SR5
Systematic Review

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EVIDENCE-BASED ENVIRONMENTAL MANAGEMENT

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Temporal trends of perfluoroalkyl acids in humans and in the environment

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Summary

Per- and polyfluoroalkyl substances (PFASs) are a broad class of man-made substances that have been produced and used in a wide variety of products and in industrial processes for several decades. Their toxicological and refractory properties, in combination with their widespread occurrence and bioavailability, have raised concerns about both the environment and human health. Accordingly, to reduce further pollution by PFASs, some of them have been regulated through legislation or voluntarily phase-outs by the industry in parts of the world. Here we summarise the findings of a systematic review on global temporal trends of perfluoroalkyl acids (PFAAs) and their precursors in the environment and in humans. Individual PFASs are usually denoted by an acronym, and those included in the systematic review are shown in Table 1.

In regions where regulations and phase-outs have been implemented, human concentrations of PFOS, PFDS, and PFOA are generally declining, while previously increasing concentrations of PFHxS have begun to level off. Rapid declines for PFOS-precursors (MeFOSAA, EtFOSAA, FOSAA, 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. Concentrations of perfluorinated carboxylic acids (PFCAs) with longer carbon chains (9-14 carbon atoms) in humans are generally increasing or show insignificant trends. However, most of the insignificant trends are based on datasets with low statistical power to detect any trend and they provide therefore limited information.

For abiotic and biological environmental samples there are no clear patterns of declining trends. Most substances show mixed results, but a majority of the trends are insignificant and based on datasets with low power to detect a trend. The evidence base for environmental samples is thus relatively weak. Nevertheless, in biological environmental samples, increasing trends predominate for concentrations of PFCAs with 9-14 carbon atoms (C9-C14 PFCAs).

Results suggest that declining PFOS, PFOS-precursor and PFOA concentrations in humans likely resulted from removal of certain PFASs from commercial products or from food packaging. Increasing concentrations of C9-C14 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 are necessary to evaluate the effectiveness of past and continuing regulatory mitigation measures. The environmental persistence of many PFASs likely results in long environmental disappearance half-lives that will be difficult to detect in datasets without high statistical power. 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. Also, data from the Southern hemisphere is practically non-existent.

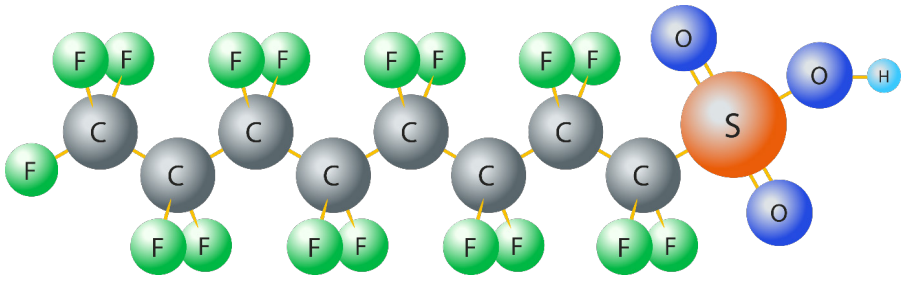

Figure 1. Depiction of a PFOS molecule (not to scale). Illustration: Claes Bernes.

Per- and polyfluoroalkyl substances (PFASs)

PFASs have been produced and used in products such as 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.

Simply put, PFAS molecules consist of carbon chains with attached fluor atoms (one example is shown in Figure 1). In perfluoralkyl substances, fluor atoms occupy all positions where normally a hydrogen atom would have been situated in an aliphatic substance, except for those in functional groups. In polyfluoralkyl substances some, but not all, hydrogen atoms are replaced by fluor atoms.

In the systematic review summarized here, we focused on two groups of perfluoralkyl acids and their precursors (precursors are substances that may break down and form the perfluoralkyl acids):

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

Individual substances included in the systematic review are shown in Table 1.

Owing to the wide diversity of PFASs (i.e. chain-length, molecular weight, degree and pattern of fluorination, presence of polar functional groups), it is difficult to generalize their production histories, properties and environmental fate. However, the extreme strength and stability of the C-F bond renders perfluorinated carbon chains resistant to environmental degradation processes.

Why study temporal trends of PFASs in the environment?

As a consequence of their use and production history, many PFASs have been released to the environment. In 2001 it was shown that PFASs occur in the environment even in very remote areas in the Arctic, and it has since then been established that they are distributed across the globe. This is especially unfortunate as it also has

Table 1. PFASs included in the systematic review.

Group	Chain length	PFAS acronym	PFAS full name	Chemical formula
PFCA	C7	PFHpA	Perfluoroheptanoic acid	$C_6F_{13}COOH$
PFCA	C8	PFOA	Perfluorooctanoic acid	$C_7F_{15}COOH$
PFCA	C9	PFNA	Perfluorononanoic acid	$C_8F_{17}COOH$
PFCA	C10	PFDA	Perfluorodecanoic acid	$C_9F_{19}COOH$
PFCA	C11	PFUnDA	Perfluoroundecanoic acid	$C_{10}F_{21}COOH$
PFCA	C12	PFDoDA	Perfluorododecanoic acid	$C_{11}F_{23}COOH$
PFCA	C13	PFTrDA	Perfluorotridecanoic acid	$C_{12}F_{25}COOH$
PFCA	C14	PFTeDA	Perfluorotetradecanoic acid	$C_{13}F_{27}COOH$
PFSA	C4	PFBS	Perfluorobutane sulfonic acid	$C_4F_9SO_3H$
PFSA	C6	PFHxS	Perfluorohexane sulfonic acid	$C_6F_{13}SO_3H$
PFSA	C8	PFOS	Perfluorooctane sulfonic acid	$C_8F_{17}SO_3H$
PFSA	C10	PFDS	Perfluorodecane sulfonic acid	$C_{10}F_{21}SO_3H$
Precursor	C8	FOSA	Perfluorooctane sulfonamide	$C_8H_2F_{17}NO_2S$

The included PFASs consist mainly of two types of perfluoroalkyl acids (PFAAs), i.e. perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkane sulfonic acids (PFSAs).

been shown that some PFASs accumulate in organisms and furthermore possess toxic properties. For example, although PFCAs are not acutely toxic based on standard toxicity endpoint, they have been reported to have endocrine disrupting properties. Bioaccumulation and toxicity tends to increase with increasing length of the carbon chain, but partly because PFASs are very persistent in the environment, little is known about their environmental fate.

There is a concern that PFASs may have negative effects on both the environment and on human health. Consequently, various actions have been undertaken by the industry and regulators to reduce the use and emissions of especially long-chain[1] perfluoralkyl acids and precursors. For example, in 2000, 3M announced a global phase-out by 2002 of its production of products based on perfluoroalkyl chains containing 6, 8 and 10 carbons, including PFOA. 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. 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. 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.

On the other hand, many alternative fluorinated products have been introduced, and new alternative industrial processes and products have resulted in new sources of PFCAs and other fluorinated substances. For example, there has likely been increasing emissions of PFHxA due to the increasing use of side-chain polymers based on 6:2 FTOH (a fluorotelomer alcohol) in surface treatment products. Also, although some PFASs are being phased out by the industry and to some extent are regulated in Western Europe, North America, and Japan, new manufacturers (largely in continental Asia) have begun to produce long-chain PFCAs and their precursors.

The objective of the systematic review was to investigate whether the 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. To the extent possible, another aim was to collate as much evidence as possible to understand why conflicting temporal trends may be reported.

Diverse body of evidence

The literature searches, which were described in detail in a published review protocol, generated more than 10,000 unique articles that could potentially provide useful data. The protocol also specified exactly which studies were eligible for inclusion in the review by defining sets of relevance criteria and quality criteria. The systematic review included human samples as well as environmental samples. However, we did not include humans with occupational exposure to PFASs or populations exposed to point sources such as contaminated drinking water since we aimed at investigating effects of the above mentioned interventions rather than effects of local conditions.

After screening the literature, 92 articles were included in the review and in total 227 time trend datasets were used. However, all time trends should not be treated as separate studies. For instance, in one article studying polar bears, PFASs

[1] Long-chain refers to six or more carbon atoms for PFSAs and eight or more carbon atoms for PFCAs.

What is a systematic review?

In this review, we used a systematic approach to synthesise available evidence on temporal trends of PFASs in the environment. Systematic reviews are entirely based on existing studies – in this respect, they do not differ from ordinary literature reviews of scientific questions. The difference lies, instead, in the rigour. A systematic review is characterised by meticulous planning, methodical procedures and a transparent, objective and complete documentation of all assessments carried out in the course of the work. This approach is designed to increase reliability and repeatability, avoid bias and facilitate meta-analysis (quantitative conclusions based on data from several different studies).

were analysed in both kidney and liver, and these two datasets are not independent from each other.

Figure 2 shows, for 20 different PFASs, the total number of time trend datasets that were identified. The same figure also shows the number of datasets that were re-analysed in the review and the number of time trends that originally were reported by the authors of the reviewed articles, respectively. The most frequently analysed 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. Figure 3 shows the geographical distribution of included studies.

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. Two other datasets were concentrations in whole blood and in two other datasets the matrix was milk from lactating women (Figure 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 (biological environmental

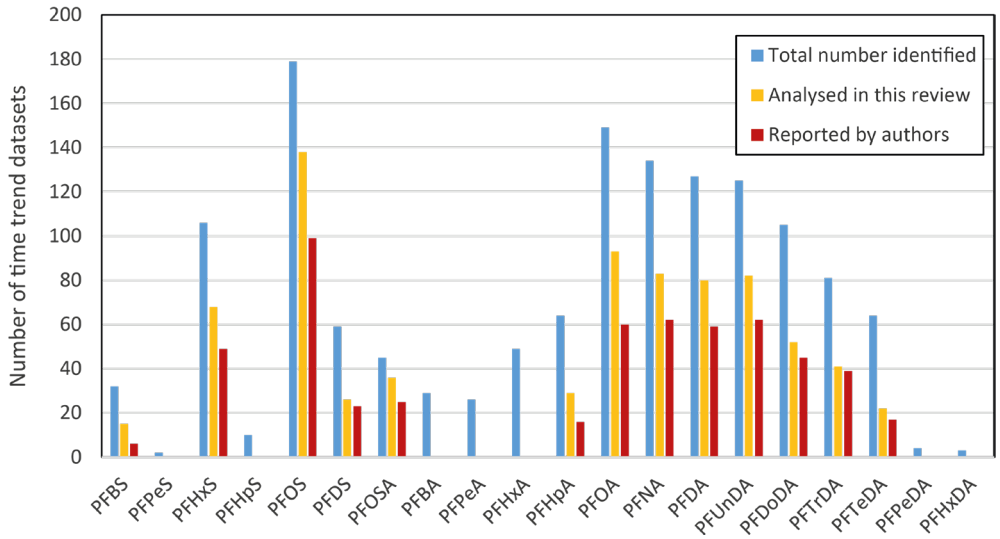

Figure 2. Total number of time series in the included articles (blue bars), number of time trends re-analysed in this review (yellow bars), and number of time trends originally reported by the authors (red bars). Low detection frequency or different focus of the paper were the main reasons authors did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

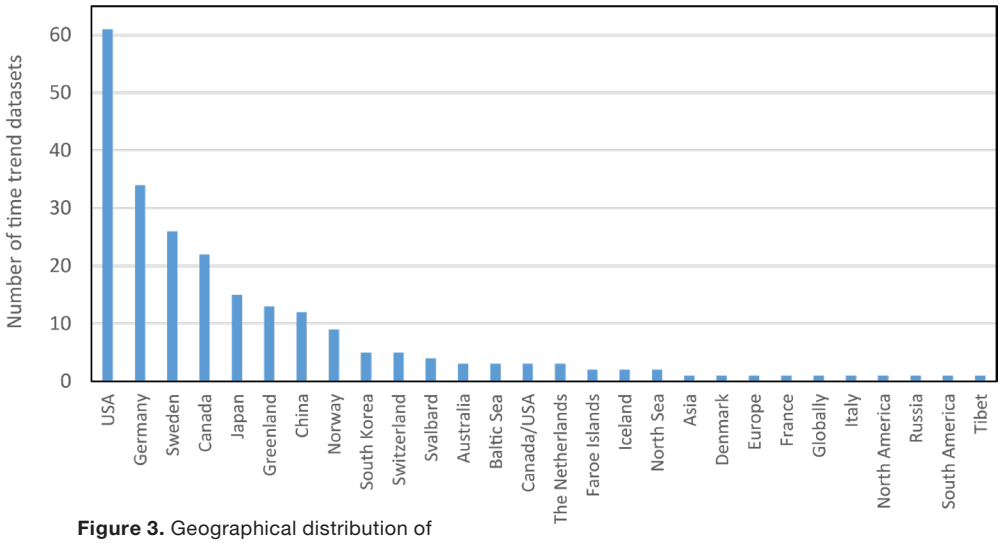

Figure 3. Geographical distribution of time trend datasets. Each dataset may include several PFASs.

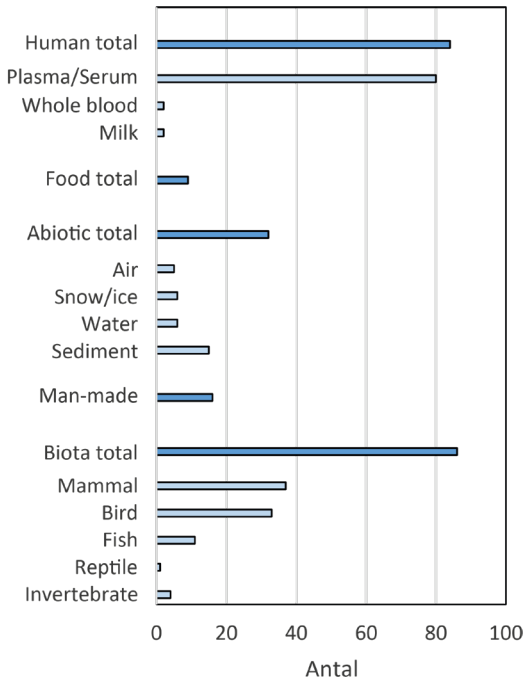

Figure 4. Number of time trend datasets in different sample categories. Man-made refers to man-made products including digested sewage sludge (biosolids). Each dataset may include several PFASs.

samples) was the largest category with 86 datasets including mammals, birds, fish, reptiles and invertebrates. Among environmental samples in general, most datasets were taken from coastal or marine environments where transportation by ocean currents may be a significant source of PFASs. However, for abiotic environmental samples most datasets were taken from inland or high altitude environments where the major source of PFASs is atmospheric deposition.

Temporal trends vary between PFASs, sample types and regions

Overall, 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. 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. Time trends of PFOS for humans are shown in Figure 5.

Concentrations of C9-C14 PFCAs (PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA) in humans are generally increasing, with no evidence of significantly declining trends in any global region. Thus, except for PFOA 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. More time will probably be needed to detect any true declining trends of 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. Time trends of PFNA for humans are shown in Figure 6.
For environmental samples (abiotic and biological) there are no clear patterns of declining trends. As exemplified by PFOS in marine and coastal mammals (Figure 7), most substances show mixed results, and a majority of the trends are statistically insignificant. However, it should be pointed out that most of these insignificant trends are based on datasets with low statistical power to detect a trend, i.e., the sampling frequency and/or study length were insufficient to detect even fairly large annual changes. This means that that there may be some real trends even though they cannot be revealed by available data. Taking also into account that the studies are too unlike each other to be used in a quantitative meta-analysis, it is not possible to draw any conclusions based on these studies.

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 FOSE and FOSA (precursors of both PFSAs and PFCAs) in the remote atmosphere have declined, and that levels of FTOHs (precursor of PFCAs) in contrast have increased in remote air between 2006 and 2012. In biological environmental samples, increasing trends predominate for concentrations of C9-C14 PFCAs. Most sediment core studies show increasing trends of PFASs. It should be noted, however, that the time resolution as well as the number of samples representing time points after the phase-outs is relatively low in many sediment cores and such studies have low power to detect changes in recent years.

How to read Figures 5-7

The bars on the left-hand side (a) show the study period for individual studies, and colour codes indicate the direction of the calculated trend. Datasets above the thick horizontal line were analysed for change-points. Other data sets provided less than 7 time points and were therefore not analysed for change-points. The power of insignificant trends refers to the chance of detecting an annual change of 10 %. This means that studies showing white bars provide little information due to insufficient sampling frequency and/or study length. The chart to the right (b) shows the magnitude of the calculated annual changes. Where change-points occur the annual change is shown for both sides of the change-point, but where the trend is insignificant on both sides the magnitude is shown for the whole period only. Insignificant trends on both sides of the change-point are indicative of a step-wise change. Bullets indicate that time trend analysis was performed also in the original study (references in square brackets). Asterisks indicate low risk of bias, other studies were judged to have medium risk of bias.

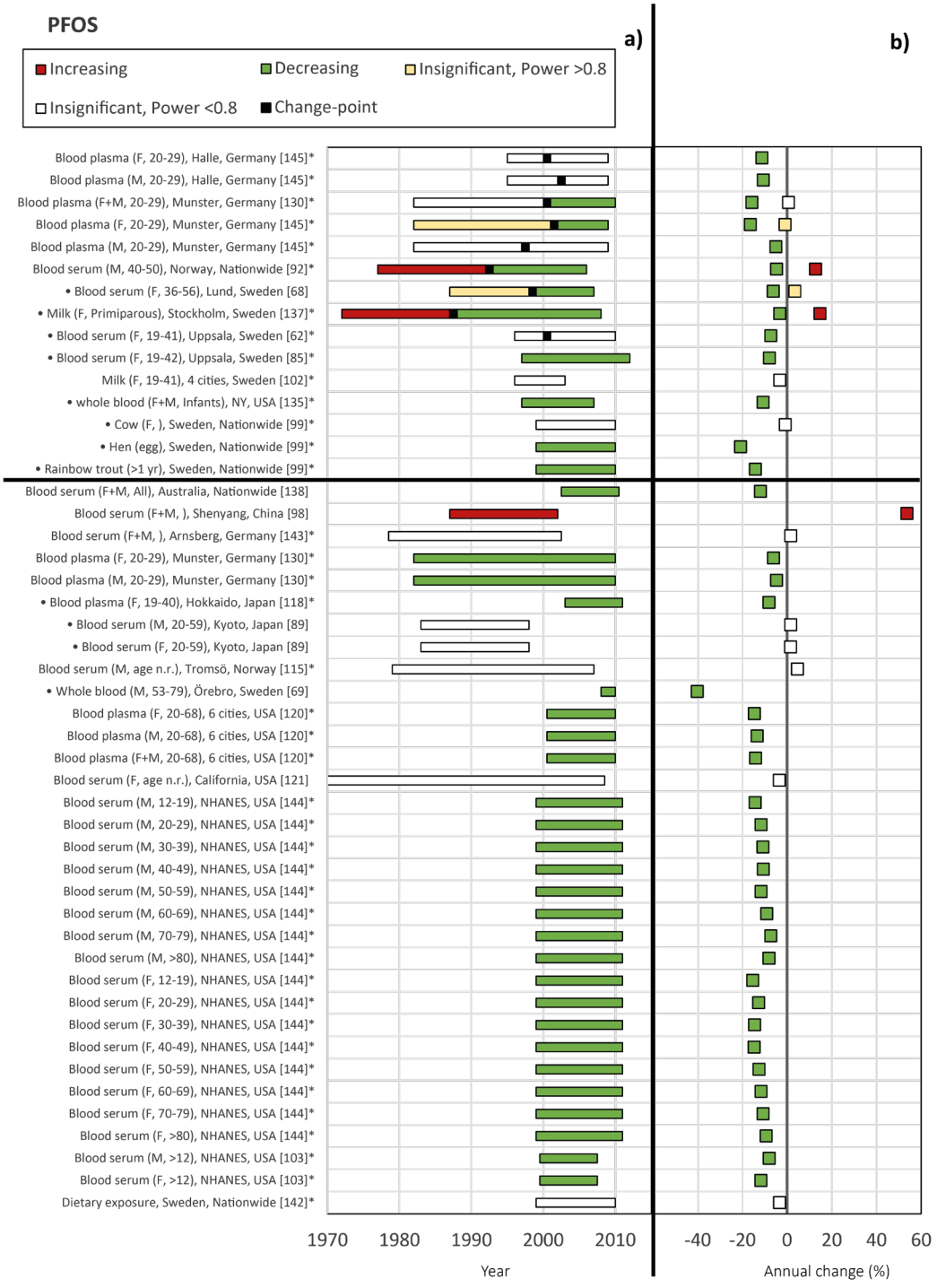

Figure 5. Calculated time trends for PFOS in human and food samples. Please see text box on page 9 for further explanations.

There are several reasons measured time trends of a particular PFAS may differ from one location to another, or from one sample type to another, or even within the same area and sample type. One important factor is the timing of the study period relative to the interventions. A study with data from just a few years directly after the intervention is likely to show a smaller effect than a more recent study covering a longer study period. Also, although the interventions are intended to have a global impact, the outcome may for several reasons vary considerably depending on the location of the studies. Since the interventions are not yet implemented globally, it is reasonable to assume that the effect may be smaller in regions close to present sources compared to regions close to past sources where the interventions have been implemented. Contaminated areas may also be a significant factor. In areas where the phase-out has been implemented, contaminated areas may still be present and leach the phased-out substances to the surrounding environments. In more remote regions, such as the Arctic, the outcome may depend on the predominating mode of transport. 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 quicker compared to coastal areas where the PFAS source is dominated by direct long-range transport in the aquatic environment. The measured outcome may also depend on sample type. For example, different species may accumulate or excrete PFASs differently, resulting in different doubling times or half-lifes in the body.

Implications for policy and 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, the consistent declining trends of PFOS and PFOA in humans in regions where phase-outs have been implemented are in contrast to ambient environmental monitoring, and in humans in China where manufacturing has continued and increased. Overall, data are therefore suggestive that the declining human trends are attributable to lower exposure from direct contact with commercial materials and food-contact media containing PFOS, PFOS-precursors and PFOA. This indicates that phase-outs and regulatory actions have had a positive effect on humans in regions where such phase-outs and regulatory actions have been implemented.

On the other hand, although 15 years have passed since interventions for PFOS and PFOA were put in place, no clear impact on the environmental concentrations can yet be observed. Also, there is not yet any evidence that implemented phase-outs of C9-C14 PFCAs have resulted in declining concentrations in humans or in the environment. This may be caused by an increased use of alternative PFASs.

Due to the very limited degradation of PFASs in the environment, ecosystems will be exposed to PFASs for a long time leading to further distribution worldwide. To obtain a more rapid response in the environment, the phase-outs and regulatory actions will probably need to be implemented globally.

The systematic review also showed that there are often large variations in measured levels between years. This is always a problem with wildlife studies, as there are many factors that can affect the levels, and if long-term changes are also slow, it can be difficult to detect trends. However, studies that do not show statistically significant trends at the moment can possibly do so if they continue and are designed appropriately.

The systematic review included numerous studies using archived samples and directly

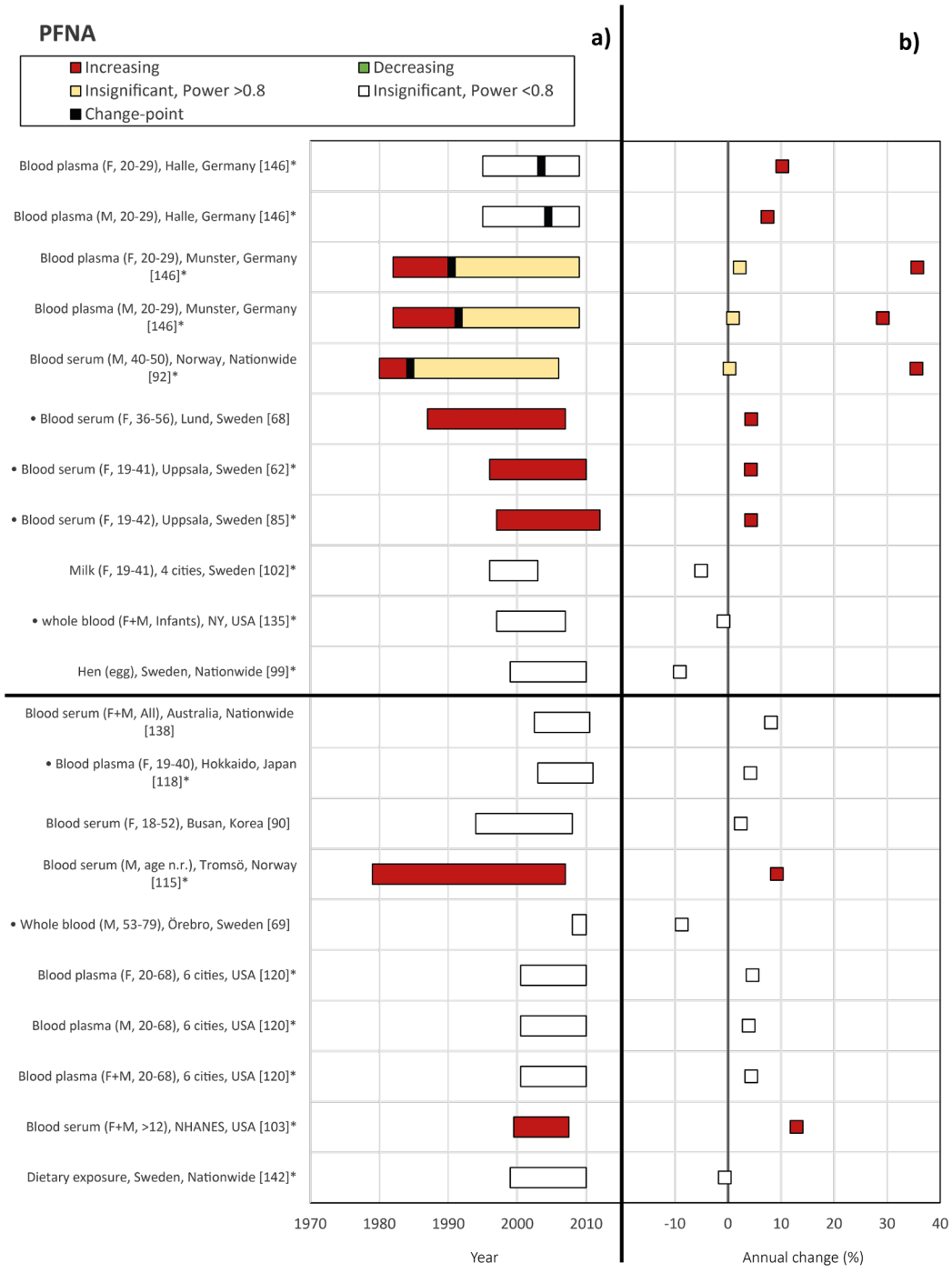

Figure 6. Calculated time trends for PFNA in human and food samples. Please see text box on page 9 for further explanations.

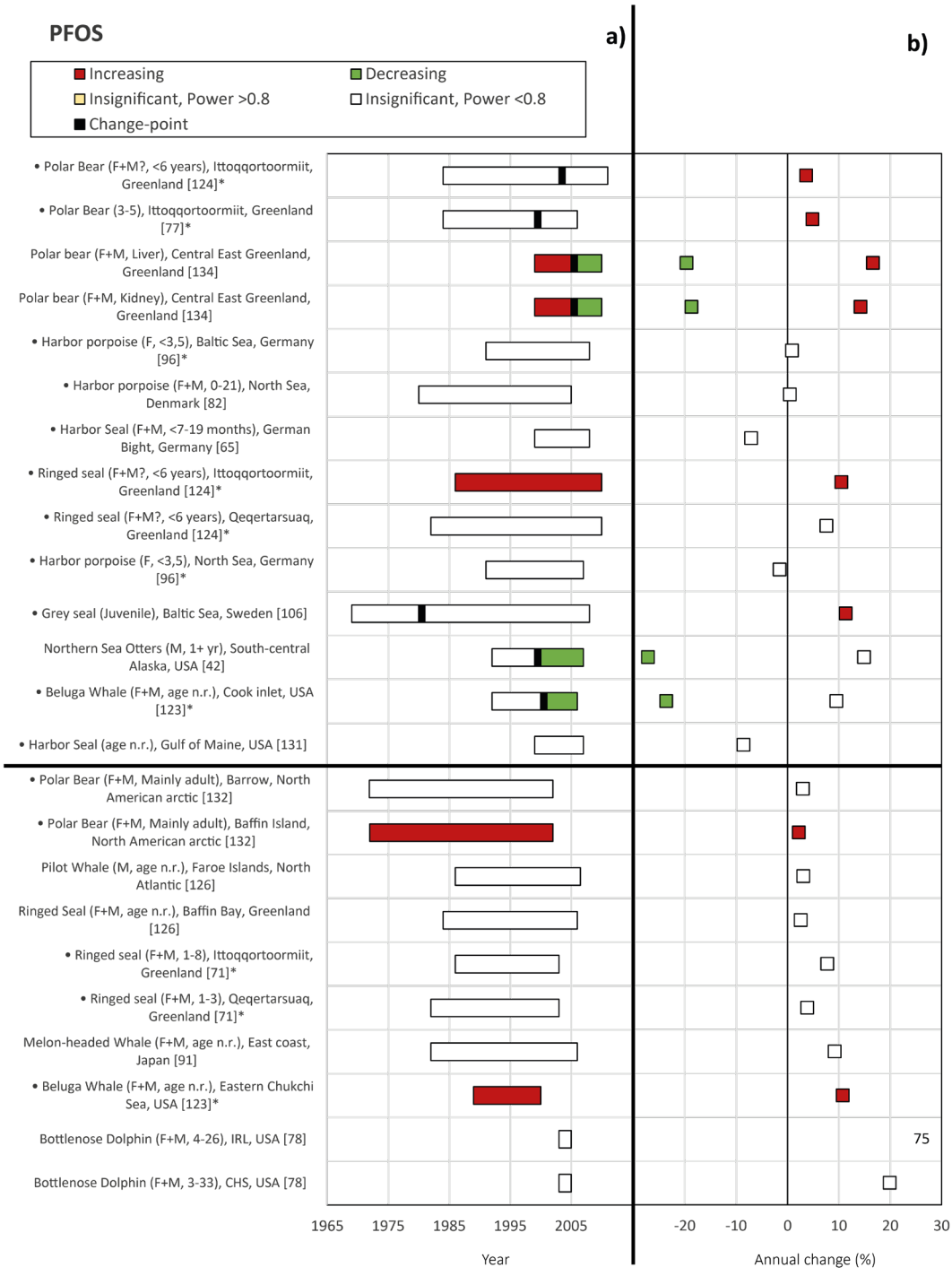

Figure 7. Calculated time trends for PFOS in marine and coastal mammals. Please see text box on page 9 for further explanations.

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. Continued support is also encouraged for on-going monitoring programmes.

Implications for further 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 more targeted sampling, well studied matrices/species, long time periods both before and after intervention points, enough time points, good analytical methods and practice, and proper statistical treatment. The systematic review directly highlights the value of studies using archived samples. Continued support for systematic archiving and storage of human and environmental samples is encouraged.

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. Due to a 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.

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 the systematic review. However, a widespread atmospheric transport of C9-C14 PFCA 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.

How the review was conducted

During the planning phase of the systematic review, Swedish stakeholders with an interest in mitigation of PFAS pollution were invited to comment on the scope and focus of the review. The final design of the review was described in a protocol that was published in the peer-reviewed journal *Environmental Evidence* in January 2015.

Searches for scientific literature were made in seven different literature databases. Grey literature was searched for using Google. and by searching websites of specialist organisations. Generally, the first 100 hits were examined in the searches using Google and on specialist websites. In addition to searches using English search terms, searches were performed using Swedish, Norwegian, French, and German search terms.

The search strings used in the searches generated more than 10,000 unique articles and reports (Figure 8). Based on title and abstract, most of them could be excluded for lacking relevant results. However, 590 articles and reports were read in full, and during that process 212 articles and reports were found to provide information relevant to our question. These 212 articles were then critically appraised. This means that they were evaluated against a set of *a priori* defined quality criteria regarding 1) selection bias, 2) accuracy of dating of samples, 3) sample integrity, 4) analytical quality, and 5) study

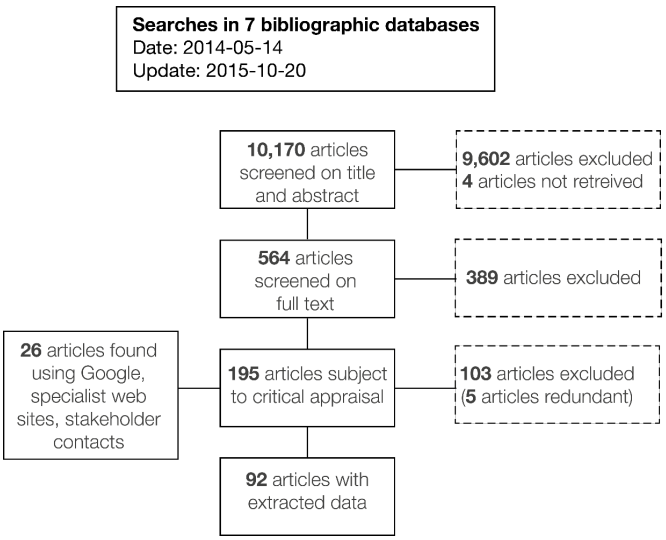

Figure 8. The searches identified 10,170 unique records. Four of the articles that passed the abstract screening could not be retrieved in full text. Five articles were excluded at critical appraisal because the same data ware published elsewhere.

design. After critical appraisal and removal of redundant articles, 92 articles remained for full data extraction.

We compiled reported time trends from all of the included articles, but we also synthesised time trends based on our own analysis of raw data published in the included articles. The main reason for analysing raw data is that a wide range of different statistical methods were used by different authors to calculate time trends and change-points. We deemed it necessary to treat all datasets the same way and use the same objective method for all studies to make various datasets more comparable. To calculate time trends we used a log-linear regression model, and the resulting rates of change in concentration are expressed in units of % year^{-1}.

This systematic review was initiated and financed by the Mistra Council for Evidence-Based Environmental Management (EviEM). The review was conducted by a specially appointed team of researchers chaired by Cynthia de Wit, professor at the Department of Environmental Science and Analytical Chemistry (ACES), Stockholm University, Sweden. The project was managed by Magnus Land, EviEM.

Free access to full report

The full report on this systematic review has been published in the journal *Environmental Evidence* (http://environmentalevidencejournal.biomedcentral.com/). The report is available on EviEM's website (www.eviem.se).

EviEM

The Mistra Council for Evidence-Based Environmental Management (EviEM) strives to ensure that environmental management in Sweden is informed by the best possible scientific evidence. Through systematic reviews of relevant research, we aim to improve the basis for decisions in environmental policy. Funded by the Swedish Foundation for Strategic Environmental Research (Mistra) and hosted by the Stockholm Environment Institute, EviEM is financially and politically independent.

MISTRA EviEM
EVIDENCE-BASED ENVIRONMENTAL MANAGEMENT

EviEM Summary 2018

The manufacturing and use of some potentially harmful per- polyfluoroalkyl substances (PFASs) have been restricted or phased-out in some countries, but as these substances often are extremely persistent and may be transported over long distances it is not obvious what effect the regulatory actions have had on the concentrations in humans and in the environment. In a systematic review that is summarised here, Mistra EviEM has assessed the evidence for temporal trends in a global context.

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EviEM conducts systematic reviews of environmental issues identified as important by public agencies and other stakeholders. These provide an overall assessment of the state of scientific knowledge and help to improve the basis for environmental decision-making in Sweden.

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