human and food samples. **a** Study period and direction of trend. Datasets above the thick horizontal line were analysed for change-points. Other data sets provided less than 7 time points and were not analysed for change-points. The power of insignificant trends refers to the chance of detecting an annual change of 10%. **b** Magnitude of annual change. Where change-points occur the magnitude is generally shown before and after the change-point, but where the trend is insignificant on both sides the magnitude is shown for the whole period only. Colour codes are the same in **a**, **b**. Bullets indicate that time trend analysis was performed also in the original study (reference in square brackets). Asterisks indicate low risk of bias, other studies were judged to have medium risk of bias

In the US, NHANES is a rich source of data for PFASs in serum beginning in 1999. The data are publically available but our systematic review only included two studies that had the explicit objective to analyze PFAS temporal trends in the NHANES database. Calafat et al. [74] is limited in that it only included a statistical test between two time points (i.e. 1999–2000 and 2003–2004). Nevertheless, the study is important because these two time points span the phase-out by 3M Co. in 2002, and thus provides nationally representative data that may measure the effect of the phase out. For PFOS, Calafat et al. [74] reported statistically significant decreases in 2003–2004, compared to 1999–2000, while accounting for age, sex and race/ethnicity (Additional file 8, Figure S11). Kato et al. [103] examined NHANES data across 4 study periods (99–00, 03–04, 05–06, and 07–08) by sex, age, and ethnicity and for PFOS significant declines were evident in both men and women (> 12 years); the rate of decline was faster in women than in men (Fig. 6).

One peer-reviewed study by Wong et al. [144] reported PFOS concentrations from the NHANES database between 1999 and 2011, categorized by sex and age for the nationally representative samples. Although the authors did not use the data for temporal trend analysis, we interpolated data from their published figures and used them here in an independent analysis for temporal trends. As shown in Fig. 6, in every age category for both men and women, PFOS concentrations declined significantly over the entire period. By visual inspection of the trends, rates of decline were close to linear over the whole period, and the rate of the decline was faster in the younger (i.e. > 15% annual change in the 12–19 age class) than in older age classes (e.g. < 10% annual change for the > 80 age class) among both males and females. Other datasets of PFOS temporal trends in the US, including in new-born infant blood spots (New york, 1996–2006) [135], and in plasma of adults aged 20–68 (6 cities, 2000–2010) also showed significantly decreasing trends corresponding to the approximate time of the 3M Co. phase out. Although the data could not be extracted for independent analysis, a significant age-adjusted decline of serum PFOS (11% per year, 2003–2013) was also reported for Gullah African Americans in coastal South Carolina after the phase-out [87].

In Sweden, where all adequately powered human temporal trend studies of PFOS showed a decline, it was useful to compare with trends for important Swedish dietary items [99, 142]. Nationally or regionally representative archived samples of hen eggs and farmed rainbow trout muscle showed significant and rapid decreasing trends between 1999 and 2010. The analysis of data from cow's milk was not adequately powered and did not show a significant trend [99]. Similarly, PFOS in total dietary intake for Swedes showed no statistically significant temporal trend. Although dietary intake was estimated to be lower after the phase-out [142], statistical power was low to detect a trend in this dataset.

Whether declining PFOS concentrations in Swedes are a direct consequence of declining PFOS concentrations in dietary items, such as eggs and farmed fish, has been discussed [99, 142] but remains uncertain. One inconsistent result is that the PFOS isomer pattern (linear: branched) in eggs has become more linear over time, increasing from approximately 1:1 in year 2000 to approximately 3:1 in the year 2010 [99]. This is contrary to two independent studies where the serum of Swedes was reported to increase in branched PFOS content over the same period [85, 109]. Liu et al. [109] suggested that the branched PFOS isomer pattern, and concomitant increasingly non-racemic proportions of 1 *m*-PFOS isomer in the same Swedish serum samples, post year 2000, indicated a role of PFOS-precursors in human exposure.

PFOS precursors

Concomitant with declining PFOS in Swedish human serum from Uppsala (Fig. 6), Gebbink et al. [85] reported rapid declines (1.8–3.5 year disappearance half-lives) for four PFOS-precursors (MeFOSAA, EtFOSAA, FOSAA, FOSA) in the same period, between 1996 and 2012. Declining trends of the PFOS-precursor, FOSA, is furthermore demonstrated by analysis of two datasets on male serum from Norway, both of which showed an inverted U-shape temporal trend for FOSA [92, 115]. For Norwegian men (40–50 year) [92], a significant increase of FOSA between 1977 and 1985 (change-point) was followed by a statistically significant decline to 2006, with later concentrations being non-detectable. In their longitudinal study of male serum, Nost et al. [115] reported a significant 60% decline for FOSA between 2001 and 2007 in male serum from Tromso, Norway. Also, in Germany (Halle and Munster), declining concentrations of three PFOS-precursors (MeFOSAA, EtFOSAA, FOSAA) in human plasma were observed after 1995, whereas concentrations of another PFOS precursor (Di-SAm-PAP) showed no temporal trend at either location [145]. Also consistent with the trend for PFOS in the same samples, FOSA declined in infant whole blood from the US [135], and no change-point could be detected in either case. In this study, our estimated rate of decline for FOSA (30% per year) was much more rapid than for PFOS [135], consistent with the report of Gebbink et al. [85]. Overall, most temporal data for PFOS precursors in human samples show declining concentrations consistent with the time of the 3M Co. phase-out of these chemicals by 2002.

PFHxS

Change point analysis For PFHxS in human samples, the same twelve datasets as for PFOS were evaluated by change point analysis (Additional file 7, Figure S2). Eight of these twelve datasets (67%), all in Europe, had a significant change point. Among datasets with a significant change point, five had change points detected between 2000 and 2005, while the three others had change points between 1985 and 1993 [68, 92, 145]. Among sufficiently powered datasets with a change point, all (six) showed a significant increasing trend prior to the change point, two showed a significant decrease after the change point, and one study showed no change after the change point. Five of the datasets with a change point showed no significant change after the change point but were underpowered by our analysis.

None of the studies that showed a significant decrease of PFOS after the change point (Fig. 6) showed a concomitant decrease of PFHxS after the change point (Additional file 7, Figure S2). Moreover, the only two studies showing a significant decrease for PFHxS after the change point (male and female plasma, Halle, Germany [145]) did not show a significant decrease in PFOS after the change point. Together these data suggest that any interventions leading to lower PFOS exposure in Europe did not simultaneously lead to lower PFHxS.

General observations Several datasets (with no change point, or not analyzed for change point) showed evidence for increasing PFHxS in humans. In male and female serum from Arnsberg, Germany, a continuous significant increase was detected between 1977 and 2004 [143], but few samples were available from after the 3M Co phase-out. One slightly longer dataset from Norway (1979–2007) also showed a significant increasing trend for the whole period, but concentrations in 2001 (2.0 ng/mL) were very similar to 2007 (1.9 ng/mL), suggesting a levelling-off. This is consistent with serum of Norwegian men [92], where concentrations were significantly higher in post-1985 samples, but no significant temporal trend was evident between 1985 and 2006. The biological half-life of PFHxS is known to be longer than for PFOS [150, 151], thus relatively longer biomonitoring may be necessary to see a decrease in human serum in response to any intervention.

The strong increasing trend for PFHxS in serum of Swedes from Uppsala was evident from two studies [62, 85] (Additional file 7, Figure S2). The increase of PFHxS, however, was concluded to be due to a drinking water supply that had been contaminated by firefighting foams beginning in the 1990s [88]. Thus, PFHxS data from Uppsala should not generally be extrapolated for a larger area. Women living outside of Uppsala [88], nevertheless, showed a significant increase (approximately doubled) of PFHxS in serum when comparing samples from 1996 to 1999 to samples from 2008 to 2011; but this result should be treated with caution due to only two time points. Three Swedish dietary items (milk, eggs, farmed fish) showed no evidence of an increasing trend for PFHxS, and concentrations in eggs actually decreased significantly between 1999 and 2010; no trend was detected in milk or farmed fish, but these datasets had low power [99].

Based on NHANES data, Calafat et al. [74] reported statistically significant decreases in PFHxS for 2003–2004 (post phase-out) compared to 1999–2000 (pre phase-out) while accounting for age, sex and race/ethnicity (Additional file 8, Figure S5); one exception was PFHxS in Mexican Americans which was not significantly different between years. Kato et al. [103] continued the NHANES analysis into 2005–2006 and 2007–2008 and confirmed the initial decline, from 1999 to 2005, but by 2007-08 the concentrations had again increased. Thus, in our independent analysis of datasets from Kato et al. [103], no significant temporal trend was detected for males nor females (Additional file 7, Figure S2), consistent with our analysis of two other datasets for the US (female serum from 6 cities, and combined males and females from the same 6 cities [120]), all of which had low power to detect a trend.

Nevertheless, two more US datasets showed significant decreases in PFHxS (infant blood spots from New York [135], and male serum from 6 cities [120]). Similarly, and although the data could not be extracted for independent analysis, a significant age-adjusted decline of serum PFHxS (6% per year, 2003–2013) was also reported for Gullah African Americans in coastal South Carolina after the 3M Co. phase-out [87]. Compared to PFOS in the same samples, the rate of decline for PFHxS (< 10% annual change) was always slower than for PFOS (> 10% annual change).

Given the rapid increase of PFOS in Shenyang China [98], and that PFHxS is the second most prominent PFAS in Chinese human blood [152], a current data gap is the lack of any temporal trend study for PFHxS in Chinese biological samples.

PFBS

PFBS is a likely degradation product of perfluorobutanesulfonyl fluoride-based chemicals which were known replacements for perfluorooctanesulfonyl-based products. One dataset for PFBS in Norwegian male serum between 1977 and 2006 [92] (Additional file 7, Figure S1) showed PFBS in most samples at low levels (0.06–0.18 ng/mL) until 2001 when concentrations fell below detection limits for all subsequent samples (i.e. < 0.050). Although not statistically significant, the onset of this apparent decline corresponds with the phase-out of

perfluorooctanesulfonyl chemistries, suggesting that the low levels of PFBS (pre 2001) may be due to the presence of residual PFBS in PFOS-containing products.

In contrast to this trend in Norway, in Uppsala, Sweden, Glynn et al. [62] reported an increase in PFBS between 1996 and 2010 for women (Additional file 7, Figure S1). A follow up in the same samples showed no significant trend for PFBS [85]. Nevertheless, our analysis of the Glynn et al. data [62] detected a change point in 1998, when concentrations increased approximately tenfold in the subsequent 12 years. However, as described above for PFHxS, Gyllenhammar et al. [88] case study in Uppsala strongly suggests that the increasing trend for PFBS in people from Uppsala was due to contamination of drinking water by firefighting foam. Although our independent analysis of the data could not show a significant increase between the two time points (based on data extractable from the paper), a high rate of change was observed. Moreover, the detection of elevated PFBS in drinking water in and around Uppsala [88] means that human PFBS data in Uppsala are not likely representative of other geographic locations.

PFDS

Five human datasets were included for PFDS (Additional file 7, Figure S12). Three of these were for adult German serum (Munster and Halle [145]) and showed no significant trends, but were underpowered. PFDS was only detected in up to 50% of the samples, and in later years (i.e. after 2005) the frequency of detection decreased which prevented a quantitative temporal trend analysis across the whole dataset. Nevertheless, we take this decline in detection frequency as qualitative evidence for a decline of PFDS in these German cities. The two other datasets were for Uppsala, Sweden [62, 85], and significant declining trends (> 10% per year) were shown in both cases. Similar to the datasets discussed above from Germany, for the study by Gebbink et al. [85] in Uppsala, Sweden, the concentrations of PFDS were below detection limits for the most recent samples from 2012. For the dataset from Glynn et al. [62], a significant change point was detected in 2000, corresponding to the time of the 3M Co. phase out.

PFOA (C8 PFCA)

Change point analysis For PFOA in human samples, eleven datasets were evaluated by change point analysis (Additional file 7, Figure S15). Eight of these datasets had a significant change point for PFOA, seven in Europe and one in the US. Among datasets with a significant change point, only 2 of 8 showed a significant increasing trend prior to the change point [92, 137], while 6 of 8 showed no significant trend before the change point, but all of these were statistically underpowered. The two datasets showing an increasing trend prior to the change point were also the datasets with the oldest archived samples; showing an increasing trend in adult male serum from Norway between 1978 and 1993 [92] and in primiparous female serum from Stockholm, Sweden between 1972 and 1988 [137]. Consistently, all of the studies with a change point (8/8) showed a significant decreasing trend for PFOA after the change point.

General observations Among all datasets showing a significant decrease in PFOA across all years, or a decrease after the change point, the rate of decline was more modest (typically < 5% annual change) than for PFOS. Two exceptions to the general pattern above is that Nost et al. [115] reported a significant 23% decrease in serum PFOA in adult males from Tromso, Norway, between 2001 and 2007 in a longitudinal study (Additional file 8, Figure S18). The corresponding decrease for PFOS over the same period was 22%, and the overall temporal trends looked very similar for PFOA and PFOS, suggesting that PFOA exposure in this Norwegian population was largely of electrochemical origin. The other exception was for Australia [138], where PFOA and PFOS declined at similar rates of annual change of approximately 10% after the 3M Co. phase out (Additional file 7, Figure S15).

Based on NHANES data, Calafat et al. [74] first reported statistically significant decreases for PFOA in 2003–2004 (post phase-out) compared to 1999–2000 (pre phase-out) while accounting for age, sex and race/ethnicity. This suggested that the 3M Co. phase out had resulted in lower human exposure to PFOA in the US, however Kato et al. [103] continued the NHANES analysis for PFOA into 2005–2006 and 2007–2008. Similar to the trends for PFHxS, PFOA concentrations did not continue to decline and may have risen in 2007–2008, particularly for males. Thus, in our independent analysis no overall statistical temporal trend was detected (Additional file 7, Figure S15), and the overall dataset was underpowered to detect a significant trend in both males and females. Other PFOA datasets from the United States [120, 121] have also largely been underpowered to detect a significant temporal trend, but interestingly analysis of three datasets from Olsen et al. [120] showed a significant decrease for adult women, but not for men, in serum from 6 American cities. A significant decline was detected for PFOA in infant whole blood spots from New York State [135] over the entire study period 1997-2007, but we did not detect a significant decline subsequent to a detected change point in 2001. Although the data could not be extracted for independent analysis, a

significant age-adjusted decline of serum PFOA (7% per year, 2003–2013) was reported for Gullah African Americans in coastal South Carolina after the 3M Co. phase-out [87].

As with PFOS, the only PFOA dataset available for people in China showed a significantly strong and rapid increase (> 20% annual change) of PFOA concentrations in male and female serum from Shenyang [98]. By simple visual observation, the exponential shape of the trend was similar to PFOS, showing that concentrations began to increase in the mid-1990s, but with a more rapid increases after 1999. Unfortunately, all samples were only from one city, and moreover the most recent samples available were from 2002. Nevertheless, the maximum PFOA concentration in Shenyang (year 2002) was approximately 3 ng/mL, which is lower than in many other countries at the same time. The increasing temporal trend of PFOA between 1983 and 1998 in adult male serum (but not females) from Kyoto, Japan, is similar in magnitude (~ 10% annual change) to what was observed before the change-points in Stockholm (milk of primiparous women) or Norway (serum of adults), but the lack of any samples after year 2000 in Kyoto prevents any extrapolation beyond this time. Two other more contemporary datasets from Asia, Hokkaido Japan (2003–2011) and Busan Korea (1994–2008), did not show a significant temporal trend but were both underpowered to detect a trend.

PFHpA (C7 PFCA)

Results on temporal trends of PFHpA were mixed (Additional file 7, Figure S15). A significant change point was detected in 3 datasets of blood plasma from Germany between 1998 and 2002. Among females in Munster, plasma concentrations of PFHpA significantly increased after the change point in 1998, whereas in plasma of males from Munster PFHpA concentrations decreased after the change point in 2002 [146]. In plasma of adults in Halle, Germany, only in males was a significant decrease detected, for females no significant trend was detected, but statistical power was low [146]. The only other human dataset from Europe with a significant trend was for longitudinal sampling of male serum in Tromso, Norway, between 1979 and 2009, whereby concentrations were not detected in years prior to the 1990s, and average concentrations were consistently low at 0.1 ng/mL at each time point afterwards [115]; thus concentrations were increasing over the whole study period but stable through the 3M phase-out period. Similarly, no trend was detected in female serum from Uppsala, Sweden, and no trend was detected for cow's milk in Sweden over a similar timeframe. A dataset from Busan, Korea, was the only data available for Asia, and no significant temporal trend was detected between 1994 and 2008 but power was low. In 6 cities in the United States, PFHpA declined significantly in plasma of females, whereas no significant trend was detected for males [120].

Longer-chained PFCAs (C9–C14 PFCAs)

Results for the temporal trends of PFNA (Fig. 7), PFDA, PFUnDA, PFDoDA, PFTrDA and PFTeDA (Additional file 7, Figures S23, S28, S33, S37, S40) in human sample datasets can be categorically generalized as showing no evidence for any significant decreasing temporal trends at any global location. The only possible exception was for one dataset of PFUnDA in Norway [92], where our independent change-point analysis suggested a significant decrease in adult male serum between 1986 and 2006. However, this trend was driven by a high mean concentration detected in 1986, with all subsequent years showing no apparent trend. Moreover, in the same dataset, no significant change was detected for PFNA (power > 0.8), PFDoDA (power < 0.8) or PFTrDA (power < 0.8), and higher concentrations were detected for PFDA after a change point in 1991.

The overall weight of evidence for datasets from Europe (Germany, Sweden, Norway) was that longer-chained PFCAs continue to increase, or have increased and have stabilized after a significant change point. In general, the rates of increase were $\leq$ 10% per year. Analysis of hen eggs and of the broader Swedish diet between 1999 and 2010 showed no significant temporal trends for PFNA, PFDA or PFUnDA in food during this critical time period [99], however statistical power was also low in most cases. The exception was for PFDoDA where a statistically significant increase in the Swedish diet was seen [142], consistent with the rate of increase of serum PFDoDA in adult females from Uppsala, Sweden [85] over a similar time period.

No datasets from China were identified in the systematic review for these longer-chained PFCAs. Other datasets from Asia [90, 118] mostly showed no significant trends for PFNA, PFDA, or PFUnDA but were all underpowered to detect a trend. Nevertheless, a significant increasing trend was detected for PFDoDA in serum of women from Busan, Korea [90].

Using NHANES data, Calafat et al. [74] reported statistically significant increases in PFNA concentrations in 2003–2004, compared to 1999–2000 for every age, sex, and race-ethnicity category. Kato et al. [103] continued the NHANES analysis into 2005–2006 and 2007–2008, and a significant increasing trend was detected for PFNA across the whole time period for a population including both males and females (Fig. 7). All other datasets for PFNA, PFDA, PFUnDA and PFDoDA in the US showed no significant changes over the time periods

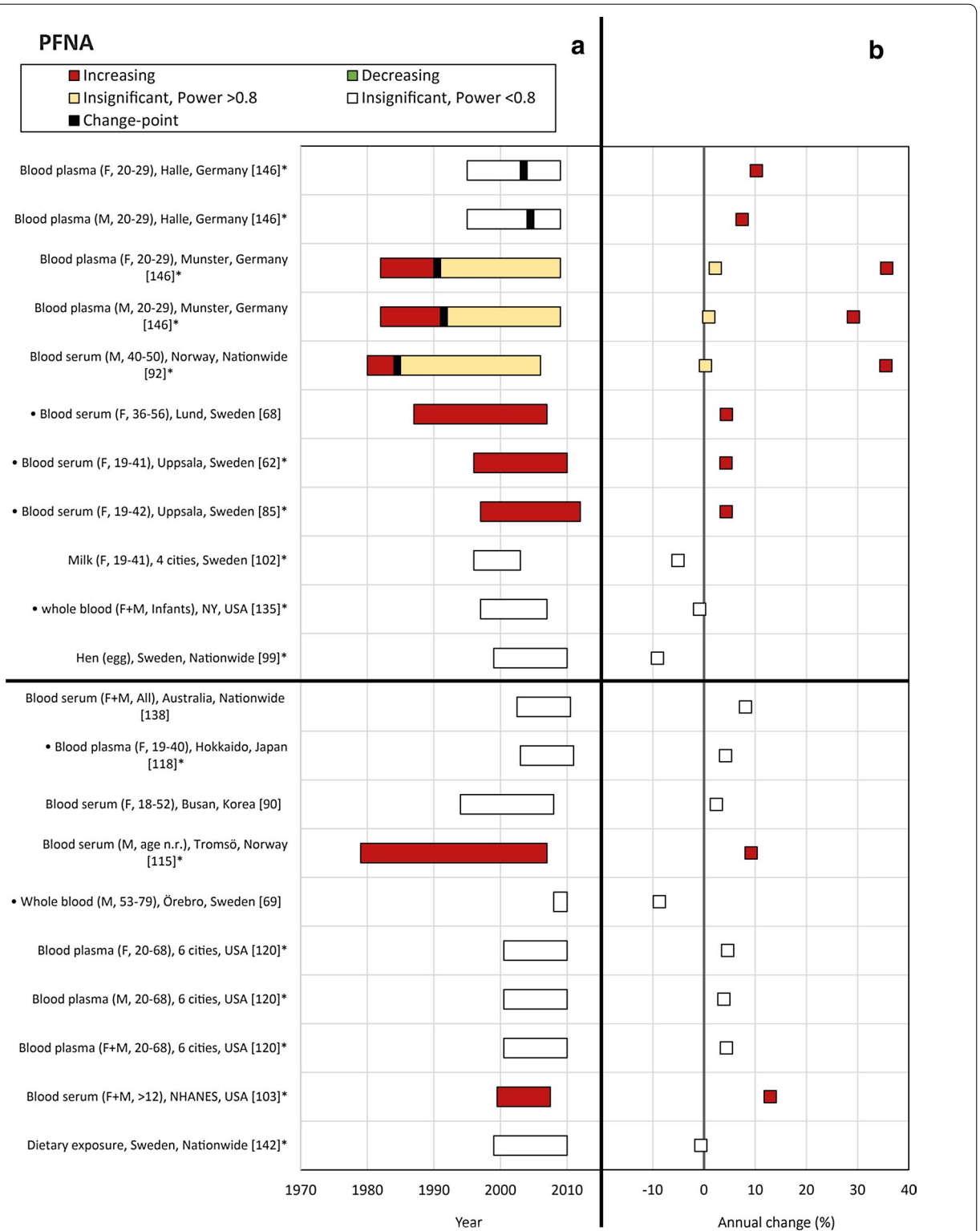

Fig. 7 Calculated time trends for PFNA in human and food samples. **a** Study period and direction of trend. Datasets above the thick horizontal line were analysed for change-points. Other data sets provided less than 7 time points and were not analysed for change-points. The power of insignificant trends refers to the chance of detecting an annual change of 10%. **b** Magnitude of annual change. Where change-points occur the magnitude is generally shown before and after the change-point, but where the trend is insignificant on both sides the magnitude is shown for the whole period only. Colour codes are the same in **a**, **b**. Bullets indicate that time trend analysis was performed also in the original study (reference in square brackets). Asterisks indicate low risk of bias, other studies were judged to have medium risk of bias

examined but were also all underpowered to detect a trend. Although the data could not be extracted for independent analysis, significant age-adjusted declines of serum PFNA, PFDA and PFUnA (4–5% per year, 2003–2013) were reported for Gullah African Americans in coastal South Carolina after the 3M Co. phase-out [87]. This exceptional result was described by the authors as perhaps only a local phenomenon, or possibly consistent with trends in the NHANES database among non-hispanic blacks over the same time period. Based on the increasing temporal trends of PFNA presented by Kato et al. [103] for non-hispanic blacks, we suggest the former explanation is most likely, that this is indeed a local phenomenon.

Abiotic samples

Temporal trend studies were identified in the following "abiotic" samples: consumer products, digested sewage sludge (known in North America as "biosolids"), air, snow and ice cores, surface waters (freshwater and marine), and benthic sediment cores (freshwater and marine). A graphical summary of the analysis of temporal trends in abiotic datasets is displayed in Additional file 7. Below the abiotic media are discussed "substance by substance". We then also summarise the abiotic media temporal trends on a "media by media" basis in the order listed above. This order was chosen because it represents the logical flow of PFASs from sources to the receiving environmental media [i.e. product use, product disposal, receiving mobile environmental media (i.e. air and water), and stationary environmental media (i.e. ice, snow and sediments)].

PFOS For PFOS in abiotic samples, change points were detected in a snow core sampled in Tibet [38] and in three sediment cores sampled in Canada in two separate studies [93] (Fig. 8). The Tibetan snow core dataset had a change point in 1984, but showed no significant trend and low power over the whole period sampled. One of the Canadian sediment core studies (Kempenfeldt Bay, Lake Simcoe [33]) showed a significantly increasing temporal trend in a sediment core before the change point (in 2002) and an insignificant trend (power < 0.8) after the change point. The other Canadian sediment study in Lake Ontario [90] showed significantly increasing trends before and after the change points (in 1979 and 1987) in two separate cores (stations 1004 and 1034). In a third core (station 1046) from this Canadian study [90] no change point was detected.

PFOS showed statistically significant declining trends in several surface waters, namely; in Tokyo Bay between 2004 and 2006 [129], in marine and fresh waters on the west coast of South Korea between 2008 and 2012 [95] and in Bohai Bay on the east coast of China between 2011 and 2013 [140]. The other significant downward trends for PFOS were observed in a digested sewage sludge sampled in Hinwil in Switzerland between 1998 and 2008 [136], in a Snow core from the Devon ice cap [91] and in a sediment core in the Haihe River (core S6, dated 1952–2006) in China [149]. The majority of sediment cores, from five separate studies sampled in China, North America and Japan, showed statistically significant increasing temporal trends for PFOS.

Other PFSAs Only one study reported statistically significant temporal trends for PFSAs other than PFOS in abiotic studies (Additional file 7, Figures S1, S6, S12, S42). PFHxS showed a statistically significant declining trend in marine water on the west coast of South Korea between 2008 and 2012 [95] and PFDS showed a significantly increasing trend in the same seawater. Liu et al. [108] also reported an increasing temporal trend in PFSAs for one product (a carpet shampoo). They attributed the increasing PFSA trend in the carpet shampoo to the increased use of PFBS in recent years, but no statistical analysis was performed in the Liu et al. study and the data were insufficient to perform a statistical analysis in this present study.

PFOA (C8 PFCA)

For PFOA in abiotic samples, the independent change point analysis revealed change points (Additional file 7, Figure S17) for sediment cores in three separate studies in Canada/USA [90], China [64] and Japan [3]. For the two cores in the Canada/USA study [90] where change points were identified (stations 1004 and 1034), statistically significant increasing trends were observed before and after the change points (in 1979 and 1988, respectively). For the Chinese study [64], there was no significant temporal trend in one sediment core (core 1) before the change point in 1967, after which a significant increasing trend was observed. For the two other cores in the Chinese study [64] (cores 2 and 3) no change point was detected. For the Japanese study [3], there was no statistically significant trend observed before or after the change point in 2001.

PFOA showed statistically significant downward trends in several different consumer products, whereas it showed significant increasing trends in food contact paper (Category H in Additional file 7, Figure S17) [108]. PFOA showed statistically significant declining trends in the same surface waters for which declining PFOS trends were also observed, namely; in Tokyo Bay between 2004 and 2006 [129], in marine and fresh waters on the west coast of Korea between 2008 and 2012 [95] and in Bohai Bay on the east coast of China between 2011 and 2013 [140].

Fig. 8 Calculated time trends for PFOS in abiotic samples. **a** Study period and direction of trend. Datasets above the thick horizontal line were analysed for change-points. Other data sets provided less than 7 time points and were not analysed for change-points. The power of insignificant trends refers to the chance of detecting an annual change of 10%. **b** Magnitude of annual change. Where change-points occur the magnitude is generally shown before and after the change-point, but where the trend is insignificant on both sides the magnitude is shown for the whole period only. Colour codes are the same in **a**, **b**. Bullets indicate that time trend analysis was performed also in the original study (reference in square brackets). Asterisks indicate low risk of bias, other studies were judged to have medium risk of bias

A significant downward trend for PFOA was also observed in a sediment core in the Haihe River (core S6, dated 1952–2006) in China [122]. Similar to PFOS, sediment cores tended to show statistically significant increasing temporal trends for PFOA, although there were a few exceptions where no significant trend or a declining trend was observed (Haihe River). A statistically significant increasing temporal trend was also observed in a snow core from Mt. Mutzugata in Tibet between 1996 and 2007.

Other PFCAs (C7, C9–C14 PFCAs)

Liu et al. [108] reported that the PFCA content showed an overall downward trend in consumer products from 2007 to 2011. Our analysis showed statistically significant downward trends (and in some cases large annual changes) for PFHpA, PFNA, PFDA, PFUnDA and PFDoDA in various products (see Additional file 7, Figures S14, S22, S27, S32, S36 for details), whereas other products showed no significant trends (the statistical power to detect trends was however low in those cases).

For PFHpA, PFNA, PFDA and PFUnDA statistically significant declining trends were also observed in marine waters on the west coast of South Korea between 2008 and 2012 [95], but most surface water sampled showed no significant trends for PFCAs other than PFOA.

For PFHpA, PFNA, PFDA and PFUnA, a significant change point (in 2004 in all cases) was determined by the independent change point analysis in a compacted snow ("firn") core (dated: 1997–2007) from the Italian Alps (Additional file 7, Figures S14, S22, S27, S32) [104]. For PFHpA no significant change was observed before the change point and a significant decrease was observed after the change point. For PFNA and PFDA significant increasing trends were observed before the change point and significant decreasing trends after the change point. For PFUnDA a significant increasing trend was observed before the change point and no observable trend was observed after the change point. A significant increasing trend of PFNA was also observed in an ice core (dated: 1991–2006) sampled from Svalbard [37].

Change points were also identified in sediment cores from China for PFHpA, PFDA and PFUnDA [122]. However, in no cases were there significant declining trends before or after a change point and change points were identified in the 1970s and 1980s well before any known intervention. In Chinese sediment cores [64], statistically significant increasing temporal trends were observed for PFHpA, PFNA, PFDA, PFUnDA, PFTrDA and PFTeDA.

Change points were also identified for PFNA, PFUnDA and PFTeDA in sediment cores from Canada [7, 33]. Again, no significant declining trends were identified before or after change points. Statistically significant increasing trends were observed for PFNA and PFUnDA until a change point (in 1993) in Lake Opabin cores, after which there was no significant temporal trend observed. For PFUnA (in Lake Oesa [7] and Kempenfeldt Bay [33]) and PFTrDA (in all cores) statistically significant increasing trends were observed for the entire time period sampled.

Change points were observed for PFNA, PFDA, PFUnDA and PFTeDA in sediment cores from Japan [3]. The change point was always identified to occur in 1987 well before any known intervention. For PFNA and PFUnA there was no significant temporal trend before the change point (Power < 0.8) and a statistically significant increasing trend afterwards. For PFDA and PFTeDA there was no significant trend before or after the change point.

PFSA and PFCA precursors

There is some indication of declines of N-alkyl perfluorooctane sulfonamides and N-alkyl perfluorooctane sulfonamidoethanols (precursors of both PFSAs and PFCAs) in the global atmosphere, but FTOHs (precursors of PFCAs) appeared to be stable or even to have increased between 2006 and 2012 [83] (see also AMAP, 2016 [153]). FOSA, a PFOS precursor, showed significantly increasing trends in two sediment cores from Canada in two separate studies [70, 93], which is consistent with the increasing PFOS trends observed in the same sediment cores.

General conclusions on a media by media basis

Decreasing temporal trends of PFCAs were observed in recent years in many consumer products in the one study performed [108]. These reductions in levels in consumer products have not apparently led to a reduction in the levels of PFCAs in digested sewage sludge where no temporal trends have been observed (the only decline was for PFOS). The few studies that reported temporal trends in surface waters all studied coastal areas, likely impacted by municipal waste and industrial discharges from the coast. These studies showed that there may have been recent reductions in releases of PFOS and PFOA that have led to statistically significant declines in surface water concentrations. However, these observed declining temporal trends in PFOS and PFOA in surface waters may not have occurred in remote waters because water bodies remote from emission sources are expected to have a slower time response compared to water bodies nearer to sources. It is not possible to prove this hypothesis because no temporal trends are available for PFCAs and PFSAs in remote surface waters. Remote air has been sampled and there are indications that levels of N-alkyl perfluorooctane sulfonamides and *N*-alkyl perfluorooctane

sulfonamidoethanols have declined in the remote atmosphere, but that FTOH levels have increased between 2006 and 2012. Sediment cores showed (for some substances and study sites) statistically significant increases for some PFCAs and for PFOS for the time periods monitored. However, it should be stressed that most sediment cores cover relatively long time periods with relatively low resolution. As a result, the number of sampled time points after the major phase-outs is often relatively low and therefore changes in trends may not be revealed by the available samples.

Biological samples

Within the eligible literature for this critical review, we analysed PFAS temporal trends in terrestrial and marine organisms as well as organisms inhabiting the coastal zone such as seabirds. The majority of the organisms described in the literature, however, were either of marine or coastal origin. These included mammals such as polar bears, seals, cetaceans, and seabirds, loggerhead sea turtles, some fish species and mussels. A few species were from inland aquatic sites, such as great blue heron, lake trout and otter. Terrestrial organisms included roe deer, tawny owl and peregrine falcon. To discuss our findings we will distinguish between (1) mammals (terrestrial and marine), (2) birds, and (3) fish, mussels, and other species. Tissues analysed were primarily eggs in birds and liver or serum/plasma in other organisms, but for details for each study, see Additional file 6: Narrative synthesis table. We will also attempt to assess regional differences. The studies included in the review were predominantly from continental North America (the USA, Canada), the Arctic (Alaska, Arctic Canada, Greenland, northern Norway), and northern Europe (Norway, Sweden, Denmark, Germany, the Netherlands, France, the North Sea, the Baltic Sea). One study was available from Japan, otherwise no other studies from Asia nor from the southern hemisphere were available. As there were only three data sets with truly terrestrial organisms (roe deer [79], peregrine falcon [12], tawny owl [11]), it was not possible to make any comparisons of temporal trends for any PFASs between terrestrial and aquatic/marine species.

PFOS All temporal trend data were from the northern hemisphere, predominantly from the continental USA and Canada, the Arctic (Alaska, Arctic Canada, Greenland), Europe (Norway, Sweden, Germany, France, the Netherlands), the North Sea and the Baltic Sea. In total, 41 time trends of organisms were eligible for change point analyses. In addition, 21 studies were included which fulfilled the systematic review criteria, but contained less than 7 time points (Additional file 7, Figures S8–S10). No change point was determined in these studies, but they were analysed statistically using regression analysis. Further scrutiny of these temporal trends revealed that several studies presented singly, were not independent of each other. The polar bear study (Ittoqqortoormiit, Greenland) covering the time period 1984–2011 [124] is based on the same data presented by Dietz et al. [77] (1984–2006), but with additional years of sampling. Thus, we use the longer temporal trend with more time points in our discussion. Similarly, ringed seal from Ittoqqortoormiit (East Greenland) and Qeqertarsuaq (West Greenland), published by Bossi et al. [71] (1986–2003 and 1982–2003, respectively, 4 time points each) and Riget et al. [124] (1986–2010 and 1982–2010, respectively, 7 time points each) are also essentially the same studies but one has been extended with more time points. Thus the study with 7 time points for each site is included in our discussion. The temporal trends seen in polar bear liver and kidney from the same individuals [134] are also not independent and only the liver data will be discussed here. Similarly, the study of herring from Kattegatt [139] used both muscle ($n = 21$ time points) and liver ($n = 5$ time points) from the same individuals. The muscle data will be discussed here as there were more time points available for this tissue compared to liver. Herring gulls from three colonies (Heuwise, Mellum, Trischen) on the German coast have also been the subject of three separate studies ([80, 105, 128]). Again, these are built on the same material by adding more samples and extending the time period studied. For PFOS, we have therefore chosen the studies with the most time points and longest temporal trends for discussion (Heuwise (1991–2008, 13 time points) [105], Trischen (1988–2008, 21 time points) and Mellum (1988–2008, 21 time points) [80].

After removing the replicate studies, 33 datasets that underwent change point analysis and 18 that underwent regression analysis were available for further analysis, a total of 51 datasets (see Figures S8–S10 in Additional file 7). Of the 33 change point datasets, 13 were found to have change points, and 20 showed no change point. Within the group of 13 studies exhibiting change points, seven studies showed decreasing concentrations after the change point (roe deer [79], polar bear liver [134], herring gull eggs (Trischen) [80], northern sea otter [42], beluga whale [123], eelpout [128], and herring [139]). Four studies exhibited insignificant change both prior and post change point (polar bear [124], grey seal [106], herring gull eggs (Mellum) [80], guillemot eggs [94]). However, in three of these four studies, the concentrations after the change point were significantly higher than before the change point (stepwise increase rather than a continuous increase). In one case (herring gull from Mellum) there was no change and the trend before the change point was of significant power (> 0.8) to have detected a trend. One dataset showed increasing trends prior to the change

point and then no significant trend after the change point (peregrine falcon [12]). Where insignificant trends were found, most were of insufficient power (< 0.8) to detect a trend.

Of the 20 datasets without a detectable change point, five exhibited increasing PFOS concentrations over time (otter [125], herring gull egg (Heuwise) [105], white tailed sea eagle [100], ringed seal (E. Greenland) [124], blue mussel (Königshafen) [128]) and continuously decreasing concentrations were seen in blue mussels (Eckwarder-shörne) [128]. The remaining 14 datasets showed no significant changes over time but the power to detect such trends was below optimum (< 0.8) (tawny owl [11], lake trout [86], harbor porpoise (Baltic Sea, North Sea [96], North Sea/Denmark [82]), ringed seal (Qeqertarsuaq) [124], harbor seal (Maine) [131], double-crested cormorant [112], great blue heron (Fraser R.) [112], northern fulmar, thick-billed murre [40], eelpout (2 sites) [128], blue mussels (Darsser Ort) [128]).

For the remaining 18 datasets with less than 7 time points that underwent regression analysis, two showed increasing trends (beluga (E. Chukchi) [123]), polar bear (Baffin Island) [132]), one showed decreasing trends (blue mussel (France) [113]) and the remaining 15 showed no significant changes over time, but the power to detect such trends was below optimum (< 0.8).

In addition to our own statistical analysis, Figures S7–S9 and S11 in Additional file 8 show the results of statistical analyses reported by the authors themselves. Interestingly, when we compared these with our statistical analyses (Additional file 7, Figures S8–S10) we found 11 datasets showing clearly diverging results (tawny owl [11], polar bear (Ittoqqortoormiit) [124], beluga (Cook Inlet) [123], polar bear (Barrow) [132], herring [139], eel (Haringvliet East, Lobith [107]), herring gull (Heuwiese [80], Mellum—3 sets [80, 105, 128]). In eight cases, our statistical analyses resulted in insignificant trends, with low power to detect a trend, whereas the authors found significantly decreasing trends in seven (tawny owl [11], eel (Haringvliet East, Lobith [107]), herring gull (Heuwiese [80]), herring gull (Mellum-3 datasets [80, 105, 128]) and significantly increasing trends in one of these datasets (polar bear, Barrow [132]). For one dataset (polar bear (Ittoqqortoormiit [124]), our results showed no significant trends on either side of the change point but statistically significantly higher concentrations after the change point, whereas the authors found a significant increasing trend before the change point and significant decreasing trend after. For two datasets, our analysis found significantly declining trends, whereas the authors found an increasing trend in one dataset (beluga from Cook Inlet [123]) and no significant trend in the other (herring [139]). This illustrates the difficulties in choosing proper statistical methods in temporal trend studies that make it possible to compare the results of different studies. As the error incurred in the original studies' analyses seems most often to be finding significant changes up or down where they may not actually be present, this may have led to faulty conclusions in these published studies.

In conclusion, PFOS is not exhibiting any overall trend over time in the organisms studied for temporal changes. Insignificant trends were predominant in mammals and birds, with a few increasing and decreasing trends, but in fish, mussels and loggerhead sea turtle, insignificant and decreasing trends were equally predominant.

The general geographical pattern indicates insignificantly changing PFOS concentrations in North America, a mixed pattern for Europe and the Arctic with a predominance of insignificant change, and insignificant or increasing trends in the Baltic Sea. Thus, PFOS concentrations do not yet appear to be declining on a global scale after the phase outs. The tendency to increasing temporal trends in the Baltic Sea may be due to its slow turnover time, reflecting a possible delay in the temporal trends as concentrations have not yet reached a plateau. Data are missing for the southern hemisphere and only one dataset was available from Asia (Japan) showing no significant change in trends in melon-headed whales [91].

FOSA For the PFOS precursor FOSA, after removal of one replicate study, change point analysis of 14 datasets showed that four had change points (Additional file 7, Figures S41, S42), where loggerhead sea turtle [116] had insignificant trends before and after the change point but significantly higher concentrations after the change point. Northern sea otters [42] and harbor porpoise (Baltic Sea) [96] had significantly decreasing trends and polar bear from Ittoqqortoormiit [124] showed insignificant change but with high power to detect a trend before the change point. Of the majority of 10 remaining change point datasets, three had significantly decreasing trends and seven had insignificant trends. For the 10 datasets (after removing three replicate studies) that underwent regression analysis, one showed an increasing trend, three showed decreasing trends and six were insignificant with low power. Evaluating all 22 datasets, two showed increasing trends, eight decreasing trends and 14 insignificant trends, which is similar to the results of the analysis performed for PFOS.

No obvious trends were seen based on animal group or geographical location, but the number of data sets was low.

PFBS Only six datasets were available for PFBS after removing one replicate, (Additional file 7, Figure S1) with one showing significantly declining trends (grey

seal [106]), and the remaining five showing insignificant trends (northern fulmar [40], thick-billed murre [40], herring [139], loggerhead sea turtle [116], harbor seal [65]). The northern fulmar was the only insignificant trend with high power (> 0.8).

PFHxS Thirty-five PFHxS datasets were available for statistical analysis. Several studies presented singly were not independent of each other. Two studies were excluded in our discussion due to replication: ringed seal from Ittoqqortoormiit (East Greenland) where we use the longer dataset from Riget et al. [124] and herring from Kattegatt [139] where we use the longer dataset (n = 21 timepoints) for muscle and exclude the shorter dataset for liver (n = 5) from the same individuals.

Overall, of the 21 datasets analyzed for change points (Additional file 7, Figures S3–S5), 6 had change points ranging from 1983 to 2005, and 15 did not. Seven of the 33 datasets showed increasing trends, four showed decreasing trends and the large majority of 22 showed insignificant changes over time, most of which were of low power. The annual change for statistically significant studies excluding loggerhead sea turtle varied between − 17 and + 36%. For loggerhead sea turtle [116], annual change was − 30% before and + 40% after the change point.

Figures S4 and S5 in Additional file 8 show the results of statistical analyses by the authors of the primary studies. For 9 of these, we were not able to perform change point or regression analyses. In total, one showed increasing trends, one showed decreasing trends and 7 showed insignificant trends. These results are generally in line with the results from the change point and regression analyses.

In summary, insignificant trends of PFHxS were by far predominating in mammals, birds and other species, followed by increasing trends. Only three mammal and one fish dataset showed decreasing concentrations. In general, there do not seem to be any differences between geographical areas, and the general pattern from our analysis indicates increasing PFHxS or insignificantly changing temporal trends, with only three datasets showing declines. As for PFOS, this indicates that concentrations do not yet seem to be declining on a global scale after phase-outs. Data are missing from the southern hemisphere and Asia.

PFDS Seventeen PFDS datasets were available for statistical analysis. The time trends for all biota cover the time period between 1969 and 2012. Several studies presented singly were not independent of each other. One study was excluded in our discussion due to replication: herring from Kattegat [139] where we use the data for muscle in the same individuals.

After removing the replicate study, 17 datasets were available for continued analysis. Of these, nine underwent change point analysis and eight underwent regression analysis (Additional file 7, Figure S12). Of the nine datasets analyzed for change points, eight had change points and one did not. Two studies exhibited insignificant change both prior and post change point (grey seal [106], peregrine falcon [12]), but the concentrations after the change point were significantly higher than before the change point. One dataset showed an increasing trend before the change point and an insignificant trend with low power to detect a trend after the change point (Baltic Sea harbor porpoise [96]). Double-crested cormorant [112] showed a significant increase before and a decrease after the change point. Four other datasets showed insignificant trends before the change point and significantly decreasing concentrations after (great blue heron (Fraser River) [112], tawny owl [11], lake trout [86], herring [139]). Change points varied from 1983 to 2005. The remaining dataset without a change point showed insignificant trends with low power (harbor porpoise (North Sea [96]). Of the eight datasets that underwent regression analysis, four showed increasing trends (otter [125], pilot whale [126], herring gull (Norway-2 sites) [141] and four had insignificant trends (great blue heron (Minnesota) [76], harbor seal [65], rhinoceros auklet (2 sites) [112]).

Overall, seven of the 17 PFDS datasets showed increasing trends, five showed decreasing trends and five showed insignificant changes over time, with low power. The annual change for statistically significant studies varied between − 14 and + 25%.

Figures S12 and S13 in Additional file 8 show the results of statistical analyses by the authors of the primary studies. For 9 of these, we were not able to perform change point or regression analyses. One of these studies included seven datasets for herring gulls from seven colonies in the Canadian Great Lakes, with all but one (insignificant trend) showing decreasing PFDS concentrations [84]. Bald eagle from the Great Lakes area showed a decreasing PFDS trend [127], and lake trout from Lake Ontario showed an insignificant trend with low power [86]. In total, two studies showed insignificant trends and seven showed decreasing trends. These results are generally in line with the results from the change point and regression analyses.

There are few studies for examining differences between animal groups, but mammals tend towards increasing trends, fish towards decreasing trends and birds show a mixed picture with similar numbers of increasing, decreasing and insignificant trends. Due to the low number of studies for each geographical area it is difficult to draw firm conclusions. Data are missing from the southern hemisphere and Asia.

PFOA (C8 PFCA) We found 18 studies on time trends of PFOA in organisms that were eligible for our statistical analysis fulfilling the systematic review criteria and also containing at least 7 time points for change point analyses. In addition, 9 included studies contained less than 7 time points (Additional file 7, Figure S16). As above, no change point was determined in these studies, but they were analysed statistically using regression analysis. Further scrutiny of these temporal trends revealed that several studies presented singly were not independent of each other as previously discussed.

After removing the replicate studies, 15 datasets that underwent change point analysis and 9 that underwent regression analysis were available for analysis, a total of 24 datasets. Of the 15 change point datasets, five were found to have change points, three of which showed insignificant trends (roe deer [79], tawny owl [11], northern fulmar [40]) and two showed increasing trends (polar bear (Ittoqqortoormiit) [124], grey seal [106]). The change points ranged from 1992 to 2007. For the remaining 11 datasets showing no change point, all showed insignificant trends (great blue heron (Fraser R.) [112], double-crested cormorant [112], thick-billed murre [40], herring gull (3 German sites) [80, 128], ringed seal (West and East Greenland) [124], eelpout (2 German sites) [128], loggerhead sea turtle [116]). Of the remaining 9 datasets with less than 7 time points that underwent regression analysis, two showed increasing trends (polar bear (Baffin Island [132]), otter [125]) and the remaining 7 showed insignificant trends (polar bear (Barrow) [132], herring gull (Norway) [141], pilot whale [126], harbor seal (German Bight) [65], ringed seal (Baffin Bay) [126], bottlenose dolphin (2 sites) [78]).

Overall, 4 of the 25 PFOA datasets showed increasing trends while the large majority of 21 datasets showed insignificant trends over time, 18 of which had low power to detect a trend. The calculated annual change for statistically significant studies varied between + 2.3 and + 30%.

Figure S17 in Additional file 8 shows the results of statistical analyses by the authors of the primary studies. For 8 of these, we were not able to perform change point or regression analyses. One of these studies included four datasets for herring gulls from four colonies in the Canadian Great Lakes, with one dataset showing decreasing PFOA concentrations and three showing insignificant changes [84]. Bald eagle [127] from the Great Lakes area showed decreasing trends, harbor porpoise from the Baltic and North Seas [96] both showed insignificant trends, and increasing PFOA concentrations were found in California sea otters [101]. In total, one showed increasing trends, two showed decreasing trends and five showed insignificant trends. These results are generally in line with the results from the change point and regression analyses.

Summarising, for mammals, PFOA trends showed increasing or insignificant trends, while for birds, eelpout and loggerhead sea turtle, all PFOA trends were insignificant. For PFOA, due to generally low detection rates, there were fewer data sets available for spatial analysis than for PFOS. No spatial pattern was apparent in PFOA trends. The general geographical pattern from our own analysis indicates predominantly insignificantly changing PFOA temporal trends globally with a few showing statistically significantly increasing trends. As for PFOS, this indicates that concentrations do not yet seem to be declining on a global scale after phase-outs. Data are missing from the southern hemisphere and Asia.

PFHpA (C7 PFCA) Grey seal [106] showed an insignificant trend for PFHpA with high power before the change point (Additional file 7, Figure S14). One author-based analysis showed insignificant trends in loggerhead sea turtle [116], with low power (Additional file 8, Figure S14), and another author-based analysis showed a significant decrease in adult female polar bears but insignificant change in cubs [73] (Additional file 8, Figure S15).

Longer-chained PFCAs (C9–C14 PFCAs)

We found 23 studies on PFNA qualifying for change point analyses after removing two replicates (polar bear study (Ittoqqortoormiit) [77] and herring gulls (Heuwise) [80]). In addition, 15 datasets were analyzed statistically using regression analysis after removing two replicates (ringed seal, 2 sites in Greenland, [71]), giving a total of 38 datasets for our discussion (Additional file 7, Figures S19–S21)).

Of the 23 change point datasets, six were found to have change points, with four showing insignificant change both prior and post change point, but the concentrations after the change point were significantly higher than before the change point (stepwise increase rather than a continuous increase) (roe deer [79], peregrine falcon [12], northern fulmar [40], grey seal [106]). One dataset showed an increasing trend (thick-billed murre) [40] and one showed a decreasing trend (beluga (Cook Inlet) [123]). For the remaining 17 datasets showing no change point, six showed increasing trends (polar bear (Ittoqqortoormiit) [124], tawny owl [11], herring gull (Heuwise) [128], harbor porpoise (Baltic Sea) [96], ringed seal (Ittoqqortoormiit) [124], otter [125]), one showed a decreasing trend (great blue heron (Fraser River) [112]) and 10 showed insignificant trends (double-crested cormorant [112], herring gull (2 German sites) [128], lake trout [86], northern sea otter [42], ringed seal (Qeqertarsuaq) [124], harbor porpoise (North Sea) [96], eelpout (2 German

sites) [128], loggerhead sea turtle [116]). Of the remaining 15 datasets with less than 7 time points that underwent regression analysis, seven showed increasing trends (polar bear, Barrow and Baffin Island [132]), rhinoceros auklet (Lucy Island) [112], Leach's storm petrel (2 sites) [112], pilot whale [126], beluga (Eastern Chukchi) [123]) and the remaining eight showed insignificant trends (great blue heron (Minnesota) [76], harbor seal [65], ringed seal (Baffin Bay) [126], bottlenose dolphin (2 sites) [78], rhinoceros auklet (Cleland Island) [112], herring gull (Norway-2 sites) [141]).

Overall, 18 of the 38 PFNA datasets showed increasing trends, two showed decreasing trends and 18 showed insignificant trends over time, all of which had low power to detect a trend. The calculated annual change for statistically significant studies varied between − 12 and + 27%.

Figures S20–S22 in Additional file 8 show the results of statistical analyses by the authors of the primary studies. For 8 of these, we were not able to perform change point or regression analyses. One of these studies included seven datasets for herring gulls from seven colonies in the Canadian Great Lakes, with two datasets showing increasing PFNA concentrations and five showing insignificant changes [84]. Bald eagle from the Great Lakes area showed insignificant trends [127]. These results are generally in line with the results from the change point and regression analyses.

The general trend in mammals and birds indicates significantly increasing or insignificant trends, and only insignificant trends in other species. No spatial pattern was apparent in PFNA trends. The general geographical pattern from our own analysis indicates significantly increasing or insignificantly changing (with low power to detect trends) PFNA temporal trends globally. Data are missing from the southern hemisphere and Asia.

For PFDA, PFUnDA, PFDoDA, PFTrDA, and PFTeDA (Additional file 7: Figures S24–S26, S29–S31, S34–S36, S40), the results of change point analysis, regression analysis, analyses based on animal group and geographical area are very similar to those of PFNA. This indicates that the long-chain PFCAs have similar sources to the environment. The large majority of included time trends show increasing concentrations or non-significant changes with low power to detect changes.

Discussion

Reasons for heterogeneity

First of all it must be emphasized that different PFASs have different production histories and properties. Different PFASs are therefore not expected to show identical responses to the interventions studied here. Indeed, the results of this systematic review confirm that differences in time trends between different PFASs in the same studies are abundant. But there are also abundant heterogeneities when a particular substance is considered. One of the most striking differences is between human studies and environmental studies for PFOS, PFDS, PFOA, FOSA, and to some extent also PFHxS. For these substances the type of sample is a clear reason for heterogeneity. This is possibly related to differences in the routes of exposure between the sample types. For humans, exposure to these PFASs through commercial products and food contact paper has probably decreased, resulting in declining concentrations in human blood serum. In contrast, due to the very limited degradation of PFAS in the environment, ecosystems continue to be exposed to PFASs already released, and although 15 years have passed since interventions for reducing exposure to PFOS and PFOA were put in place, no clear impact on the environmental concentrations can yet be observed.

Among human studies, study geographic location can be a reason for heterogeneity. Although there is only one study from China available, this study shows increasing trends for PFOS and PFOA whereas studies in Europe and North America show declining trends. However, this has probably more to do with the scale of the interventions rather than the interventions themselves. The phase-outs and regulations have not been implemented in China, but the production of these substances has rather increased during recent years and the studied population is presumably closer to and more exposed to present sources. The situation in China may thus be considered as a baseline for the regions where the interventions have been implemented. Another example where the study location is a reason for heterogeneity is the situation in Uppsala, Sweden, where contamination of the drinking water probably has affected measured trends of PFBS and PFHxS in human blood serum. In biological (non-human) and abiotic samples the study location may also be a reason for heterogeneity, but no clear patterns could be seen from the available evidence.

For human studies the choice of population within a study site may also be a reason for heterogeneity. For example, in Munster, Germany, the trend for PFHpA after a change-point was increasing in females whereas it was decreasing in males [145]. In Shenyang, China, there was a significant increase in PFOS concentrations in females from 1999 to 2002, whereas it was statistically insignificant in males. It also seems that age contributes to heterogeneity. Taking NHANES data from the USA, there are significant decreasing trends for PFOS in all age groups, but for both females and males the magnitude of the decreasing trend increased with decreasing age [144]. On the other hand, in a study on polar bears [73], it was shown that concentrations of PFHpA and PFOA in adult

females (mothers) decreased from 1998 to 2008, whereas no significant change was observed in cubs. We do not have any explanation for these heterogeneities observed for sex and age. It has been suggested that elimination of PFOS is enhanced by menstruating women [144], and menstrual clearance will vary with age, but this factor alone cannot explain the difference between males and females seen in the Chinese study from Shenyang. Differences between males and females have also recently been observed in Australia and the USA [154] but were not fully understood.

There were no clear differences between studies with low and medium risk of bias, respectively. However, as expected, studies with seven or more time points were more likely to detect significant trends or show non-significant trends with high power than studies with a lower number of time points. Other potential reasons for heterogeneity could not be evaluated based on the available evidence.

Review limitations

Literature searches in bibliographic databases captured the bulk of relevant studies, judging by the fact that no additional articles was identified when the bibliographies of relevant review articles were screened. The success of grey literature searches were more difficult to assess. Search words in a limited number of languages were used, and specialist websites in a limited number of countries were searched. It is therefore possible that this review has overlooked some evidence, especially from Asia and the southern hemisphere. Future updates of this review should include search for literature published in Chinese languages. All identified grey literature was excluded during critical appraisal due to lack of detail in descriptions of methods, which also could result in overlooking parts of the evidence base. On the other hand, we observed that relevant data found in grey literature in many cases were published also in the academic literature. We believe that the vast majority of reliable high quality data can be found in the academic literature and that grey literature is less important for the question reviewed here.

There are several limitations in the available evidence base. Most of the included studies were performed in regions where interventions have been implemented (Europe and North America). Little or very little is known about temporal trends of PFASs in Asia and the southern hemisphere. This is troublesome since production of PFASs has been picked up in regions with weaker voluntary phase-outs and regulations, and there are indications that concentrations are increasing in these regions. Due to long-range transport, PFASs released to the environment in these regions may eventually affect also regions where interventions have been implemented. One of the most important limitations in the evidence base is perhaps the limited amount of data on alternatives to phased-out long-chain PFCAs and PFSAs and their precursors. If these substances are replaced by other equally harmful substances very little is gained. However, it is not always clear what the substitutes are and what to look for.

Looking at the existing studies and datasets, it can be concluded that many of them, especially those investigating environmental samples, have low power to detect significant trends due to short study periods and low frequency of sampling. The inter-annual variation is often relatively large and in such cases fairly long study periods with a high sampling frequency are needed to obtain high statistical power. It can also be concluded that different authors have used different statistical methods to calculate trends, which can make it difficult to compare trends. When we applied the same methods on all available datasets we sometimes observed that our results differed from the results given in the original studies. One additional limitation of the evidence base is that different conclusions may be reached depending on the choice of statistical approach. We are not claiming that our statistical approach is necessarily better (in some cases other approaches can probably be justified), but we have used a consistent and objective method. Also, one limitation in the evidence base is that there is no proper baseline throughout the study periods. Since the interventions are widely implemented and potentially have a global impact it is only possible to compare trends or concentrations before and after an intervention (BA study design), but there is no way to know what the concentrations or trends would have been in the absence of any intervention (CI or BACI study design). Concentration trends in regions where interventions have not been implemented (e.g. China) may be regarded as a post-intervention baseline, but here data are very sparse and they may be affected by the interventions implemented elsewhere.

We could not see any systematic difference in study results between studies with low and medium risk of bias, respectively. This can be interpreted in two ways. One is of course that the quality of methods is not critical for obtaining reliable results. The other is that our methods for critical appraisal and assessment of risk of bias are flawed. Another limitation of this review is the lack of quantitative synthesis, but for reasons explained in the Methods section we judged it was not feasible to conduct meta-analyses.

Review conclusions

Implication for policy/management

The variations in study results between study locations and sample types make it difficult to extrapolate the

available evidence to other locations and sample types than those in the studies. Nevertheless, in regions where the studied interventions have been implemented, the concentrations of PFOS, PFDS, and PFOA in humans are generally declining, and increasing concentrations of PFHxS have started to level off in recent years. Rapid declines for PFOS-precursors (MeFOSAA, EtFOSAA, FOSAA, FOSA) have also been seen in human studies. The weight of evidence therefore supports that the 3M Co. phase out resulted in a significant and rapid (measurable over approximately 10 years) mitigation of human exposure in North America and Europe. These consistent declining trends in humans are in contrast to results for environmental monitoring, and overall data of our analysis are therefore suggestive that the consistent declining human trends are attributable to lower exposure from direct contact with commercial materials and food-contact media containing electrochemical PFOS, PFOS-precursors and PFOA.

In contrast, limited data indicate that human concentrations of PFOS and PFOA are increasing in China where the production of these substances continued after the 3M Co. phase out. Concentrations of longer-chained PFCAs (PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA) in humans are generally increasing, with no evidence of significantly declining trends in any global region. Thus, the available data do not support that the US EPA Stewardship program, which commenced in 2006, has resulted in significantly declining trends in humans. However, it should be noted that the stewardship program consisted of gradual phase-outs until 2015, whereas only a small number of datasets included samples from years after 2010. Moreover, companies bound to the terms of the Stewardship program represent only 69% of the global capacity for fluoropolymer production, with the other 31% occurring mainly in China, India and Russia by non-signatory companies [155]. More time will probably be needed to detect any true declining trends of PFNA and longer PFCAs in humans, owing to their biological persistence. New regulatory measures have also only recently been adopted, for example in January 2016 the United States Food and Drug Administration banned C8–C18 polyfluoroalkyl phosphate esters (PAPs) in food contact applications [156].

For environmental samples (abiotic and biological) there are no clear patterns of declining trends. Most substances show mixed results, and a majority of the trends are insignificant with low power. A small number of studies on coastal surface waters close to urbanized areas have shown decreasing concentrations of PFOS and PFOA, but it is unknown whether trends are similar in more remote areas. However, there are indications that the levels of *N*-alkyl perfluorooctane sulfonamides and N-alkyl perfluorooctane sulfonamidoethanols (precursors of both PFSAs and PFCAs) in the remote atmosphere have declined, and that levels of FTOH (precursor of PFCAs) in contrast have increased in remote air between 2006 and 2012. In biological (non-human) samples, increasing trends predominate for concentrations of long-chain PFCAs such as PFNA-PFTrA.

Even with time trends covering more than 7 time points, no clear trends could be detected in many of the studies of biological (non-human) samples. There was often also considerable between year variations, which is always a problem with wildlife studies, as there are many confounders that can affect contaminant levels. These studies may be able to show statistically significant trends if they are continued.

To conclude, there are indications that the implemented phase-outs and regulations have had a positive effect, but not yet universally and not for all PFASs. Different PFASs have different production histories and properties and are therefore not expected to show identical responses to the interventions. Considering a particular substance, one reason for heterogeneity in study results may be related to differences in the route of exposure to PFASs. For humans, the exposure to some PFASs through commercial products and food contact paper has probably decreased, resulting in declining concentrations of these substances in humans. In contrast, due to the very limited degradation of PFAS in the environment, ecosystems will be exposed to already released PFASs for a long time and no clear impact on the environmental concentrations can yet be observed. This systematic review also suggests that one explanation for heterogeneity among human studies may be proximity to past and present sources, which is related to study location and where the interventions have been implemented.

Implication for research

The sampling strategy used in a large number of studies has resulted in low power to detect any trends. There is a need for better designed temporal trend studies including proper statistical treatment, long time periods both before and after intervention points, enough time points, well studied matrices/species, good analytical methods and practice, and more targeted sampling. The systematic review included numerous studies using archived samples and directly highlights the value of such material. Continued support for systematic archiving and storage of human and environmental samples is encouraged to allow future temporal trend studies.

Additional time trend studies are urgently needed for selected PFASs, especially the wide range of alternatives to long-chain PFCAs and PFSAs and their precursors.

For example, time trends of PFBS should be monitored in regions other than Europe. There are indications from the one human study available that the temporal trends in China may be different than seen in North America and Europe. Only one study of biological non-human samples was available from Asia. Due to this general lack of data from Asia and the indications of regional differences between Asia and the rest of the world, there is a need for many more temporal trends studies in Asia in both humans and biota. Another clear knowledge gap is the lack of data from the southern hemisphere. In this review only two studies from the southern hemisphere were included, one on PFAAs in human populations in Australia and one on PFCA precursors in air in South America.

Most environmental studies were in coastal areas (freshwater, marine) and very few in terrestrial species. Thus, discernment of the impact of atmospheric deposition versus transport in rivers and by ocean currents was not possible in this systematic review. However, as the temporal and spatial trends for most long-chain PFCAs were similar and showed increasing trends, even in the few terrestrial species studied, a widespread atmospheric transport of these or precursors that are degraded to these cannot be ruled out but needs to be confirmed. Long-term monitoring of PFASs in abiotic media, especially air, is needed and will likely contribute to a better understanding of the sources leading to increasing long-chain PFCAs in humans and the environment. Also, analysis of multiple PFASs (i.e. multiple PFAS classes, homologues within a class and their structural isomers) in the same temporal sample sets can provide useful information on sources. Continued monitoring of PFOA and longer-chained PFCAs well beyond 2015 will allow the impact of the EPA 2010/2015 Stewardship Program to be properly evaluated.

Additional files

Additional file 1. List of abbreviations.

Additional file 2. Searches.

Additional file 3. Articles not used.

Additional file 4. Critical appraisal checklist.

Additional file 5. Critical appraisal table.

Additional file 6. Narrative synthesis table.

Additional file 7. Reanalysed time trends.

Additional file 8. Reported time trends or changes in concentrations.

Authors' contributions

This review is based on a draft written by CdW, DH, JM, IC, and ML. All authors assisted in editing and revising the draft. Statistical analyses of datasets with 7 or more time-points, including change-point detection, were performed by AB. Statistical analyses of datasets with less than 7 time points were performed by ML. All authors read and approved the final manuscript.

Author details

[1] Mistra EviEM, Stockholm Environment Institute, Box 24218, 104 51 Stockholm, Sweden. [2] Department of Environmental Science and Analytical Chemistry, Stockholm University, 106 91 Stockholm, Sweden. [3] Swedish Museum of Natural History, Box 50007, 104 05 Stockholm, Sweden. [4] NILU, Norwegian Institute for Air Research, FRAM Centre, Tromso, Norway. [5] Division of Analytical and Environmental Toxicology, University of Alberta, Edmonton, AB T6G 2G3, Canada.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data generated or analysed during this study are included in this published article, its additional files, or in the original publications included in this review.

Consent for publication

Not applicable.

Ethics approval and consent to participate

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