Environmental Science and Policy 174 (2025) 104275

Contents lists available at ScienceDirect

Environmental Science and Policy

journal homepage: www.elsevier.com/locate/envsci

The unintentional role of chemical regulation in regrettable substitution: The case of PFAS

Olasunkanmi Dosunmu [a], Rob Whiting [b], Avtar Matharu [c], Nigel Watson [a], Andrew J. Sweetman [a,*]

[a] Lancaster Environment Centre, Lancaster University, LA1 4YQ, United Kingdom
[b] WSP, Reading, RG1 3EU, United Kingdom
[c] Green Chemistry Excellence Centre, University of York, United Kingdom

ARTICLE INFO

Keywords:
PFAS
Chemical regulations
Chemical substitutions
Regrettable substitutions
Chemicals of concerns
REACH
U.S. TSCA

ABSTRACT

As we approach a century since their discovery, per- and polyfluoroalkyl substances (PFAS) have become integral in various applications, from medical devices and electronics to home and personal care products, due to their unique properties. However, PFAS are now recognised for their persistence, bioaccumulation, toxicity, and mobility (PBTM), posing significant risks to human health, and the environment. Regulating complex chemicals has historically been challenging, which is exemplified with the case of PFAS and the regrettable substitutions of one PFAS with another. As a response to changing regulations, the chemical industry has introduced a plethora of replacement substances, often with shorter chains, which are still persistent and mobile. We highlight the inadequacies in regulatory responses to global spread of PFAS, revealing an unintentional role that the approach to chemical management can create in regrettable substitution. To improve chemical regulation, we propose evaluating substances prior to issuance of registration numbers, comprehensive evaluation of policy impacts, such as the universal PFAS restriction, the need to harmonise the fragmented regulatory frameworks and encourage integration and communication both nationally and globally.

1. Background

Per- and polyfluoroalkyl substances (PFAS) were first discovered in the 1930s, and are synthetic chemicals known for their multiple carbon-fluorine bonds. They have been manufactured at scale since the 1940s (Buck et al., 2011; Environment Agency, 2021; Interstate Technology and Regulatory Council ITRC, 2020; Kissa, 2001; Wang et al., 2017) due to their unique surface-active properties, which has led to their widespread use since the 1950s (Brase et al., 2021; Brendel et al., 2018; Gaber et al., 2023; Gaines, 2023). Figs. 1 and 2 provide a brief synopsis of the PFAS timeline covering industry and regulatory activities in decades, the supplementary information (PFAS Timeline) contains chronological information on PFAS timeline highlighting key events and activities from various stakeholders. Their widespread use is due to their carbon-fluorine (C-F) bond which impacts stability and persistence, while their hydrophobic chain and hydrophilic head provide water, oil, and dirt repellency, temperature resistance, and friction reduction (Environment Agency, 2021; Gaber et al., 2023; Gaines, 2023; Lemal, 2004; O'Hagan, 2008; Wang et al., 2017).

These special dual water and oil repelling properties means PFAS has widely been used in industrial and consumer applications, including firefighting foam (aqueous film forming foams, AFFF), textiles, leather, household goods, and many others (Birnbaum and Grandjean, 2015; Brase et al., 2021; Gaines, 2023; Glüge et al., 2020; Joerss and Menger, 2023; KEMI, 2023). Some PFAS uses may be considered essential for health, safety, and societal functioning (e.g., medical devices), but others are not e.g., use in products like textiles and cosmetics (Cousins et al., 2019b). The (very) persistence and resistance to degradation in the environment and/or biota of the vast majority of PFAS have earned them the name "forever chemicals" (Allen, 2008; Brase et al., 2021; Cousins et al., 2020; Environment Agency, 2021; Glüge et al., 2020; Joerss and Menger, 2023) and also becomes the basis for using persistence alone as basis for chemical management (Cousins et al., 2019a; 2020).

Until around 2000, the chemical industry incorrectly assumed that PFAS were inert and biologically unreactive, similar to the assumption

* Corresponding author.
E-mail addresses: o.a.dosunmu@lancaster.ac.uk (O. Dosunmu), rob.whiting@wsp.com (R. Whiting), avtar.matharu@york.ac.uk (A. Matharu), n.watson1@lancaster.ac.uk (N. Watson), a.sweetman@lanacaster.ac.uk (A.J. Sweetman).

https://doi.org/10.1016/j.envsci.2025.104275
Received 9 October 2024; Received in revised form 26 September 2025; Accepted 5 November 2025
Available online 14 November 2025

for polytetrafluoroethylene (PTFE, in Teflon) (Tepper, 1962). However, evidence from industry data suggests as early as the 1960s that PFAS may pose risks to humans and the environment (Gaber et al., 2023; Richter et al., 2021). Over the last thirty years, mounting evidence has linked PFAS with impacts on the environment and human health (Brase et al., 2021; Brendel et al., 2018; Brennan et al., 2021; Buck et al., 2011; Cousins et al., 2020; Glüge et al., 2020; Joerss and Menger, 2023; Munoz et al., 2019; Wei et al., 2018). The two most widely studied PFAS are long-chain perfluoroalkyl carboxylic acids, also known as C8, (perfluorooctanoic acid (PFOA)), and long-chain perfluoroalkyl sulfonic acids, (perfluorosulfonic acid (PFOS)) (Wang et al., 2017). These legacy PFAS (Brase et al., 2021; Zhang et al., 2024), were primarily produced by 3 M and DuPont. Due to their significant human health and environmental effects, PFOA and PFOS are subject to regulatory controls and listed under Annex A and B of the Stockholm Convention on Persistent Organic Pollutants (POPs), respectively (UNEP, n.d.).

1.1. PFAS properties and impact

The properties of PFAS vary widely based on their chemical structure, chain length and functional groups. PFOA and PFOS, for instance, are highly persistent, bioaccumulative, toxic and mobile (PBTM). Many PFAS have been reported in remote locations far from their point of use or manufacture while others are not (Brendel et al., 2018; Buck et al., 2011; Cousins et al., 2020; Gaber et al., 2023; Jones., 2021; Jones and de Voogt., 1999; Sweetman., 2020). In the environment, some PFAS like perfluorobutanesulfonic acid, (PFBS), and perfluorohexanoic acid, (PFHxA) are mobile (Arp et al., 2017; Arp and Hale, 2022; Brendel et al., 2018). Others, such as PFOA are bioaccumulative while some, like perfluorobutane sulfonate (PFBS) have lower bioaccumulation potential (Cousins et al., 2020; Groffen et al., 2025). PFAS have been detected in various environmental matrices including water, soil, and in human serum (Brase et al., 2021; Calafat et al., 2007; Joerss and Menger., 2023). Exposure to PFOA and PFOS persists despite production and use being phased out (Gaber et al., 2023), although their concentrations are decreasing (ATSDR., 2021). Direct exposures to specific PFAS are linked to a range of adverse health effects, including immune system damage, liver issues, thyroid disruption, and low birth weight amidst widespread environmental contamination especially drinking water (Blake and Fenton., 2020; Brendel et al., 2018; Calafat et al., 2007; Gaber et al., 2023; Gebbink and van Leeuwen., 2020; Lohmann et al., 2020; Wee and Aris., 2023). PFAS are identified as one of the eight issues of concern under the Strategic Approach to International Chemicals Management (SAICM), alongside chemicals in products (CiP), endocrine disrupting chemicals (EDCs), environmentally persistent pharmaceutical pollutants (EPPPs), highly hazardous pesticides (HHPs), lead in paint, nanotechnology and manufactured nanomaterials (Nanomaterials) (UNEP., 2020).

1.2. Regulatory scrutiny and alternatives development

Due to increased regulatory scrutiny of PFAS in the late 1990s and early 2000s, many shorter-chain alternatives were developed. Countries and regions including Australia, Canada, European Union (EU) and the United States (U.S.) heightened their regulations on PFAS due to concerns over their adverse effects on humans and the environment (Brase et al., 2021; T. Wang et al., 2009).

In 2000, the announcement by 3 M, a major PFOS manufacturer to voluntarily phase-out PFOS production by the end of 2002 (U.S. EPA, 2000) and the PFOA Voluntary Stewardship Program between U.S. EPA and eight U.S. manufacturers at the end of 2015 (U.S. EPA, 2023b) led to the introduction of plethora of alternatives to PFOA and PFOS including shorter chain PFAS. Although many of these alternatives have subsequently been shown to have similar properties, including persistence, mobility, and long-range transport potential, despite a reduced potential to bioaccumulate and lower toxicity than PFOA and PFOS (Brendel et al., 2018; Renner, 2006; U.S. EPA, 2024). The performance of these alternatives often requires larger quantities to be used in products to ensure similar levels of functionality, as the C8 chain length is optimal for surface activity (Poulsen et al., 2005; Renner, 2006). Although thousands of PFAS are identified, data for assessing their hazards and risks are available for only a few, like PFOA and PFOS, the major legacy PFAS (Blake and Fenton, 2020; Cousins et al., 2020; Gaber et al., 2023). Hence, current understanding of toxicity and other hazards of PFAS are

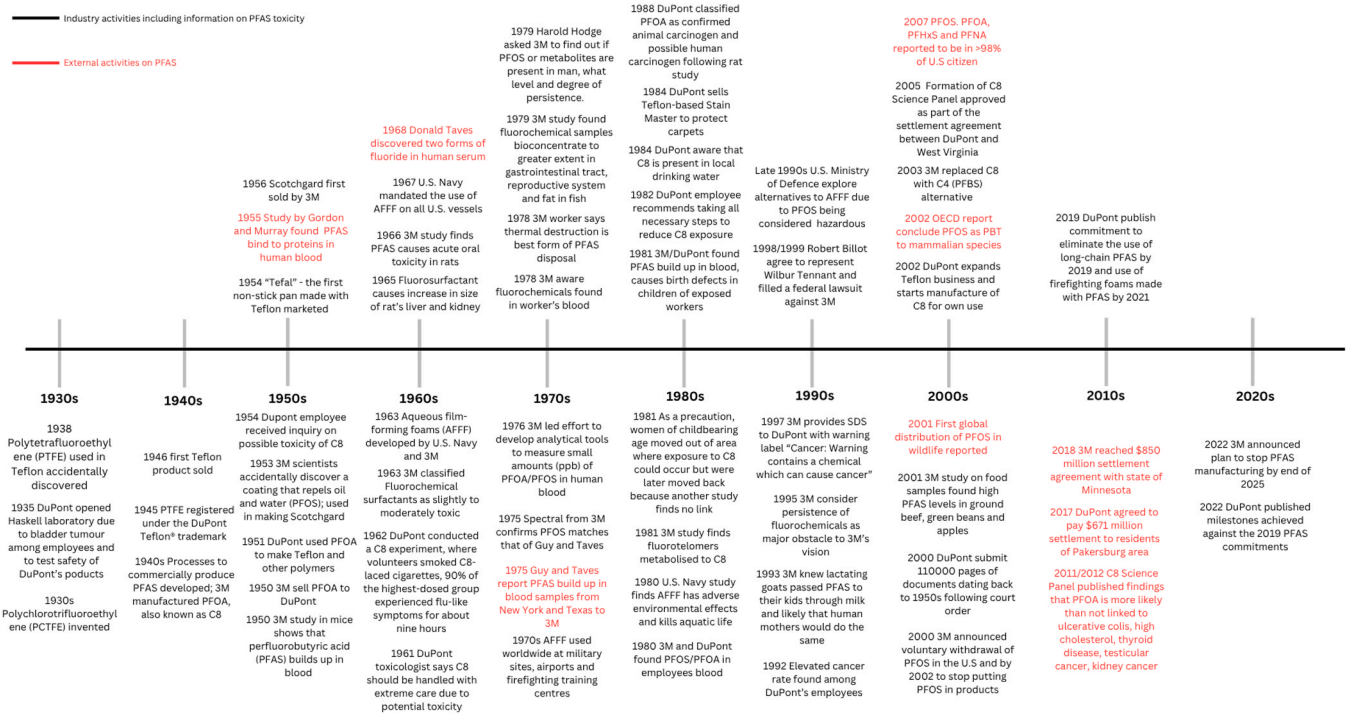

Fig. 1. Synopsis of PFAS timeline in decades – Industry activities.

limited (Cousins et al., 2020). PFAS such as perfluorohexane sulfonic acid (PFHxS), PFBS and ammonium salt of hexafluoropropylene oxide dimer acid (HFPO-DA, trademark as GenX) are now gaining attention and focus from regulatory agencies. The persistent nature of PFAS ensures their continued presence in the environment long after production and use restrictions or bans. In the U.S., regulation targets specific PFAS compounds like PFOA and PFOS, whereas the EU has suggested a group approach (Bock and Laird, 2022). As part of the Chemicals Strategy for Sustainability (CSS), the EU developed a PFAS action plan to eliminate all non-essential uses of PFAS, resulting in the publication of a universal proposal to restrict or ban about 10,000 PFAS by the European Chemical Agency (ECHA) in February 2023 (Bock and Laird, 2022; European Commission, 2020a; ECHA, 2023). After reviewing over 5600 stakeholder comments from the 2023 consultation by the dossier submitters, ECHA published an updated PFAS restriction proposal in August 2025 that, alongside a full ban, considers alternatives options such as continued use under risk-controlled conditions, time-limited derogations for specific applications, and other risk-reduction measures (ECHA, 2025).

The work of Gaber et al., (2023) highlights the role and actions of the chemical industry in contributing to global spread of PFAS. Similarly, Richter et al., (2021) highlighted systematic gaps in knowledge within U.S. chemical regulation by analysing the regulatory pathway under the Toxic Substances Control Act (TSCA). They used PFAS as a case study to demonstrate how both knowledge and ignorance are produced within this framework. This article examines the role of chemical regulation in the widespread prevalence of substances with adverse health effects, using PFAS as a case study. By focusing on the Registration, Evaluation, Authorisation and Restrictions of Chemicals (REACH) regulation, we suggest ways to better protect humans and the environment from substances of concern. The ubiquitous nature of PFAS in the environment and human results from both chemical industry (in)actions and regulatory frameworks intended to protect against them. Learning from past mistakes is crucial in the drive towards a zero-pollution ambition from substances of concern. We examined these points as two sides of the same coin, highlighting the interplay between regulatory (in) effectiveness and chemical industry (in)actions that have led to widespread PFAS exposure. The lapses in regulatory policies and subsequent chemical industry practices regarding PFAS are discussed in the following sections.

2. Chemical regulation and unintentional consequences of regulation

Across many jurisdictions, chemical regulations are developed and implemented to ensure a high level of protection of human health and the environment from the impacts of substances with adverse health effects. Making informed decisions on the potential risks to human health and the environment from these chemicals requires data availability, adequate and effective scientific evaluation, interaction and know-how. The supplementary information (Regulatory history) provides brief information on the background to U.S. TSCA and EU chemical regulations. The implementation of adequate risk management measures requires a generation of information on hazards, exposure including uses and lifecycles. Tools such as the globally harmonised system of classification and labelling (GHS) are developed and implemented in many jurisdictions to communicate information on hazards across the supply chain, to consumers and for regulatory decisions. Various chemical regulations have been implemented locally, nationally and globally to address the impact of chemicals of concerns. For example, the U.S. TSCA, EU/UK REACH and Stockholm Convention as a global treaty on Persistent Organic Pollutants (POPs).

In the U.S. and the EU/UK for example, the TSCA and REACH regulations are to address the risks from chemicals of concerns and manage their safe use. But history suggests both the TSCA and REACH regulations have unwittingly contributed to continuous environmental and human exposure to substances of concerns as the proliferation of PFAS suggest. Under the REACH Regulation, Substances of Very High Concern (SVHC) are those that meet the criteria of REACH Article 57, which aims to target substances with hazardous properties that could cause severe and often irreversible damage to human health or the environment, including carcinogenicity, mutagenicity, toxic for reproduction,

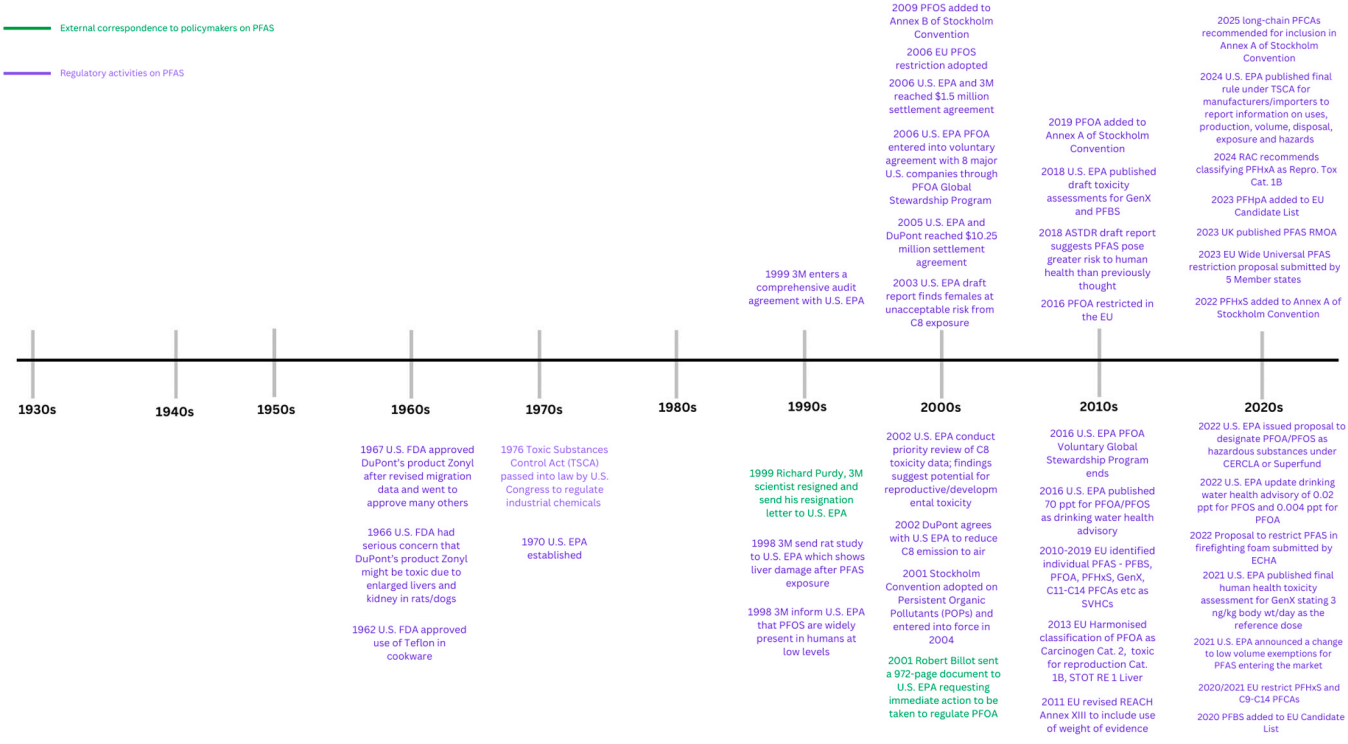

Fig. 2. Synopsis of PFAS timeline in decades – Regulatory activities.

persistence and bioaccumulation with the identified substances prioritised for inclusion on the EU/UK SVHC Candidate List based on their use patterns, inherent hazard properties and market volume.

As a result of the implementation of the REACH Regulation, improved protection of workers, consumers and the environment from harmful chemicals are reported including advancing the operation of the internal market (ECHA., 2021). It can however be argued that the way that the policies are developed, written and implemented can unintentionally contribute to the continued exposure and ubiquity of PFAS. In essence, chemical regulations have fallen short to adequately safeguard against PFAS risks, revealing systemic flaws in chemical management frameworks, for instance while the first restrictions on PFOS were implemented in the EU in 2006, the risks associated with the wider family of PFAS required follow-up work on a substance by substance basis, before the universal PFAS restriction proposal (Annex XV dossier) published in 2023, nearly two decades later, see Fig. 2. The environmental ubiquity of PFAS is both a factor of oversights (systematic weaknesses/failures preventing from ensuring safe production and use) from the chemical industry and that of the regulatory frameworks set up to protect human health and the environment from the impact of them. The failures of chemical regulations using PFAS as an example are discussed under the following headings.

2.1. *The chemical regulation 'arms race'*

History and current experience suggest that continuous and intense efforts by regulatory bodies are required to keep pace with the vast number of chemicals on (and entering) the market creating a cycle where regulators strive to mitigate risks through legislation while the industry innovates within these constraints. This often leads to gaps in regulatory systems and ongoing challenges in ensuring environmental and human health safety leading to what can be termed a 'regulation arms race'.

The United States Environmental Protection Agency (EPA) was established in 1970, decades after PFAS discovery and use. In 1976, the TSCA came into force due to increasing concerns about the risks of chemicals to human health and the environment. Existing regulations at the time were considered inadequate, and TSCA aimed to address these shortcomings (Markell., 2010). The EPA's administrator, Russell Train, declared TSCA "one of the most important pieces of 'preventive medicine' legislation" and that "the legislation represents a major step toward an increasingly effective preventive approach toward the 'environmental disease' that has been called the 'disease of the century'" (U.S. EPA., 1976). TSCA was anticipated as a toolbox that the EPA would use to address the risks associated with chemicals (Markell., 2010). Despite its ambitions, TSCA faced challenges, like managing the vast number of existing chemicals and assessing their toxicity, which hampered its effectiveness. The regulation was therefore widely considered ineffective in identifying, managing their risks, and encouraging the development of safer alternatives (Allen., 2013; Applegate., 2008).

For decades, chemical regulation has lagged behind chemical production, use and innovation, increasing the exposure burden under the weight and number of chemicals it is required to manage. For this reason, it always appears that chemical regulation is always playing catch-up and preoccupied with intervention (which was one of the drivers for creation of the REACH Regulation in the EU in the first place) (European Commission., 2001). However, the preventive impact of intervention is highly dependent on the timing of its application. Harremoës et al., (2013) collects fourteen historical case studies of chemicals with well-known hazards to workers, public and the environment to describe how well governments and civil societies dealt with their impacts. The authors show that early, credible indications of harm were ignored, suppressed, or inadequately acted upon, with time lags between first warning signs and effective policy/regulatory response were often decades (30–100 years in many instances) (Gee., 2005).

As mentioned, PFAS was discovered in the 1940s and in use commercially since the 1950s, but significant regulatory attention only began in the late 1990s. In 1998, 3 M, prompted by overwhelming evidence of the wide presence in humans of PFOS at low levels and pressure from one of their own ecotoxicologists, notified the EPA about PFOS contamination in blood and its presence in environmental samples. In 1999, the EPA entered into a comprehensive audit agreement under the Self Disclosure Policy of TSCA with 3 M between April 1999 and April 2000. In 2001, following litigation against DuPont by the local farmer and complainant Wilbur Tennant, Tennant's Attorney Robert Billot sent a 972-page document to the EPA and all relevant regulatory authorities requesting immediate action to regulate PFOA, while the U.S EPA perform a priority review of PFOA in 2002; it was not until 2005–2006 that the U.S EPA fined both 3 M and Dupont and also announced the voluntary PFOA Stewardship program, see Fig. 2.

For existing chemicals under TSCA, manufacturers are required to obtain and report data on risk, manufacture, and processing, adverse health effects including published and unpublished health, and safety studies and 'substantial risks' to the EPA (Applegate., 2008). However, 3 M and DuPont did not fulfil these requirements until PFAS had become ubiquitous in the environment. In 2006, a settlement agreement of $1.5 million was reached between the EPA and 3 M for these violations (U.S. EPA., 2006). The agreement between the EPA and 3 M states that "3 M neither admits nor denies that reporting and mitigation by 3 M… constitute a violation of TSCA but nonetheless agrees to pay a civil penalty…" (3M., 2001; U.S. EPA., 1999, 2001, 2006). Similarly, in 2004 enforcement action was taken against DuPont by the EPA for violation relating to PFOA under TSCA (Section 4e) and Resource Conservation and Recovery Act (RCRA) due to multiple failures to report information about substantial risk of injury to human health or the environment between June 1981 and March 2001. This resulted in DuPont being fined $10.25 million in addition to $6.2 million for two supplementary environmental projects (SEPs), the largest civil penalty ever obtained by the EPA (Bergman., 2004; Gaber et al., 2023; U.S. EPA., 2023d). Following the 2016 TSCA amendment (Frank Lautenberg Act), since 2021, the U.S. EPA has strengthened the TSCA framework by enhancing the review process for new chemicals, particularly PFAS and other persistent, bioaccumulative, and toxic substances, to ensure thorough safety evaluations prior to manufacture. Additionally, the 2023 PFAS Reporting Rule now requires comprehensive disclosure from manufacturers and importers on PFAS use, production, and disposal from 2011 to 2022, with compliance mandated by October 2026 (U.S. EPA., 2025).

In the EU, several regulatory actions concerning some PFAS have been taken since the first restriction of PFOS in 2006 due to its very persistent, very bioaccumulative and toxic properties (European Commission., 2006). These actions include the harmonised classification of PFOA as a Category 2 Carcinogen and Category 1B Reproductive toxicant in 2010 and its inclusion on the EU Candidate List (list of Substances of Very High Concern (SVHCs) that may be prioritised for inclusion on the authorisation list) in 2013. Other PFAS identified as SVHCs, added to EU Candidate List and/or have their use restricted are C11-C14 perfluoroalkyl carboxylic acids (PFCAs), PFNA, PFHxS and PFHxA. In February 2023, a universal proposal to restrict PFAS as a group in the EU was submitted by five EU countries. This universal restriction proposal is a radical change in approach from the substance-by-substance evaluation that has been the case previously, but it's meant to increase the speed of regulation, address the problem of emissions of PFAS, and reduce the practice of industry replacing one substance of concern with another from the same class, importantly to avoid regrettable substitution (ECHA., 2023).

On a global level, PFOS was added to Annex B of the POPs Convention in May 2009; 10 years later, PFOA was added to Annex A of the Convention in May 2019 and PFHxS added to Annex A in June 2022 (UNEP, n.d.). Currently, long-chain PFCAs are recommended by the POP Review Committee for listing under Annex A of the Convention with time limited specific exemptions e.g., use in semiconductors (UNEP., 2025), see Fig. 2. These regulatory actions aim to address the impact of

PFAS on human health and the environment. While commendable, they are largely a reactive approach following development of a weight of evidence over several years and mounting concerns within the scientific and policy making communities, noting that the primary objective of the Stockholm Convention is to protect human health and the environment from persistent organic pollutants. While the POP review committee carries the due scientific rigour of an international audience, the review process for candidate POPs can take several years to complete and add substances to the annexes of the Convention.

The weight of evidence approach creates a continuous cycle where regulatory bodies and the chemical industry are in a constant state of adaptation and response. Largely, current chemical regulations and policy developments are tools to address the risks already created after decades of exposure and use of these chemicals. Both REACH and TSCA require the chemical industry to generate data on the hazards and risks of their substances, including exposure estimates. However, while REACH places the full responsibility on industry to demonstrate safety, under TSCA the EPA retains primary responsibility for conducting risk evaluations and determining whether chemicals present an unreasonable risk. The effectiveness and success of this approach is partly dependent on the assumption that the chemical industry will act responsively, supported by effective regulatory oversight through evaluation and monitoring. However, the validity of this assumption is questionable.

2.2. The mistake of grandfathering existing substances

Grandfathering (exempting existing chemicals from new regulatory requirements) when little or no information on hazards and uses is available, has proven to be a significant error in judgement. Thousands of chemicals were added to existing inventory without adequate assessment when TSCA was established in 1976, six years after the EPA was formed. During this process, chemicals were classified into existing and new substances. In the late 1970s, under the TSCA, all existing chemicals were presumed safe, and about 62000 chemicals were grandfathered and added to the U.S. Inventory of existing chemicals (Krimsky., 2017; Markell., 2010; Trasande., 2016; U.S. EPA., 2023c). As of January 2024, this inventory has grown to over 86000 chemicals, with more than 42,000 (about 49 %) actively used in U.S. commerce (U.S. EPA., 2023a). This approach may have been necessary to get the legislation operational; the regulatory failure lies in assuming these substances were safe and allowed on the market without further evaluation.

In the EU, before the introduction of the REACH Regulation, substances were grouped into existing and new substances (European Commission., 2001). Before September 1981, thousands of chemicals on the EU market lacked basic safety information. Thus, on both sides of the Atlantic, little or no information on hazards and uses was available for grandfathered substances. While the EU has addressed the 'burden of the past' through the REACH regulation by ensuring both existing and new substances are subject to the same regulatory regime, the EPA is now required to evaluate both existing and new chemicals through the 2016 TSCA amendment. However, responsibility to demonstrate the safety of chemicals introduced to the U.S. market still rests with the EPA.

Grandfathering of existing substances has put regulations at a disadvantage since such chemicals are assumed safe unless evidence to the contrary is available. Richter et al., (2018) argues that regulatory frameworks prioritise incentivising rapid market entry for the chemical industry over the protection of human health and the environment. Once these chemicals are introduced to the market, removing them becomes a complex and challenging task as evidenced by the case of PFAS. Thus, the need for more proactive and precautionary regulatory approaches to ensure chemical safety before market entry. However, generating the necessary data is both expensive and time consuming which can hinder innovation. This underscores the need to further develop and integrate high throughput screening methods, such as in vitro HTS assays and predictive modelling, into chemical risk assessment frameworks (Villeneuve et al., 2019).

2.3. The case of regulatory failures and unintended consequences of regulation

2.3.1. Voluntary initiatives and production of alternatives

To address concerns associated with PFAS, policymakers have used a 'carrot and stick' approach. In May 2000, under pressure from the EPA, 3 M, the major producer at the time, announced a voluntary phaseout of PFOS production and use by the end of 2002. This move is similar to Monsanto's 1977 voluntary withdrawal from producing polychlorinated biphenyls (PCBs). However, Monsanto's decision was driven by the combined efforts of environmental activists, regulators and the media, who highlighted the negative impacts of PCBs, damaging Monsanto's image and profits (Markowitz and Rosner., 2018). The voluntary withdrawal of PFOS production by 3 M led to a situation where, due to market demand and lack of regulation, other entities filled the void to continue producing PFOS. Between 2006 and 2015, the EPA implemented the PFOA Voluntary Stewardship Program, involving eight major producers in the U.S. By the end of 2016, the EPA declared the program a success, see Fig. 2, citing the transition to alternatives and the industry's cooperation (U.S. EPA., 2023b). However, this success was limited as the initiative was not binding on entities outside of the agreement, and the lack of data on the safety of alternatives as a result of this agreement.

The exposure of biota to PFAS is an unintended consequence of chemical regulation facilitating the industry's transition to alternatives without adequate information on their hazards. For example, in the cases of PFOA and PFOS, the EPA worked with the chemical industry to transition to alternatives where little or no data for their hazards and risk are available. The goals of the PFOA Stewardship Program were met partly through the development of alternatives like HFPO-DA/GenX and ammonium 4,8-dioxa-3H-perfluorononanoate (ADONA), as well as short-chain C6-based fluorotelomers to replace long-chain (C8) fluorotelomers (Bock and Laird., 2022; U.S. EPA., 2023b). Consequently, numerous alternatives such as PFHxS, GenX, PFHxA, ADONA, and 6:2 chlorinated polyfluoroalkylethersulfonic acid (6:2 Cl-PFESA, trademark F-53B) were developed and used in place of PFOA and PFOS and many of these alternatives are structurally similar to the original substances they replace. Many are found to persist in the environment, have the potential to cause adverse effects on human health and the environment, and as a result present an ongoing threat in the same way as the legacy PFAS (Brase et al., 2021; Gebbink and van Leeuwen., 2020; Hamid et al., 2024; He et al., 2022; Li et al., 2023; Renner., 2006; U.S. EPA., 2021; Wee and Aris., 2023; Zhang et al., 2024). The regulatory shortcoming lies in allowing these alternatives onto the market without adequate hazard or risk assessments. For example, chronic data that may be required for some endpoints such as developmental toxicity are generally unavailable and at great expense at the low tonnages that the alternatives are produced. This oversight reflects a broader issue in chemical regulation, where following the development of concerns over time it creates the focus on immediate solutions to resolve the issue as soon as possible, including phase-out windows and exemptions capped to the shortest time possible, which pressures industry decision making and can lead to regrettable long-term environmental and health risks of the replacement substances. The introduction of these alternatives highlights the need for more effective regulatory frameworks and comprehensive evaluation of new chemicals before they are approved for widespread use. And where thorough evaluation is not possible, regulators should apply the precautionary principle to manage risks in the face of scientific uncertainty and avoid endless data requests and reassessments, a situation often describe as 'paralysis by analysis' (Harremoës et al., 2013).

2.3.2. Issuance of REACH registration numbers pre-substance evaluation

Under the REACH regulation, registration numbers are issued to registrants only after the business rule check (an administrative check before the dossier can be processed) and the technical completeness check (to confirm all required information is included in the dossier) are completed. In addition, receipt of payment issued by the Agency must be received. Fig. 3 illustrates the steps from dossier submission to registration number issuance. However, these checks are not detailed scientific evaluations of the hazards or risks associated with production and use of the substances. Issuing a registration number before a detailed substance evaluation may not incentivise the chemical industry to develop and use safe alternatives. For instance, Rudin et al., (2023) analysed PFAS registered under REACH and found at least 531 registered PFAS, with 177 having full registration, meaning they are produced or imported into the EU at a rate of at least 1 tonne per year.

The current regulatory approach of allowing access to market prior to detailed substance evaluation contributes to human and environmental exposure to substances of concerns and also pushes the problem downstream. Substances are evaluated if specific concerns are identified and based on a prioritisation scheme set by the Agency. Additionally, under REACH, the fundamental assumption is that increased knowledge about hazardous properties of chemicals will prompt companies to voluntarily reduce their use, considering it a sound business practice (Coria., 2018). While this may be true to some extent, the argument for obligatory regulation remains strong, particularly where, voluntary approaches have had more limited impact reducing their use or encouraged the adoption of safe alternatives (OECD., 2003). This is primarily because voluntary measures require vocal encouragement and leadership of key players and developing the business case for why others should act. This can be less compelling than mandatory regulatory requirements or can often be more ineffective without the credible threat of regulatory actions specifying explicit targets and commitments to back-up the voluntary initiative.

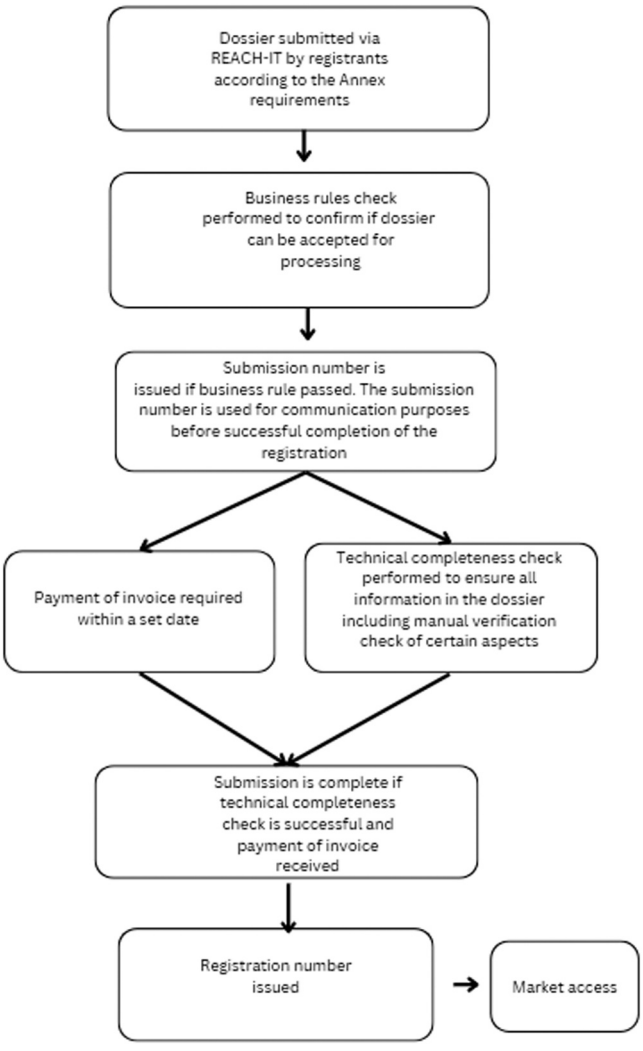

Fig. 3. Steps from dossier submission to issuance of REACH registration number.

2.3.3. The EU universal restriction of PFAS

The EU's ambitious proposal to restrict or ban PFAS as a group is of great importance, given the significant concerns about their impact on human health and the environment. Continuous exposure to these chemicals should not be allowed to persist. However, PFAS are crucial in many applications due to their unique properties, such as high performance, surface activity, durability and low quantity used, which often cannot be matched by other substances (Buck et al., 2011; Thomas., 2006; Glüge et al., 2020). For instance, PFAS are vital in medical devices and specialty applications where no substitutes currently exist (Cousins et al., 2019b).

Safe and sound management of PFAS is essential, especially in important or essential applications, while efforts to find safer alternatives continue (Blum et al., 2017). It is important to consider the broader implications of a complete ban on all PFAS since according to Cousins et al., (2019b), it is neither practicable nor reasonable to ban all PFAS uses in one step. PFAS are used due to their unique physical property of being inert and having both water and oil repellence (which in turn means they are highly resistant to degradation). Identifying and developing alternatives that meet the same technical function without same environmental consequences is an issue that requires careful consideration to avoid the same regulatory fate (i.e., regrettable substitutions). The challenge is to find ways to meet desired functions without unwanted properties. A reactive regulatory approach may not provide the necessary protection. Collaboration among industry, policymakers, and other stakeholders is crucial to ensure that efforts to protect human health and the environment do not lead to unintended consequences.

The concept of essentiality is inherently open to interpretation, as different stakeholders view what is essential differently. Karinen et al., (2024) examines EU citizens' views on (non)essential uses of persistent chemicals and found significant variations in how uses were rated both within and across countries. In general, safety related uses were most often regarded as essential while recreational, household and personal care uses are more frequently considered non-essential. Within the EU CSS, the essential-use concept is intended to prioritise protection while allowing critical uses to continue (European Commission., 2020b). However, when uses are labelled as 'essential,' this can create a barrier to substitution, since such uses are more likely to be exempted from restrictions or phase-outs, even if safer alternatives exist. This underscores the importance of setting clear, transparent criteria for essential use to prevent the concept from unintentionally slowing down chemical substitution and innovation.

The chemical industry should develop a detailed inventory of essential PFAS applications, categorise them into use types and sectors, and propose a timeline for the development of alternatives. Policymakers in consultation with NGOs and academia need to decide on uses that are essential and whether they pose acceptable risks. For uses where the risks are unacceptable, clear rationale should be provided in addition to an effective regulatory plan. This collaboration is necessary to prevent the development of regrettable substitutions, where new chemicals might present similar or new hazards. Questions such as how to develop alternatives that are not persistent or do not break down into persistent products, and whether using reduced amounts of a chemical of concerns is an acceptable risk compared to using larger amounts of a safer alternative, need careful consideration. Lack of regulatory certainty stifles innovation and hampers the development of safe

substitutes. Continuous changes in regulatory goals create uncertainty, undermining the purpose of regulation to promote innovation. Hence there is a need to develop a robust, transparent, and trustworthy regulatory system that will give confidence to consumers, the chemical industry, and all stakeholders. This system should ensure that the aim of protecting human health and the environment from chemicals of concern is achieved without leading to further unintended consequences.

2.3.4. The fragmentation of regulatory frameworks and siloed regulatory regimes

Chemicals are currently regulated based on their specific use, such as pesticides, industrial chemicals, biocides or food contact materials, etc. This fragmented approach does not provide sufficient protection from the myriads of chemicals to which humans, and the environment are potentially exposed (Munthe et al., 2019; Topping et al., 2020; van Dijk et al., 2021; Evans et al., 2016) and also contributes to the current levels of exposure due to different scopes, criteria and enforcement impacting on their effective management. For example, in 1966, the U.S. Food and Drug Administration (FDA) raised concerns about the toxicity of DuPont's food packaging product Zonyl RP, which has the potential to breakdown to PFOA, due to liver and kidney issues in animal studies (Benesh., 2022; Crunden and Wittenberg., 2022; Hayes., 2019). However, this information was not shared with the EPA after it was established in the 1970s. Despite these concerns, many PFAS chemicals were later authorised for use in food contact materials, see Fig. 2 and supplementary information (PFAS Timeline). Under the original TSCA, the EPA could not mandate actions such as requiring health and safety data without undergoing the formal and often lengthy Final Rule process. This significantly limits EPA's ability to act swiftly on chemical risks, however, the 2016 amended TSCA addresses this limitation. The revised law grants EPA clearer authority to require data, conduct risk evaluations, and regulate substances without the need for full rulemaking in every case, thereby strengthening chemical oversight and enabling more timely public health and environmental protections.

The REACH Regulation in the EU functions independently of other chemical regulatory programs, with certain exclusions (Bergkamp and Herbatschek., 2014). Pharmaceuticals, biocides, and veterinary materials/products are not required to register under REACH (Lahl and Hawxwell., 2006; Stokes and Vaughan., 2013; Williams et al., 2009), because they are regulated under different directives such as Biocides Regulation (EC) No 528/2012, pharmaceuticals Directive 2001/83/EC and veterinary products Directive 2001/82/EC (van Dijk et al., 2021). This fragmentation can result in inconsistencies and gaps in chemical safety regulation and according to Topping et al., (2020), the EU's chemical regulation is fragmented, and could be improved to better protect both human health and the environment. Fragmentation is not limited to the EU; it is a global issue that results in divergent regulatory approaches and methods. Hence, closer cooperation, harmonisation and information exchange are necessary to manage chemicals effectively (Munthe et al., 2019). In response to the fragmentation, in December 2023, the European Commission adopt the 'one substance, one assessment' policy with the purpose of streamlining chemicals assessment across the EU, strengthen knowledge base of chemicals and enable early detection and actions on chemicals of emerging concerns (European Commission., 2023). The ubiquitous nature of PFAS underscores the need for a more integrated and coordinated regulatory approach for chemicals bearing in mind the international trade of chemicals and products containing chemicals.

The siloed nature of chemical regulation, where different policy elements work independently with limited interaction and communication, exacerbates the problem. A review by van Dijk et al., (2021) found that chemicals not approved under one regulatory framework might still be allowed under another, for example banned pesticides and biocides are allowed on the market under REACH. This siloed approach hinders the holistic and efficient development and implementation of chemical regulations. To address these issues, it is essential to integrate all regulatory regimes and create effective communication channels between them. This integration will help reduce confusion and ensure adequate protection of human health and the environment. Enhanced cooperation, harmonisation, and information exchange among regulatory frameworks and stronger interactions between science and policy are crucial (Munthe et al., 2019). Chemicals are used in numerous applications and the lack of information on their uses and lifecycles, coupled with the complexity of the supply chain, demands addressing the fragmentation and siloed working nature of chemical regulation. In the EU CSS, the EU regulatory system is considered fragmented, limited and needs to be consolidated and simplified (European Commission., 2020b). Therefore, integrating regulatory regimes and improving communication channels will better protect human health and the environment.

A related challenge is the need to break down barriers between different stakeholders across the chemical supply chain from production through to end-of-life product disposal particularly in the case of PFAS. Since demonstrating safe use at upstream level often relies on certain assumptions and conditions that may not hold further downstream. When chemicals are used differently or at greater extent than anticipated, this can lead to unintended or emissions that can become problematic. Such gap illustrates how fragmented regulatory approaches which often addresses only parts of the supply chain in isolation can miss critical risks. Strengthening dialogue, information sharing (Harremoës et al., 2001) and better integrated regulatory frameworks is essential to close these gaps and ensure consistent protection of human health and the environment across the supply chain.

The role of the chemical industry in the ubiquitous nature of PFAS is discussed below.

3. From innovation to contamination – the case of industry oversight

The delay in disclosing PFAS toxicity and environmental impact can be attributed to scientific uncertainties, questionable business practices, delayed and ineffective regulatory control, and financial interests. Fluorochemicals, such as chlorofluorocarbons (CFCs), were initially developed in the 1920s to replace problematic refrigerants like ammonia, methyl chloride and sulfur dioxide, which were flammable, corrosive, and toxic (Okazoe., 2009; Hamilton., 1963). CFCs were stable, had low acute toxicity, and were non-flammable, which made them ideal refrigerants. However, these same properties also made them potent ozone-depleting chemicals (Box., n.d.). The production of Freon (CFCs) in the 1930s exemplifies how the chemical industry solves societal challenges through innovation. According to Okazoe., (2009), the need to reduce the environmental burden from organic materials such as plastics led to products that are durable, stable and last longer, but these solutions can have hidden or unknown problems as we now know. For example, CFCs were later found to deplete the ozone layer (Box., n.d.; Molina and Rowland., 1974; Okazoe., 2009), which led to the implementation of the Montreal Protocol on Substances that Deplete the Ozone Layer to address the issue (UNEP., 1987).

Similar to the CFCs, the properties that make PFAS very useful also confer on them unwanted impacts on human health and the environment. The industry became aware of the potential toxicity of PFAS during the 1950s and 1960s, see Fig. 1 and supplementary information (PFAS Timeline). For example, a 1950 study by 3 M indicated that perfluorobutyric acid could accumulate in blood (Hayes., 2019). In 1954, a DuPont employee received an inquiry into the potential toxicity of C8 and by 1955, a study from Stanford University found that PFOA (C8) binds to proteins in human blood (Nordby and Luck., 1956). In 1961, a DuPont in-house toxicologist said that C8 should be handled with care due to its potential toxicity. DuPont's internal study dated from 1968 to 1981 reported C8 has "moderate toxicity when injected and highly toxic when inhaled" (Gaber et al., 2023). While public

knowledge about PFAS toxicity was limited due to reduced knowledge and data disclosure, the chemical industry had significant internal awareness (Gaber et al., 2023; Richter et al., 2021). The limited public awareness meant reduced political and market pressure to demand effective control and safer products.

Knowledge generation and disclosure can be influenced by the position of an entity or individual (Dalglish et al., 2021; Richter et al., 2021). In August 1975, Guy and Taves reported the potential for PFAS to accumulate in blood samples, bringing this issue to the attention of the chemical industry (3 M) (3M., 1975). In response, 3 M researchers were tasked in September 1975 to compare the NMR spectra of PFOA and PFOS with those presented. By November 1975, 3 M confirmed that PFOS matched the spectra reported by Guy and Taves (3M., 1977). This was approximately 20 years after the production and use of PFOS started. In 1976, 3 M began the internal screening of their employees that may have been exposed to C8, finding concentrations ranging from "50–1000 times normal" in the blood of employees (3M., 1977). In a 3 M meeting held with H.C. Hodge (a toxicologist) in 1979 to review the results of fluorochemicals in blood serum, the question of whether toxic effects observed in animal studies were attributed to fluorochemicals was raised (3M., 1979). Despite this, 3 M did not disclose these findings to the public or regulators until PFAS became widespread.

The chemical industry faces a challenging and complex set of issues. On the one hand, technical function, price, and compatibility of substances to existing processes and mixtures will take priority for business continuity reasons. This can mean consideration of human health and environmental risks are pushed down the pecking order and potentially considered later in the substitution process. On the other hand, businesses rely upon regulatory certainty and tend to take their cue from the developing regulatory process, which by its nature is reactive to the situation presented. These issues are further exacerbated by the fact that underlying data to understand and identify possible regrettable substitution requires specialist technical skills, is potentially costly, and in the case of toxicological data can take extended periods of time to develop, with a negative outcome resetting the entire substitution process (i.e., if the results of testing identify a regrettable substitute, a new alternative has to been identified and researched). Psychologically this can set in place a flawed approach whereby industry and regulators play continuous catch-up with one another, *on the basis that if a substitute is regrettable, it's tomorrow's problem and other priorities are more pressing today.*

4. Conclusions and recommendations

To prevent repeating past mistakes and failures, there is an urgent need to learn from them. Learning from past mistakes and successes will help move us forward toward effective chemical management and a sustainable future (UNEP., 2020). The exposure of humans and the environment to chemicals of concern should not be allowed to continue. Therefore, we propose the following key insights for further discussion.

4.1. Considerations for the chemical industry

Selective dissemination of favorable information may benefit the chemical industry in the short term by delaying regulatory scrutiny and public awareness. However, this practice erodes confidence and trust in the long term. Although PFAS has been important for the chemical industry's profitability and success, decisions on environmental pollution should be based on current state of science, and the precautionary principle applied.

The delay by the chemical industry in disclosing the toxicity of PFAS to the public and regulators, along with the continued use of PFAS in non-essential applications, has damaged stakeholder trust and contributed to the ubiquitous presence of PFAS in the environment. The chemical industry must play a crucial role in restoring public trust not only in their products but also in their words and actions so that the gap between narrative and action is narrowed. The chemical industry should encourage full disclosure, open dialogue, and commitment to voluntarily withdrawing PFAS from all non-essential uses or where alternatives exist.

When no suitable alternatives or technologies are available, the industry should collaborate with all stakeholders to find solutions that avoid unintended consequences. Historically, the industry's focus has been on chemical functionality, however, increased knowledge suggests that adopting safe and sustainable chemistry practices in addition to function is essential. The recent announcement by 3 M to exit PFAS manufacturing and discontinue PFAS use across its portfolio by the end of 2025 is a positive step (3M., 2022). However, past announcements have led to the development of alternatives with similar hazards to the PFAS they replaced. 3 M's announcement is timely and should be applauded but more needs to be done to ensure humans and the environment are protected from negative effects from chemicals. Other companies should commit to eliminating all non-essential PFAS uses and propose timelines for finding and implementing safe alternatives. DuPont., (2019) commitment to eliminate long-chain PFAS in integrated operations by the end of that year (DuPont., 2019) falls short of the necessary commitment to reduce all PFAS impacts on human health and the environment. The chemical industry should not only follow the letter but the spirit of regulations, ensuring all alternatives resulting from these commitments are safe, sustainable, and not mere drop-in replacements as previous practice suggests.

We propose that the chemical industry follow its sustainability commitments with concrete actions that build trust and ensure chemicals of concern are used only for essential functions. One way to achieve this is to holistically engage with substitution, seeing it as an opportunity for innovation to solve the challenges of the 21st century. In this context, the European Commission's exploration of a network of substitution centres could provide valuable guidance and support to industry, helping them identify safer alternatives, foster innovation, and reduce the risk of regrettable substitutions (European Commission., 2024). Another appropriate action for PFAS would be to create an inventory of applications and uses that are considered essential, identify where alternatives are available, and propose timelines for developing alternatives when they are not. As part of this process, industry should allow transparent participation of all relevant stakeholders, including industry, academics, regulators, NGOs, and consumers, during the alternative selection process. By doing so, the chemical industry can move toward effective chemical management and a sustainable future, ensuring that the continued exposure of humans and the environment to the negative impact from chemicals is reduced.

4.2. Considerations for policymakers

Under REACH regulation, registration numbers are issued before adequate scientific evaluation, which contributes to continued exposure. Issuing registration numbers only after substance evaluation would align with the goal of REACH regulation to encourage innovation and propel the chemical industry towards development and use of safe alternatives. As an initial step, a review of key hazard properties such as carcinogenicity, mutagenicity and reproductive toxicity (CMR) and PBT should be incorporated into the technical completeness check before issuing of registration numbers. This can be achieved through an automated traffic light model which would flag potential high-risk substances early in the process, ensuring that substances that are flagged for these hazards undergo thorough evaluation before entering the market. Registration numbers and market access should be granted only when adequate and relevant data are available, risks are known and deemed acceptable, and safety is ensured.

Secondly, using group assessment and universal restrictions, as with PFAS, offers policymakers an opportunity to save time and cost, evaluate more substances, prompt regulators to look horizontally across chemical group(s) and prevent the replacement of chemicals with similar alternatives compared to the traditional substance by substance evaluation.

While this approach has benefits, it may also have unintended consequences. We are aware of the risk posed to humans and the environment from the uncontrolled use of chemicals of concern and the need for policymakers to make bold and ambitious decisions to effectively manage this. But the need to consider unintended consequences of such approach should be explored and appropriate steps required to mitigate them should not be ruled out either.

The universal restriction could set a precedent for future approaches and such major policy changes should not be rushed without thorough evaluation of their implications, not only for European safety and well-being but also for the competitiveness of the European chemical sector. This is more necessary since policymakers from other geographies may be taking their cue and learning from the EU approach. It is thus important to remember that not all chemicals including those that are persistent are inherently harmful; many are crucial for achieving the United Nations' sustainable development goals and the European Commission's zero-pollution ambition when used safely and sustainably. Therefore, consulting and listening to all stakeholders, including the chemical industry, is essential, taking full account of the assumptions, values and expertise of different groups. It is also crucial for policymakers to continue to have an open-door policy that creates a channel for constructive engagement with the chemical industry and all stakeholders.

Addressing the fragmentation of chemical management requires concerted efforts to harmonise regulations from local to global levels, enhance coordination and cooperation, and leverage modern technologies and methods such as the need for increased capacity building in the use of New Approach Methodologies (NAMs). For example, establishing a single database where information on all chemicals irrespective of use is easily accessible could help address the current fragmented information, which hampers early action. To this end, we support the European Commission's proposal in this direction as part of the 'one substance, one assessment' initiative. Effective information exchange is crucial for efficient management of chemicals and transparency on decision making and data interpretation is important in this regard. Chemicals play a significant role in achieving the zero-pollution ambition; thus, their safe production, use, and management is everyone's responsibility. Our operations should be conducted within the safe operating space available on our planet.

CRediT authorship contribution statement

Rob Whiting: Writing – review & editing, Conceptualization. **Olasunkanmi Dosunmu:** Writing – original draft, Methodology, Investigation, Conceptualization. **Andrew J. Sweetman:** Writing – review & editing, Funding acquisition, Conceptualization. **Avtar Matharu:** Writing – review & editing. **Nigel Watson:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was funded by the Natural Environment Research Council (NERC) under Grant No. NE/VO13041/1. The authors acknowledge Prof. Kevin Jones (Lancaster University) for their feedback in the planning and development of the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envsci.2025.104275.

References

3M (1975). *Fluorocarbons in Human Blood Plasma - Record of a Telephone Conversation- August 14, 1975*. ⟨https://docs.house.gov/meetings/GO/GO28/20190910/109902/HHRG-116-GO28-Wstate-SwansonL-20190910.pdf⟩.
3M (1977). *Organic fluorine compounds in blood chronology*.
3M (1979). *MEETING MINUTES - MEETING WITH H.C. HODGE*.
3M (2001). *3M Company TSCA Section 8(e) Compliance Audit - Disclosure of Phase Two Findings*.
3M (2022, December 20). *3M to Exit PFAS Manufacturing by the End of 2025*. ⟨https://news.3m.com/2022-12-20-3M-to-Exit-PFAS-Manufacturing-by-the-End-of-2025⟩.
Allen, J.G. (2008, January 2). *Opinion: These toxic chemicals are everywhere — even in your body. And they won't ever go away*. Washington Post. ⟨https://www.washingtonpost.com/opinions/these-toxic-chemicals-are-everywhere-and-they-wont-ever-go-away/2018/01/02/82e7e48a-e4ee-11e7-a65d-1ac0fd7f097e_story.html⟩.
Allen, J.H., 2013. The wicked problem of chemicals policy: opportunities for innovation. J. Environ. Stud. Sci. 3 (2), 101–108. https://doi.org/10.1007/s13412-013-0117-0.
Applegate, J.S., 2008. Synthesizing TSCA and REACH: practical principles for chemical regulation reform. Source. Ecol. Law Q. 35 (4). ⟨https://about.jstor.org/terms⟩.
Arp, H.P.H., Hale, S.E., 2022. Assessing the persistence and mobility of organic substances to protect freshwater resources. ACS Environ. Au 2 (6), 482–509. https://doi.org/10.1021/acsenvironau.2c00024.
Arp, H.P.H., Brown, T.N., Berger, U., Hale, S.E., 2017. Ranking REACH registered neutral, ionizable and ionic organic chemicals based on their aquatic persistency and mobility. Environmental Science Processes Impacts 19 (7), 939–955. https://doi.org/10.1039/C7EM00158D.
ATSDR. (2021, May 5). *Toxicological Profile for Perfluoroalkyls CAS# 335-67-1, 1763-23-1, 355-46-4, 375-95-1*. https://doi.org/10.15620/cdc:59198.
Benesh Melanie. (2022, February 10). *For decades, the FDA knew toxic 'forever chemicals' were dangerous but continued to allow their use*. EWG. ⟨https://www.ewg.org/research/decades-fda-knew-toxic-forever-chemicals-were-dangerous-continued-allow-their-use⟩.
Bergkamp, L., Herbatschek, N., 2014. Regulating chemical substances under REACH: the choice between authorization and restriction and the case of dipolar aprotic solvents. Rev. Eur. Comp. Int. Environ. Law 23 (2), 221–245. https://doi.org/10.1111/reel.12083.
Bergman Cynthia. (2004, August 7). *EPA Takes Enforcement Action Against DuPont For Toxic Substances Reporting Violations*. ⟨https://www.epa.gov/archive/epapages/newsroom_archive/newsreleases/afdc5785fd9ee05585256ecb00522cee.html⟩.
Birnbaum, L.S., Grandjean, P., 2015. Alternatives to PFASs: perspectives on the Science. Environ. Health Perspect. 123 (5). https://doi.org/10.1289/ehp.1509944.
Blake, B.E., Fenton, S.E., 2020. Early life exposure to per- and polyfluoroalkyl substances (PFAS) and latent health outcomes: A review including the placenta as a target tissue and possible driver of peri- and postnatal effects. Toxicology 443, 152565. https://doi.org/10.1016/j.tox.2020.152565.
Blum, C., Bunke, D., Hungsberg, M., Roelofs, E., Joas, A., Joas, R., Blepp, M., Stolzenberg, H.C., 2017. The concept of sustainable chemistry: Key drivers for the transition towards sustainable development. Sustain. Chem. Pharm. 5, 94–104. https://doi.org/10.1016/j.scp.2017.01.001.
Bock, A.R., Laird, B.E., 2022. CHAPTER 1. PFAS Regulations: Past and Present and Their Impact on Fluoropolymers. In The Royal Society of Chemistry eBooks. Royal Society of Chemistry, pp. 1–21. https://doi.org/10.1039/9781839167591-00001.
Box, G.E.P. (n.d.). *Discussion Paper: Integrating Life Cycle Considerations in Alternatives Assessment Processes*. Retrieved 24 April 2024, from ⟨https://www.theic2.org/wp-content/uploads/2022/09/LCT-in-AA-Paper_FINAL.pdf⟩.
Brase, R.A., Mullin, E.J., Spink, D.C., 2021. Legacy and emerging per- and polyfluoroalkyl substances: analytical techniques, environmental fate, and health effects. Int. J. Mol. Sci. 22 (3), 995. https://doi.org/10.3390/ijms22030995.
Brendel, S., Fetter, É., Staude, C., Vierke, L., Biegel-Engler, A., 2018. Short-chain perfluoroalkyl acids: environmental concerns and a regulatory strategy under REACH. Environ. Sci. Eur. 30 (1). https://doi.org/10.1186/s12302-018-0134-4.
Brennan, N.M., Evans, A.T., Fritz, M.K., Peak, S.A., von Holst, H.E., 2021. Trends in the regulation of per-and polyfluoroalkyl substances (PFAS): A scoping review. In: International Journal of Environmental Research and Public Health, 18. MDPI. https://doi.org/10.3390/ijerph182010900.
Buck, R.C., Franklin, J., Berger, U., Conder, J.M., Cousins, I.T., Voogt, P.De, Jensen, A.A., Kannan, K., Mabury, S.A., van Leeuwen, S.P.J., 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: Terminology, classification, and origins. Integr. Environ. Assess. Manag. 7 (4), 513–541. https://doi.org/10.1002/ieam.258.
Calafat, A.M., Wong, L.-Y., Kuklenyik, Z., Reidy, J.A., Needham, L.L., 2007. Polyfluoroalkyl Chemicals in the U.S. Population: Data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and Comparisons with NHANES 1999–2000. Environ. Health Perspect. 115 (11), 1596–1602. https://doi.org/10.1289/ehp.10598.
Coria, J., 2018. The economics of toxic substance control and the REACH directive. Rev. Environ. Econ. Policy 12 (2), 342–358. https://doi.org/10.1093/reep/rey003.
Cousins, I.T., Goldenman, G., Herzke, D., Lohmann, R., Miller, M., Ng, C.A., Patton, S., Scheringer, M., Trier, X., Vierke, L., Wang, Z., Dewitt, J.C., 2019b. The concept of essential use for determining when uses of PFASs can be phased out. In: Environmental Science: Processes and Impacts, 21. Royal Society of Chemistry, pp. 1803–1815. https://doi.org/10.1039/c9em00163h.
Cousins, I.T., Ng, C.A., Wang, Z., Scheringer, M., 2019a. Why is high persistence alone a major cause of concern? Environ. Sci. Process. Impacts 21 (5), 781–792. https://doi.org/10.1039/c8em00515j.

Cousins, I.T., Dewitt, J.C., Glüge, J., Goldenman, G., Herzke, D., Lohmann, R., Ng, C.A., Scheringer, M., Wang, Z., 2020. The high persistence of PFAS is sufficient for their management as a chemical class. In: Environmental Science: Processes and Impacts, 22. Royal Society of Chemistry, pp. 2307–2312. https://doi.org/10.1039/d0em00355g.

Crunden, E.A., & Wittenberg, A. (2022, July 3). *Inside FDA's 'forever chemicals' catastrophe*. ⟨https://www.eenews.net/articles/inside-fdas-forever-chemicals-catastrophe/⟩.

Dalglish, S.L., Khalid, H., McMahon, S.A., 2021. Document analysis in health policy research: the READ approach. Health Policy Plan. 35 (10), 1424–1431. https://doi.org/10.1093/heapol/czaa064.

van Dijk, J., Gustavsson, M., Dekker, S.C., van Wezel, A.P., 2021. Towards 'one substance – one assessment': An analysis of EU chemical registration and aquatic risk assessment frameworks. In: In Journal of Environmental Management, 280. Academic Press. https://doi.org/10.1016/j.jenvman.2020.111692.

DuPont (2019). *PFAS Commitments – Established in 2019*. ⟨https://www.dupont.com/pfas/our-commitments-for-the-future.html#:~:text=We%20will%20eliminat%20the%20purchase,by%20the%20end%20of%202021⟩.

ECHA. (2021, June 21). Report on the operation of REACH and CLP 2021. ⟨https://echa.europa.eu/report-on-the-operation-of-reach-and-clp-2021⟩.

ECHA. (2023, December 14). *Registry of restriction intentions until outcome - Per- and polyfluoroalkyl substances (PFAS)*. ⟨https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e18663449b⟩.

ECHA. (2025, Aug 20). *ECHA publishes updated PFAS restriction proposal*. ⟨https://echa.europa.eu/-/echa-publishes-updated-pfas-restriction-proposal?utm⟩.

Environment Agency. (2021). *Poly- and perfluoroalkyl substances (PFAS): sources, pathways and environmental data*. ⟨www.gov.uk/environment-agency⟩.

European Commission. (2001). *WHITE PAPER Strategy for a future Chemicals Policy*. ⟨https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2001:0088:FIN:en:PDF⟩.

European Commission. (2006, December 27). *Directive 2006/122/EC of the European Parliament and of the Council of 12 December 2006 amending for the 30th time Council Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations (perfluorooctane sulfonates)*. ⟨https://eur-lex.europa.eu/eli/dir/2006/122/oj/eng⟩.

European Commission, 2020b. Chemicals strategy for sustainability: towards a toxic-free environment. COM(2020b) 667 Final. *Available at* ⟨Http://Ec.Europa.Eu⟩.

European Commission. (2020a). *COMMISSION STAFF WORKING DOCUMENT Poly- and perfluoroalkyl substances (PFAS)*. ⟨https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=SWD%3A2020%3A249%3AFIN⟩.

European Commission. (2023, December 7). *Commission proposes 'one substance, one assessment'' chemicals assessment reform for faster, simplified and transparent processes'*. ⟨https://ec.europa.eu/commission/presscorner/detail/en/ip_23_6413⟩.

European Commission, Directorate-General for Environment (2024, September 2025). *Call for Tenders: EU Substitution Centre – Feasibility Study*. Annex 5. Brussels: Publications Office of the European Union. Available at: ⟨https://ecga.net/wp-content/uploads/2024/09/Annex-5-EU-Substitution-Center-Call-for-tender.pdf⟩.

Evans, R.M., Martin, O.V., Faust, M., Kortenkamp, A., 2016. Should the scope of human mixture risk assessment span legislative/regulatory silos for chemicals? Sci. Total Environ. 543, 757–764. https://doi.org/10.1016/j.scitotenv.2015.10.162.

Gaber, N., Bero, L., Woodruff, T.J., 2023. The devil they knew: chemical documents analysis of industry influence on PFAS science. Ann. Glob. Health 89 (1). https://doi.org/10.5334/aogh.4013.

Gaines, L.G.T., 2023. Historical and current usage of per- and polyfluoroalkyl substances (PFAS): A literature review. In: American Journal of Industrial Medicine, 66. John Wiley and Sons Inc, pp. 353–378. https://doi.org/10.1002/ajim.23362.

Gebbink, W.A., van Leeuwen, S.P.J., 2020. Environmental contamination and human exposure to PFASs near a fluorochemical production plant: review of historic and current PFOA and GenX contamination in the Netherlands. Environ. Int. 137, 105583. https://doi.org/10.1016/j.envint.2020.105583.

Gee, D., 2005. Late lessons from early warnings: toward realism and precaution with endocrine-disrupting substances. Environ. Health Perspect. 114 (1), 152–160. https://doi.org/10.1289/ehp.8134.

Glüge, J., Scheringer, M., Cousins, I.T., DeWitt, J.C., Goldenman, G., Herzke, D., Lohmann, R., Ng, C.A., Trier, X., Wang, Z., 2020. An overview of the uses of per- and polyfluoroalkyl substances (PFAS). Environ. Sci. Processes Impacts 22 (12), 2345–2373. https://doi.org/10.1039/D0EM00291G.

Groffen, T., Lasters, R., Xie, G., Tanjina, T., van Gestel, Bervoets, L., 2025. Bioaccumulation and toxicity of perfluorobutane sulfonate (PFBS) and perfluorobutane sulfonamide (FBSA) in Eisenia fetida and Eisenia andrei. Ecotoxicology and Environmental Safety 302, 118562. https://doi.org/10.1016/j.ecoenv.2025.118562.

Hamid, N., Junaid, M., Sultan, M., Yoganandham, S.T., Chuan, O.M., 2024. The untold story of PFAS alternatives: Insights into the occurrence, ecotoxicological impacts, and removal strategies in the aquatic environment. Water Res. 250, 121044. https://doi.org/10.1016/j.watres.2023.121044.

Hamilton Jr., J.M., 1963. The organic fluorochemicals industry. Adv. Fluor. Chem. 3, 117–180.

Harremoës, P., Gee, D., MacGarvin, M., Stirling, A., Keys, J., Wynne, B., Vaz, S.G., 2001. Late lessons from early warnings: the precautionary principle 1896-2000. Office for Official Publications of the European Communities, Luxembourg.

Harremoës, P., Gee, D., MacGarvin, M., Stirling, A., Keys, J., Wynne, B., Vaz, S.G., 2013. The precautionary principle in the 20th century: Late Lessons from Early Warnings. Routledge eBooks. https://doi.org/10.4324/9781315071985.

Hayes Jared. (2019, August 29). *For decades, polluters knew PFAS chemicals were dangerous but hid risks from public*. ⟨https://www.ewg.org/research/decades-polluters-knew-pfas-chemicals-were-dangerous-hid-risks-public⟩.

He, Y., Lv, D., Li, C., Liu, X., Liu, W., Han, W., 2022. Human exposure to F-53B in China and the evaluation of its potential toxicity: An overview. Environ. Int. 161, 107108. https://doi.org/10.1016/j.envint.2022.107108.

Interstate Technology & Regulatory Council (ITRC), 2020. History and Use of Per- and Polyfluoroalkyl Substances (PFAS) found in the Environment. ⟨https://pfas-1.itrcweb.org/⟩.

Joerss, H., Menger, F., 2023. The complex 'PFAS world' - How recent discoveries and novel screening tools reinforce existing concerns. In: Current Opinion in Green and Sustainable Chemistry, 40. Elsevier B.V. https://doi.org/10.1016/j.cogsc.2023.100775.

Jones, K.C., 2021. Persistent Organic Pollutants (POPs) and Related Chemicals in the Global Environment: Some Personal Reflections. In: Environmental Science and Technology, 55. American Chemical Society, pp. 9400–9412. https://doi.org/10.1021/acs.est.0c08093.

Jones, K.C., de Voogt, P., 1999. Persistent organic pollutants (POPs): state of the science. Environ. Pollut. 100 (1–3), 209–221. https://doi.org/10.1016/S0269-7491(99)00098-6.

Karinen, A., Tobi, H., Devilee, J., De Blaeij, A., Gabbert, S., 2024. Citizens' opinions on (non-)essential uses of persistent chemicals: A survey in seven European countries. Environ. Sci. Policy 153, 103666. https://doi.org/10.1016/j.envsci.2023.103666.

KEMI. (2023, February 15). *PFAS*. ⟨https://www.kemi.se/en/chemical-substances-and-materials/pfas⟩.

Kissa, E., 2001. Fluorinated Surfactants and Repellents, 2nd ed., 97. Marcel Dekker AG.

Krimsky, S., 2017. The unsteady state and inertia of chemical regulation under the US Toxic Substances Control Act. PLOS Biol. 15 (12), e2002404. https://doi.org/10.1371/journal.pbio.2002404.

Lahl, U., Hawxwell, K.A., 2006. REACH N. Eur. Chem. Law. ⟨https://pubs.acs.org/sharingguidelines⟩.

Lemal, D.M., 2004. Perspective on fluorocarbon chemistry. J. Org. Chem. 69 (1), 1–11. https://doi.org/10.1021/jo0302556.

Li, Z., Luo, Z.-M., Huang, Y., Wang, J.-W., Ouyang, G., 2023. Recent trends in degradation strategies of PFOA/PFOS substitutes. Chemosphere 315, 137653. https://doi.org/10.1016/j.chemosphere.2022.137653.

Lohmann, R., Cousins, I.T., DeWitt, J.C., Glüge, J., Goldenman, G., Herzke, D., Lindstrom, A.B., Miller, M.F., Ng, C.A., Patton, S., Scheringer, M., Trier, X., Wang, Z., 2020. Are Fluoropolymers Really of Low Concern for Human and Environmental Health and Separate from Other PFAS? Environ. Sci. Technol. 54 (20), 12820–12828. https://doi.org/10.1021/acs.est.0c03244.

Markell, D., 2010. An Overview of TSCA, Its History and Key Underlying An Overview of TSCA, Its History and Key Underlying Assumptions, and Its Place in Environmental Regulation Assumptions, and Its Place in Environmental Regulation. https://openscholarship.wustl.edu/law_journal_law_policy.

Markowitz, G., Rosner, D., 2018. Monsanto, PCBs, and the creation of a "world-wide ecological problem. J. Public Health Policy 39 (4), 463–540. https://doi.org/10.1057/s41271-018-0146-8.

Molina, M.J., Rowland, F.S., 1974. Stratospheric sink for chlorofluoromethanes: chlorine atom-catalysed destruction of ozone. Nature 249 (5460), 810–812. https://doi.org/10.1038/249810a0.

Munoz, G., Liu, J., Vo Duy, S., Sauvé, S., 2019. Analysis of F-53B, Gen-X, ADONA, and emerging fluoroalkylether substances in environmental and biomonitoring samples: A review. In: Trends in Environmental Analytical Chemistry, 23. Elsevier B.V. https://doi.org/10.1016/j.teac.2019.e00066.

Munthe, J., Lexén, J., Skårman, T., Posthuma, L., Brack, W., Altenburger, R., Brorström-Lundén, E., Bunke, D., Faust, M., Rahmberg, M., Sleeuwaert, F., Slobodnik, J., van Gils, J., van Wezel, A., 2019. Increase coherence, cooperation and cross-compliance of regulations on chemicals and water quality. Environ. Sci. Eur. 31 (1). https://doi.org/10.1186/s12302-019-0235-8.

Nordby, G.L., Luck, M.J., 1956. Perfluorooctanoic acid interactions with human serum albumin. https://doi.org/https://doi.org/10.1016/s0021-9258%2818%2965805-3.

O'Hagan, D., 2008. Understanding organofluorine chemistry. An introduction to the C–F bond. Chem. Soc. Rev. 37 (2), 308–319. https://doi.org/10.1039/B711844A.

OECD, 2003. Voluntary Approaches for Environmental Policy: Effectiveness, Efficiency and Usage in Policy Mixes. OECD. https://doi.org/10.1787/9789264101784-en.

Okazoe, T., 2009. Overview on the history of organofluorine chemistry from the viewpoint of material industry. In: Proceedings of the Japan Academy Series B: Physical and Biological Sciences, 85, pp. 276–289. https://doi.org/10.2183/pjab.85.276.

Poulsen, P.B., Jensen, A.A., Wallström, E., Aps, E., 2005. More environmentally friendly alternatives to PFOS-compounds and PFOA. Dan. Minist. Environ. Proj. No. 1013. ⟨https://www2.mst.dk/Udgiv/publications/2005/87-7614-668-5/pdf/87-7614-669-3.pdf⟩.

Renner, R., 2006. The long and the short of perfluorinated replacements. Environ. Sci. Technol. 40 (1), 12–13. https://doi.org/10.1021/es062612a.

Richter, L., Cordner, A., Brown, P., 2018. Non-stick science: Sixty years of research and (in)action on fluorinated compounds. Soc. Stud. Sci. 48 (5), 691–714. https://doi.org/10.1177/0306312718799960.

Richter, L., Cordner, A., Brown, P., 2021. Producing Ignorance Through Regulatory Structure: The Case of Per- and Polyfluoroalkyl Substances (PFAS). Sociol. Perspect. 64 (4), 631–656. https://doi.org/10.1177/0731121420964827.

Rudin, E., Glüge, J., Scheringer, M., 2023. Per- and polyfluoroalkyl substances (PFASs) registered under REACH—What can we learn from the submitted data and how important will mobility be in PFASs hazard assessment? Sci. Total Environ. 877. https://doi.org/10.1016/j.scitotenv.2023.162618.

Stokes, E., Vaughan, S., 2013. Great Expectations: Reviewing 50 Years of Chemicals Legislation in the EU. J. Environ. Law 25 (3), 411–435. https://doi.org/10.1093/jel/eqt024.
Sweetman, A., 2020. A Grand Challenge for Environmental Organic Chemistry: How Can We Avoid Regrettable Substitution? Front. Environ. Chem. 0, 7. https://doi.org/10.3389/FENVC.2020.00007.
Tepper, L.B., 1962. Teflon. N. Engl. J. Med. 267 (7), 349–350. https://doi.org/10.1056/NEJM196208162670709.
Thomas, R.R., 2006. In: Farn, R.J. (Ed.), Fluorinated surfactants, in Chemistry and Technology of Surfactants. Blackwell Publishing.
Topping, C.J., Aldrich, A., Berny, P., 2020. Overhaul environmental risk assessment for pesticides. Science 367 (6476). https://doi.org/10.1126/science.aay1144.
Trasande, L., 2016. Updating the Toxic Substances Control Act to Protect Human Health. JAMA 315 (15), 1565–1566. https://doi.org/10.1001/JAMA.2016.2037.
U.S. EPA, 1976. Train Sees New Toxic Substances Law as 'Preventive Medicine'. Press release. https://www.epa.gov/archive/epa/aboutepa/train-sees-new-toxic-substances-law-preventive-medicine.html.
U.S. EPA, 1999. Agreement for TSCA Compliance Audit. https://www.epa.gov/sites/default/files/documents/3m-auditagreement.pdf.
U.S. EPA, 2000. Press Release: EPA and 3M ANNOUNCE PHASE OUT OF PFOS. https://www.epa.gov/archive/epapages/newsroom_archive/newsreleases/33aa946e6cb11f35852568e1005246b4.html.
U.S. EPA, 2001. Agreement for Toxic Substances Control Act (TSCA) Compliance Audit ('Audit Agreement'). https://static.ewg.org/reports/2020/pfas-epa-timeline/2001_EPA-3M-AuditResponse.pdf?_ga=2.93418525.1253861871.1649070681-2123137255.1639662520.
U.S. EPA, 2006. CONSENT AGREEMENT AND FINAL ORDER. https://www.epa.gov/sites/default/files/documents/3m-consentagr.pdf.
U.S. EPA, 2021. United States Environmental Protection Agency Multi-Industry Per-and Polyfluoroalkyl Substances (PFAS) Study-2021 Preliminary Report. https://www.epa.gov/system/files/documents/2021-09/multi-industry-pfas-study_preliminary-2021-report_508_2021.09.08.pdf.
U.S. EPA, 2023. TSCA Chemical Substance Inventory - How to Access the TSCA Inventory. https://www.epa.gov/tsca-inventory/how-access-tsca-inventory#:~:text=The%20Inventory%20contains%2086%2C685%20chemicals,formatted%20to%20help%20you%20search.
U.S. EPA. (2023b, April 5). *Fact Sheet: 2010/2015 PFOA Stewardship Program*. ⟨https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/fact-sheet-2010201 5-pfoa-stewardship-program⟩.
U.S. EPA. (2023c, June 6). *About the TSCA Chemical Substance Inventory*. ⟨https://www.epa.gov/tsca-inventory/about-tsca-chemical-substance-inventory#whatdoesitmean⟩.
U.S. EPA (2023d, September 22). *E.I. DuPont de Nemours and Company and The Chemours Company PFOA Settlements*. ⟨https://www.epa.gov/enforcement/ei-dupont-de-nemours-and-company-and-chemours-company-pfoa-settlements⟩.
U.S. EPA. (2024, January 8). *Risk Management for Per- and Polyfluoroalkyl Substances (PFAS) under TSCA*. ⟨https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-management-and-polyfluoroalkyl-substances-pfas⟩.
U.S. EPA. (2025, September 29). *TSCA Section 8(a)(7) Reporting and Recordkeeping Requirements for Perfluoroalkyl and Polyfluoroalkyl Substances*. ⟨https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-section-8a7-reporting-and-recordkeeping⟩.
UNEP. (1987, September 16). *About Montreal Protocol*. ⟨https://www.unep.org/ozonaction/who-we-are/about-montreal-protocol⟩.
UNEP, 2020. An Assessment Report on Issues of Concern: Chemicals and Waste Issues Posing Risks to Human Health and the Environment. https://www.unenvironment.org/explore-topics/chemicals-waste.
UNEP, 2025. POPRC-20/3: Long-chain perfluorocarboxylic acids, their salts and related compounds. https://www.pops.int/TheConvention/POPsReviewCommittee/ReportsandDecisions/tabid/3309/ctl/Download/mid/28402/Default.aspx?id=29&ObjID=34369.
UNEP. (n.d.). *What are POPs?* Retrieved 9 January 2024, from ⟨https://www.pops.int/TheConvention/ThePOPs/tabid/673/Default.aspx⟩.
Villeneuve, D., Coady, K., Escher, B., Mihaich, E., Murphy, C., Schlekat, T., Garcia-Reyero, N., 2019. High-Throughput Screening and Environmental Risk Assessment: State of the Science and Emerging Applications. J. Environ. Toxicol. Chem. 38 (Number 1—pp), 12–26, 2019.
Wang, T., Wang, Y., Liao, C., Cai, Y., Jiang, G., 2009. Perspectives on the inclusion of perfluorooctane sulfonate into the Stockholm convention on persistent organic pollutants. Environ. Sci. Technol. 43 (14), 5171–5175. https://doi.org/10.1021/es900464a.
Wang, Z., Dewitt, J.C., Higgins, C.P., Cousins, I.T., 2017. A Never-Ending Story of Per-and Polyfluoroalkyl Substances (PFASs)? Environ. Sci. Technol. 51 (5), 2508–2518. https://doi.org/10.1021/acs.est.6b04806.
Wee, S.Y., Aris, A.Z., 2023. Revisiting the "forever chemicals", PFOA and PFOS exposure in drinking water. In: In npj Clean Water, 6. Nature Research. https://doi.org/10.1038/s41545-023-00274-6.
Wei, C., Wang, Q., Song, X., Chen, X., Fan, R., Ding, D., Liu, Y., 2018. Distribution, source identification and health risk assessment of PFASs and two PFOS alternatives in groundwater from non-industrial areas. Ecotoxicol. Environ. Saf. 152, 141–150. https://doi.org/10.1016/j.ecoenv.2018.01.039.
Williams, E.S., Panko, J., Paustenbach, D.J., 2009. The European Union's REACH regulation: a review of its history and requirements. Crit. Rev. Toxicol. 39 (7), 553–575. https://doi.org/10.1080/10408440903036056.
Zhang, Y., Zhou, Y., Dong, R., Song, N., Hong, M., Li, J., Yu, J., Kong, D., 2024. Emerging and legacy per- and polyfluoroalkyl substances (PFAS) in fluorochemical wastewater along full-scale treatment processes: Source, fate, and ecological risk. J. Hazard. Mater. 465, 133270. https://doi.org/10.1016/j.jhazmat.2023.133270.