EFLM Paper

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A comprehensive review on PFAS including survey results from the EFLM Member Societies

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Abstract

Objectives: Per- and polyfluoroalkyl substances (PFASs) are a large class of synthetic chemicals widely used for their unique properties. Without PFAS, many medical device and *in vitro* diagnostic technologies would not be able to perform their intended purposes. Potential health risks associated with exposure to PFAS influence their use in IVD applications. This paper aims to assess the current situation concerning PFAS, including regulations and legislations for their use. It is important to know what happens to (PFAS) at the end of their lives in medical laboratories.

Methods: A survey was conducted in March 2023 to collect information on the potential emission and end-of-life of PFAS-containing medical technologies in the medical laboratories of the EFLM member societies. A series of questions were presented to the EFLM national societies and the results were documented.

Results: Eight respondents participated in the survey, representing EFLM member societies in seven different countries including hospital laboratories, university laboratories, and private laboratories.

Conclusions: PFAS uses in MD and IVD are influenced by several factors, including evolving regulations, advances in technology, safety and efficacy of these substances. Advancements in analytical techniques may lead to more sensitive and precise methods for detecting and quantifying PFAS in biological samples, which can be essential for IVD applications related to biomarker analysis and disease diagnosis. Collaboration among regulatory agencies, industry, research institutions, hospitals, and laboratories on a global scale can aid in establishing harmonized guidelines and standards for the use of PFAS, ensuring consistency and safety within their applications.

Keywords: polyfluoroalkyl substances; perfluoroalkyl substances; REACH; *in vitro* diagnostic devices; medical devices

Introduction

Per- and polyfluoroalkyl substances (PFASs) are part of a vast family of non-polymer and polymeric fluorinated compounds. They all contain carbon-fluorine bonds, which are one of the strongest chemical bonds in organic chemistry. The PFAS family consists of thousands of known and developed compounds, but in general they all include a carbon chain of varying length, studded with fluorine atoms. This chemical structure makes them inherently inert substances, as the bond between carbon and fluorine is so strong, that it is not easily degradable and therefore can bioaccumulate. PFASs have a wide range of different physical and chemical properties. They can be gases, liquids, or solid high-molecular weight polymers. PFASs are widely used as they have unique desirable properties. Products containing PFAS have been used for decades in industrial and consumer products to make them non-stick and water-resistant, including in firefighting foams. They are stable under intense heat. Many of them are also surfactants and are used, for example, as water and grease repellents.

Due to these characteristics, perfluorinated compounds have raised concerns regarding their environmental persistence and bioaccumulation in animals, as well as for their toxicity, including human toxicity. In fact, environmental exposure to perfluorinated compounds (PFCs) is widespread and various PFCs are commonly found in human blood. It has been shown that these chemicals have a relatively long half-life (ranging from 3.8 to 8.5 years) which means that the PFAS can bioaccumulate in the human body,

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and therefore begin to impact the health of the population. To understand the full extent of exposure to PFAS, in the US alone, over 95 % of adolescents and adults have measurable serum levels of various PFAS chemicals [1–3]. Additionally, the migration of these compounds into food has been demonstrated to occur [4].

Per- and polyfluoroalkyl substances (PFASs) are highly persistent synthetic chemicals, some of which have been associated with cancer, developmental toxicity, immunotoxicity, and other health effects. PFASs in grease-resistant food packaging can leach into food and increase dietary exposure [5–9]. Epidemiological and *in vivo* studies in animal models have identified concerns for persistence in serum, other body fluids, and in the environment, as well as potent systemic and reproductive toxicity for perfluorinated compounds of eight carbons in length or greater (C8-PFCs) [7–9]. Specifically, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) can accumulate and persist in the human body for long periods of time, and evidence from animal laboratory studies and human epidemiology studies indicate that exposure to PFOA and/or PFOS can cause cancer, reproductive, developmental (e.g., low birth weight), cardiovascular, liver, kidney, and immunological effects.

The aim of this paper is to assess the current situation concerning PFAS, including both existing regulations and recent developments. Additionally, it initiates the collection of data from a recent survey regarding how laboratory members of the EFLM are addressing the issue of PFAS presence.

PFAS in medical and *in vitro* diagnostic devices

PFAS are either a component of the final medical device or IVD, or a device part of an integral drug-device combination, or a processing aid used during upstream manufacturing. PFAS substances are often key to achieving the required high performance and durability of the products [1].

Blood contact invasive devices – e.g., grafts/covered stents, catheter tubings for infusion of medication and IV fluids and drug-eluting stents (DES) – blood flow within/between arteries and veins and for DES to control drug release to inhibit the vessel from re-narrowing are some examples of how PFAS are used in medical devices. Medication contact components that minimise drug-device interactions and surgical sutures with pledgets made of polytetrafluoroethylene – Teflon (PTFE) that serve as suture abutments when suturing soft tissue represent other contexts where these materials are used. Additionally, PFAS are essential in heart valve operations [1].

PFAS are also present in IVD testing kits for hemostasis products that detect blood coagulation and heat-transfer agents in IVD clinical chemistry diagnostic testing instruments that are essential to the functioning of the instrument. Surfactant properties in *in vitro* diagnostic assays due to the containment of PFAS allow measurement of various parameters such as magnesium concentration in serum, plasma and urine. Fluoropolymers like PTFE and Polyvinylidene fluoride (PVDF) are used in several components for analytical instruments for coating on the dispense tip, tubing and tubing connectors, distributors, seals and gaskets, syringe pump valves, O-rings and sealants [1].

The latest developments in REACH, CLP and PFAS regulations

The existing EU legal framework on chemicals, in particular the REACH and Classification, Labelling and Packaging (CLP) Regulations, are the strictest legislation in the world, regulating chemical substances, affecting industries throughout the world. The Chemicals Strategy suggests that they should be reinforced with targeted revisions of both Regulations to ensure that there is sufficient information on chemicals manufactured or imported into the EU.

Implementation and enforcement of European chemicals legislation is needed to ensure compliance for the whole life cycle of chemicals: production, placing on the market, release, and disposal. Currently almost 30 % of the alerts on dangerous products on the market involve risks due to chemicals. Also, only one third of the registration dossiers of the chemical substances registered by industry under REACH are fully compliant with the information requirements.

The Commission will carry out audits on the enforcement systems of the Member States and make proposals to further strengthen the principles of ‘no data, no market’ and the ‘polluter-pays’.

Substances identified as of very high concern under REACH as well as those listed in Classification, Labelling and Packaging (CLP) Regulations as having chronic effect on health and the environment.

In order to prevent negative long-term effects, the exposure of humans and the environment to these substances of concern should be minimised and substituted as far as possible. The most harmful ones should be especially banned from consumer products and allowed only for proven essential societal use and where no acceptable alternative exist.

The authors of the hazardous chemicals module of the EFLM Task Force-Green and Sustainable Laboratories

(TF-GSL) collected information on the potential emission and end-of-life of medical technologies containing Per- and polyfluoroalkyl substances (PFASs). This information is relevant for preparing to meet the reporting requirements outlined in the upcoming PFAS pre-publication and can be valuable throughout the subsequent 6-month public consultation period [1].

The recent information on the advancements in the EU Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), Classification, Labelling and Packaging (CLP) and PFAS regulations is shared with the EFLM member societies and *in vitro* diagnostic (IVD) and medical devices (MD) industries. This includes updates on changes in regulations, guidelines on compliance, and best practices for managing chemical substances in *in vitro* diagnostic and medical devices.

EFLM and its functional units related to the regulations and legislations represent the interests of its member societies and Corporate members in discussions with regulatory authorities, such as the European Chemicals Agency (ECHA), to ensure that the regulations are practical and feasible for the IVD and MD industry. As the end stage users of chemicals, and representing medical laboratories in Europe, EFLM can advocate for clear guidance on how to comply with REACH and address PFAS concerns effectively.

A close collaboration between EFLM and IVD/MD Industry aims at developing safer and more sustainable materials and chemicals for *in vitro* diagnostic and medical devices. This can involve partnerships with academic institutions and research organizations to explore alternatives to PFAS and other potentially harmful chemicals.

Compliance and Reporting: IVD and MD companies can work with EFLM to develop reporting mechanisms and compliance strategies to meet REACH requirements, especially in cases where it is challenging to replace certain substances and chemicals used *in vitro* diagnostic and medical devices.

EFLM, also in collaboration with IVD and MD industry, intends to organize training sessions and workshops to educate EFLM members about the intricacies of REACH and PFAS regulations, concurrently promoting environmentally responsible practices and encouraging the reduction, recycling, or proper disposal of materials that may contain PFAS or other hazardous substances.

Methods

PFAS are used in medical technologies; however, there is little information available to the industry about what happens to these medical technologies that use PFAS in hospitals and laboratory settings. It is important to know what happens to Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS) at the end of their lives in medical laboratories. Therefore, from the 1st to the 31st of March of 2023, a survey was conducted to collect information on the potential emission and end-of-life of PFA-containing medical technologies in the medical laboratories of the EFLM member societies. A series of questions were made available to the national societies affiliated with EFLM and the results were documented. Questions included information about the type of respondent, country of origin, and treatment and disposal of PFAS, as well as measures to safely dispose of, reduce emissions, and protect workers from these chemicals (Table 1).

Table 1: Survey on per- and polyfluoroalkyl substances (PFASs).

Survey questions and responses
Response ID
Date submitted
Last page
Start language
Seed
Your Name and Surname
Your Laboratory, Institution, City
Select your Country
How are PFAS-containing products treated at the end of life? For example, are they disposed of as clinical waste, are they reused, incinerated, or end up as landfill?
Are there arrangements for PFAS-containing technologies to be taken back by the manufacturer or recyclers?
What are the quantities or volume of PFAS that are collected in laboratories at the end of life of those technologies?
What measures are taken to dispose safely the PFAS-containing technologies?
What measures are taken to control or reduce the emissions of PFAS?
How are workers protected from potential emissions of PFAS during their use phase?

Results

Eight respondents participated in the survey, representing EFLM member societies in seven different countries as depicted in Figure 1: Hungary, Italy, Macedonia, Slovakia,

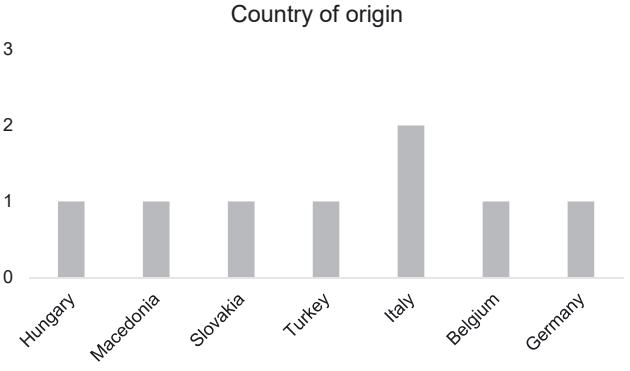

Figure 1: Survey respondents' country of origin.

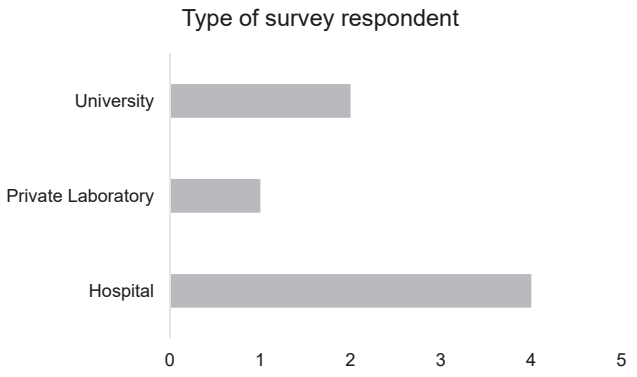

Figure 2: Type of institution of the survey respondents.

Turkey, Belgium, and Germany. These respondents were affiliated with various institutions, including hospital laboratories (four respondents), university laboratories (two respondents), and private laboratories (one respondent), as illustrated in Figure 2.

End-of-life treatment strategies for PFAS in laboratory settings

When considering the disposal of PFAS-containing products at the end of their lifecycle, the majority of respondents (n=5) reported discarding them as clinical waste, while one respondent disposed of them as chemical waste, and two opted for incineration. Notably, all respondents unanimously mentioned that they did not have any arrangements in place for these chemicals to be returned to the manufacturer or to be recycled, except for one respondent who did not utilize PFAS-containing products.

Strategies for volume disposal of PFAS at end-of-life

The general perception regarding the volume of PFAS disposal was notably limited. Four survey participants indicated that it was unknown, while two respondents mentioned that it was a low quantity but did not provide specific volume details.

Measures for the safe disposal, emission reduction, and worker protection from PFAS

In addition to the disposal methods mentioned earlier, which included clinical or chemical waste disposal and incineration of PFAS-containing products, only one respondent suggested an approach involving the gradual phase-out and replacement of existing PFAS with shorter-chain alternatives as a means of safe disposal.

In efforts to minimize PFAS emissions, two respondents indicated a shift toward using alternative materials with similar chemical properties. However, two survey participants did not have any specific strategies in place to control emissions. Notably, one institution mentioned actively engaging with the manufacturer to address this concern.

Regarding the protection of workers from potential PFAS emissions during product use, none of the respondents presented a dedicated protocol for handling PFAS. One respondent justified this by highlighting that PFAS exposure is not limited to occupational settings but extends throughout the entire food chain, necessitating a comprehensive approach. Three of the respondents mentioned adherence to general laboratory safety precautions, such as the use of gloves and goggles.

Discussion and exploring insights with literature review

Toxicological evaluation of PFAS: unraveling potential health impacts

Most published studies on this topic have predominantly centered around PFOA and PFOS, primarily due to their widespread usage. Even though these two chemicals are no longer made in the US, and their use is prohibited in Europe (apart from specific uses where they may not be effectively replaced), people can still be exposed to them.

The International Agency for Research on Cancer (IARC) classified PFOA as “possibly carcinogenic to humans” (Group 2B), based on limited evidence in humans that it can cause testicular and kidney cancer, and limited evidence that it can cause cancer in lab animals [10–12].

Monomers and oligomers may migrate from the polymer substance and determine the hazards associated with that polymer substance [13]. The potential toxicity of the polymer is then related to the released fragments [14].

A comprehensive technical report on short-chain Polyfluoroalkyl Substances (PFAS), excluding PFOS and PFOA, has been meticulously crafted. This report is the culmination of an extensive literature review, addressing human health effects as well as the environmental fate and impact of short-chain PFAS [15]. The publication examines the strategy of uses and applications, exposure and impact on human health and the environment, providing additional information on short-chain PFAS. The objectives of this study have

been to review thoroughly the open literature on short-chain PFAS, assessing their potential impacts on human health and the environment in comparison to long-chain PFAS.

Application of low-concern criteria and regulatory standards to fluoropolymers

It is noteworthy that the toxicological evaluation of the PFAS family has been often performed through a read-across approach (i.e., studies performed for a specific PFAS are considered valid for any other PFAS) [16].

High molecular weight (MW) polymers possess a unique combination of properties and unmatched functional performance critical to the products and manufacturing processes they enable and are irreplaceable in many uses. Concurrently, fluoropolymers have documented safety profiles demonstrating thermal, biological, and chemical stability. They are negligibly soluble in water, non-mobile, non-bioavailable, non-bioaccumulative, and non-toxic and they show low to no leachable compounds. While fluoropolymers fall within the PFAS structural definition, they exhibit distinct physical, chemical, environmental, and toxicological properties when compared to other PFAS [17, 18].

Polytetrafluoroethylene (Teflon, PTFE, CAS 9002-84-0) is an inert, acid- and heat-resistant and multi-state available material for medical applications. There is inadequate evidence for carcinogenicity of Teflon in humans and animals. Therefore, the overall evaluation for the compound is Group 3: the agent is not classifiable as to its carcinogenicity to humans [10]. Based on the ample available literature, there is no evidence of toxicological concern for PTFE. Considering the long history of the use of PTFE, and its various applications in the medical field, it can be concluded that it is safe to use it for medical applications.

However, the discussion concerning possible human toxicity for high molecular weight PFAS is open. Lohman et al. reported that fluoropolymer particles of Teflon powders vary in size. Teflon polymers may contain both high and low molecular weight fractions, potentially containing hazardous residual monomers and oligomers [19]. Fluoropolymers are made of one or several types of monomers. During the synthesis, incomplete polymerization will result in residual monomers and oligomers, and smaller ‘polymers’ with up to about 100 monomer units. These and other synthesis by-products are not bound to the polymers and may be released to air upon heating during manufacturing and processing (including sintering) and to water through wastewater streams. Many ultrashort-chain fluorinated by-products are highly volatile, and therefore difficult to remove in filters or liquid scrubber baths. Fluoropolymer particles vary in size, and may contain and transport residual monomers/oligomers long distances from their emission sources. The production of many fluoropolymers still requires the use of PFAS as surfactants or as monomers, which causes releases to the environment during manufacture, and thus may pose a risk to human health and the environment. Polymer nanoparticles have membrane crossing capabilities. There is no sufficient evidence to consider fluoropolymers as being of low concern for environmental and human health. The group of fluoropolymers is too diverse to warrant a blanket exemption from additional regulatory review. Their extreme persistence and the emissions associated with their production, use, and disposal result in a high likelihood for human exposure as long as uses are not restricted. Concluding that some specific fluoropolymer substances are of low concern for environmental and human health can only be achieved by narrowly focusing on their use phase.

Regulatory legislations concerning PFAS

Regulatory actions have been initiated by several agencies. The FDA and US Environmental Protection Agency (EPA) reached voluntary agreements with industry to phase out some short-chain perfluorinated compounds from all uses, particularly those involving direct contact with food. In the US EPA agreement, the industry pledged to eliminate C8--PFCs from emissions and products by 2015. In 2013, the FDA reached a voluntary agreement with the manufacturers of five perfluorinated food contact substances (FCSs) to eliminate the production of these compounds [15, 20, 21].

Since the early 2000s, laws, policies, and regulations have been implemented with the aim to reduce the prevalence of PFAS in the environment and exposure to PFAS [15, 17, 22, 23]. EPA has published a strategic roadmap document concerning stricter regulation and out-phasing of some PFAS [24, 25].

European Chemicals Agency (ECHA) has an open procedure for PTFE registration [26, 27], while the monomer (tetrafluoroethylene) used in the synthesis of fluorinated ethylene propylene (FEP) is registered as having chronic toxicity and carcinogenicity, including findings from human epidemiological studies [28]. ECHA currently maintains an ongoing procedure for the restriction on the manufacture, placement on the market, and use of PFASs [29].

United States Environmental Protection Agency (EPA) proposed to designate two per- and polyfluoroalkyl substances (PFAS) – perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), including their salts and structural isomers – as hazardous substances under the Comprehensive Environmental Response, Compensation,

and Liability Act (CERCLA), also known as Superfund, in late 2022 [30, 31]. EPA rulemaking endeavors to enhance transparency regarding the release of these harmful chemicals, empowering the agency to hold polluters accountable for the cleanup of their contamination. The rulemaking requires entities to immediately report releases of PFOA and PFOS that meet or exceed the reportable quantity to the National Response Center, state or Tribal emergency response commission, and the local or Tribal emergency planning committee (local emergency responders). Entities would not be required to report past releases of PFOA or PFOS as they were not yet listed as hazardous substances.

The Interstate Technology and Regulatory Council (ITRC) is a state-led coalition dedicated to minimizing barriers to the adoption of innovative environmental technologies and approaches. Its mission is to reduce compliance costs, maximize clean-up efficacy, and operate as a program under the US Environmental Research Institute.

PFAS: current restrictions

Various regulations and restrictions are applied to PFAS substances in both the EU and the US (Table 2). In 2017, the Swedish Chemicals Agency (KEMI) and the German Environment Agency (UBA) jointly proposed the restriction of six PFAS variants under REACH. This recommendation stems from their association with various health concerns, extremely slow degradation, and significant bioaccumulation potential. This marked the initiation of efforts to regulate their use, culminating in the EU's final decision in February 2023 to phase out 200 PFAS through a ban, in phases. While the ban specifically targets six long-chained PFAS chemicals, characterized by molecules containing between 9 and 14 fluorinated carbon atoms, the overall restriction encompasses 200 PFAS variants. This is because they can all be broken down into one of the banned six substances [32].

The EU-wide restriction on specific perfluorocarboxylic acids (C9-C14 PFCAs), a subgroup of per- and polyfluoroalkyl substances (PFAS), has come into effect starting February 25, 2023. After that date, PFCAs are prohibited from being placed on the market or used in most applications. "Certain uses have been granted extended transition periods [33]. The restriction will reduce or prevent exposure of people and the environment to PFCAs and avoid the regrettable substitution of PFOA, which has been globally banned since July 2020. It is in line with the EU's aspirations to phase out all non-essential uses of PFAS under the Chemicals Strategy for Sustainability. Canadian authorities have also proposed to list long-chain PFCAs as persistent organic pollutants (POPs) under the Stockholm Convention [34].

Furthermore, in March 2023, the US Environmental Protection Agency (EPA) proposed a PFAS drinking water regulation. The legally enforceable Maximum Contaminant

Table 2: Regulations and restrictions applied to PFAS substances in EU and USA.

PFAS substance	EU	US EPA
PFOS (Perfluorooctane sulfonic acid and its derivatives) (CAS No. 1763-23-1)	Restricted under EU Persistent Organic Pollutants (POPs) Regulation (EU) 2019/1021 (restricted use allowed until 2025)	Maximum contaminant level (MCL) limit in national drinking water regulation: 4.0 parts per trillion
PFOA (Perfluorooctanoic acid, its salts and related compounds) (CAS No. 335-67-1)	Banned under Regulation (EU) 2020/784, amending Annex I to Regulation (EU) 2019/1021	Maximum contaminant level (MCL) limit in national drinking water regulation: 4.0 parts per trillion
PFHxS (Perfluorohexanesulfonic acid, its salts and related compounds) (CAS No. 355-46-4)	Included in the Stockholm Convention to eliminate their use. PFHxS will be restricted in the EU by the POPs Regulation	"Group" MCL for PFHxS, PFNA, PFBS and GenX[a] chemicals at 1.0 (unitless)
PFCA (Perfluorinated carboxylic acids [C9-14], its salts and related substances)	Restricted in EU/EAA from February 2023	Long-chain PFCA, such as PFOA restricted as noted above; While persistent in the environment, PFCA chemicals with fewer than eight carbons, such as perfluorohexanoic acid (PFHxA), are stated by EPA to be generally less toxic and less bio- accumulative in wildlife and humans
PFCA (Perfluorinated carboxylic acids [C9-21])	Being considered for inclusion in the Stockholm convention and consequent global elimination	
PFHxA (Perfluoro-n-hexanoic acid, its salts and related substances) (CAS No. 307-24-4)	European Commission is currently working on an amendment of Annex XVII to REACH to restrict this group of substances	
PFNA (Perfluorononanoic acid) (CAS No. 375-95-1)	Restricted as part of PFCAs	"Group" MCL for PFHxS, PFNA, PFBS and GenX[a] chemicals at 1.0 (unitless)
PFBS (Perfluorobutanesulfonic acid) (CAS No. 375-73-5)	Regulated under REACH Annex lII, Directive 98/24/EC and Directive 94/33/EC, highlighted by ECHA	

[a]GenX chemicals are part of PFAS; it is a trade name used for the processing aid technology to make high-performance fluoropolymers.

Level (MCL) for the six PFAS variants is set between 1.0 and 4.0 parts per trillion (or 4.0 ng/L) [35].

PFAS in drinking water

Although PFAS compounds typically have low solubility in water, their unique chemical properties make them resistant to removal by conventional drinking water treatment technologies. As a result, their presence in water is widespread. EPA researchers have been studying a variety of technologies at bench-, pilot-, and full-scale levels to determine which methods work best to remove PFAS from drinking water. Specific technologies have been identified for effectively removing PFAS from drinking water, with a focus on perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), the most extensively studied compounds among PFAS. Those technologies include activated carbon adsorption, ion exchange resins, and high-pressure membranes. These technologies are applicable in various settings, including drinking water treatment facilities, water systems within hospitals or individual buildings, and even at the point-of-entry in homes – where water enters the home – or at the point-of-use, such as in a kitchen sink or a shower.

High molecular weight fluoropolymers

High molecular weight fluoropolymers, exceeding 100,000 Da, demonstrate practical insolubility in water and are impervious to long-range transport. Their molecular size prevents them from crossing cell membranes, rendering them non-bioavailable and non-bioaccumulative. This characteristic is substantiated by toxicology studies, particularly on polytetrafluoroethylene (PTFE – Teflon). Henry et al. conducted a thorough examination of distinct classes of fluoropolymers, leading to the conclusion that fluoropolymers are inherently different from other polymeric and nonpolymeric PFAS. This distinction underscores the need to separate fluoropolymers for hazard assessment or regulatory purposes [17]. As highlighted earlier, it is scientifically inappropriate to group fluoropolymers with all classes of PFAS for 'read-across' or structure–activity relationship assessment. Clinical studies on patients with permanently implanted PTFE cardiovascular medical devices reveal no signs of chronic toxicity or carcinogenicity. Additionally, there is no evidence of reproductive, developmental, or endocrine toxicity. High molecular weight fluoropolymers meet widely accepted assessment criteria to be classified as 'polymers of low concern' (PLC). PTFE-based materials exhibit inertness, with insignificant releases of monomers or constituents, and have not been associated with skin sensitization or irritation [36].

Recent regulations primarily address the monomeric products of fluoropolymers, specifically highlighting concerns related to the release of significant monomers such as hydrogen fluoride, carbonyl fluoride, and perfluoroisobutylene, particularly under high-temperature conditions [25].

PFAS regulations: implications for medical devices and IVD reagents

How do the imposed restrictions and proposed maximum contaminant levels (MCLs) affect medical devices and IVD reagents?

Numerous medical devices, including *In Vitro* Diagnostics (IVD), have coatings of PTFE composed of PFAS. This application enhances the hydrophobic nature of the device's surface, preventing the adherence of cells, fluids, or blood components.

In the assessment of medical device safety, a crucial factor is the evaluation of biocompatibility. Given the short contact durations often, a comprehensive chemical analysis is not typically conducted. The risk of chemicals, such as PFAS, leaching from a device and exposing the patient is contingent upon the duration of contact. With specific limits established for certain PFAS compounds, it becomes logical to consider regulating their exposure in medical devices. This aligns with the conventional approach to assessing toxicological risks, relying on established limits provided by guidance documents or government agencies.

Yet, it is crucial to scrutinize the applicability of these limits to medical devices, especially concerning substances like perfluorooctanoic acid (PFOA), one of the six PFAS under regulation, with an allowable limit of 4 ng/L in drinking water. The question that arises is whether this limit can be reasonably applied to a medical device with a PFAS coating. Furthermore, if our primary concern is the environmental impact, we must determine the appropriate threshold for acceptable PFAS levels in medical devices in general.

Medical device manufacturers that abstain from using PTFE or other PFAS-containing chemicals in their processes may find compliance with these restrictions to be a straightforward process, involving a simple declaration that these substances are not utilized in their devices. For manufacturers utilizing PFAS, additional justification for their necessity, including their superiority to alternative chemicals, may become imperative. This, coupled with the actual

testing for the restricted PFAS substances, presents a complex challenge. Meeting the MCLs set by the US EPA for drinking water appears to be exceptionally challenging, potentially posing difficulties in reaching these analytical thresholds for medical devices."

Finding alternatives

Without PFAS, medical technologies would struggle to fulfil their intended purposes. In some cases, the only viable alternative is another type of PFAS. Besides PFAS, it is unlikely that any alternative would match or surpass their functionalities. While the unique characteristics of PFAS that make these substances the preferred choice are the exact ones that impose a burden on the environment. As an example, a non-PFAS replacement would likely lead to, e.g., increased incidence of puncture wounds, no deliverability of the guidewire or catheter to the target lesion or other adverse events and increased incidence of device malfunction and inability of the surgeon to sufficiently visualize the surgical site. In cases where no alternative is available, and the impending PFAS restriction does not offer a derogation, it is likely to result in a shortage of supply for these essential technologies and services [1, 37].

Many applications of PFAS in medical technologies contribute to the improvement and, ultimately, the extension of patients' lives. Invasive medical technologies, which come into contact with the human body, are subject to strict regulations governed by sectoral legislations. Manufacturers are obligated to uphold a high standard in risk management, design, safety, quality, performance, as well as the assessment and validation of alternatives. Ensuring that technologies comply with sectoral legislation is a time-consuming process, and when alternatives require testing and validation, this further extends the duration. Ample transitional periods are essential to ensure that alternative technologies, where technically feasible, can be made available to users [37].

Even if medical technologies are permitted to continue using PFAS due to the absence of suitable alternatives, the medical market may not be large enough for PFAS manufacturers to sustain. Any restriction will impact the medical industry, regardless of timelines, as manufacturers have already begun discontinuing the production of these materials [1, 36, 37].

Future perspectives

The future perspectives of using PFAS in MD and IVD will likely be influenced by several factors, including evolving regulations, advances in technology, and the ongoing research on the safety and efficacy of these substances.

FDA, in US, and ECHA and EMA in Europe will introduce stricter guidelines or restrictions on the use of certain PFAS in medical devices, including IVDs. This could lead to the phase-out or replacement of specific PFAS in IVD products.

However, the development of PFAS alternatives may result particularly difficult. These alternatives should provide similar performance without the potential health and environmental risks associated with some PFAS compounds.

Advancements in analytical techniques may lead to more sensitive and precise methods for detecting and quantifying PFAS in biological samples, which can be essential for IVD applications related to biomarker analysis and disease diagnosis.

Ongoing studies will continue to assess the potential health risks associated with exposure to PFAS, which can influence the decision to use these substances in IVD applications.

IVD manufacturers may explore tailored approaches, using specific PFAS compounds only when necessary for particular diagnostic tests. This approach could minimize exposure while still leveraging the unique properties of PFAS in certain situations.

Environmental considerations

Increasing awareness of the environmental impact of PFAS may drive efforts to reduce their use in IVD products, as well as other healthcare applications. Sustainability considerations may encourage the development of more eco-friendly alternatives. Public Awareness may lead to consumer demand for PFAS-free IVD products. This could influence IVD manufacturers to prioritize alternatives.

Conclusions

In conclusion, fostering collaboration among regulatory agencies, industry stakeholders, research institutions, hospitals, and laboratories on a global scale can aid in establishing harmonized guidelines and standards for the use of PFAS, ensuring consistency and safety within its applications.

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References

1. MedTech Europe PFAS briefing 27 February 2023. Available from: https://www.eflm.eu/upload/docs/230227_MTE_PFAS_Briefing_DRAFT_V3.pdf.
2. Kato K, Wong LY, Jia LT, Kuklenyik Z, Calafat AM. Trends in exposure to polyfluoroalkyl chemicals in the U.S. population: 1999–2008. Environ Sci Technol 2011;45:8037–45.
3. Olsen GW, Lange CC, Ellefson ME, Mair DC, Church TR, Goldberg CL, et al. Temporal trends of perfluoroalkyl concentrations in American red cross adulthood donors, 2000–2010. Environ Sci Technol 2012;46:6330–8.
4. Begley TH, White K, Honigfort P, Twaroski M, Neches R, Walker RA. Perfluorochemicals: potential sources of and migration from food packaging. Food Addit Contam 2005;22:1023–31.
5. Rice PA. C6-Perfluorinated compounds: the new grease proofing agents in food packaging. Curr Environ Health Rep 2015;2:33–40.
6. Houde M, Martin JW, Letcher RJ, Solomon KR, Muir DC. Biological monitoring of polyfluoroalkyl substances: a review. Environ Sci Technol 2006;40:3463–73.
7. Loi EI, Yeung LW, Mabury SA, Lam PK. Detections of commercial fluorosurfactants in Hong Kong marine environment and human blood: a pilot study. Environ Sci Technol 2013;47:4677–85.
8. Mclachlan MS, Holmstrom KE, Reth M, Berger U. Riverine discharge of perfluorinated carboxylates from the European continent. Environ Sci Technol 2007;41:7260–5.
9. Buhrke T, Kibellus A, Lampen A. In vitro toxicological characterization of perfluorinated carboxylic acids with different carbon chain lengths. Toxicol Lett 2013;218:97–104.
10. IARC Monographs. Some chemicals used as solvents and in polymer manufacture. IARC Monographs on the evaluation of carcinogenic risks to humans. Lyon: IARC; 2016, vol 110.
11. Loveless SE, Slezak B, Serex T, Lewis J, Mukerji P, O'Connor JC, et al. Toxicological evaluation of sodium perfluorohexanoate. J Toxicol 2009;264:32–44.
12. IARC Monographs. Perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS). Lyon: IARC Monograph; 2023, vol 135. Available from: https://monographs.iarc.who.int/iarc-monographs-volume-135/.
13. Postle M, Holmes P, Camboni M, Footitt A, Tuffnell N, Blainey M, et al. Review of REACH with regard to the registration requirements on polymers – final report prepared for the European Commission (DG environment), in collaboration with PIEP. Bio by Deloitte. 2012; 070307/2011/602175/SER/D3.
14. Lithner D, Larsson A, Dave G. Environmental and health hazard ranking and assessment of plastic polymers based on chemical composition. Sci Total Environ 2011;409:3309–24.
15. Kjølholt J, Jensen AA, Warmning M. Short-chain polyfluoroalkyl substances (PFAS). A literature review on human health effects and environmental fate and effect aspects of short-chain PFAS. Copenhagen: Danish Ministry of the Environmental. Danish Environmental Protection Agency. Environmental project no. 1707; 2015.
16. Xie X. Interpretation on how to properly adopt read-across approach during substance registration and matters need attention-regulatory news-chemicals-CIRS group. Hangzhou, China: CIRS; 2022. Available from: https://www.cirs-group.com/en/chemicals/interpretation-on-how-to-properly-adopt-read-across-approach-during-substance-registration-and-matters-need-attention.
17. Henry BJ, Carlin JP, Hamamerschmidt JA, Buck RC, Buxton LW, Fiedler H, et al. A critical review of the application of polymer of low concern and regulatory criteria to fluoropolymers. Integrated Environ Assess Manag 2018;14:316–34.
18. Korzeniowski SH, Buck RC, Newkold RM, El Kassmi A, Laganis E, Matsuoka Y, et al. A critical review of the application of polymer of low concern regulatory criteria to fluoropolymers II: Fluoroplastics and fluoroelastomers. Integrated Environ Assess Manag 2022;19:326–54.
19. Lohmann R, Cousins IA, DeWitt JC, Gluge J, Goldenman G, Herzke D, et al. Are fluoropolymers really of low concern for human and environmental health and separate from other PFAS? Environ Sci Technol 2020;54:12820–8.
20. Perfluorooctanoic acid and fluorinated telomers: new chemical review of alternatives for PFOA and related chemicals. Hangzhou, China: US EPA; 2014. Available from: http://www.epa.gov/oppt/pfoa/pubs/altnewchems.html#3.
21. Rice PA, Bandele OJ, Honigfort P. Perfluorinated compounds in food contact materials. Toxicants in food packaging and household plastics. Exposure and health risks to consumers. In: Snedeker SM, editor. Molecular and integrative toxicology. New York: Humana Press (Springer); 2014:177–20 pp.
22. Brennan NM, Evans AT, Fritz MK, Peak SA, von Holst HA. Trends in the regulation of per-and polyfluoroalkyl substances (PFAS): a scoping review. Int J Environ Res Publ Health 2021;18:10900.
23. Conder JM, Hoke RA, de Wolf W, Russell MH, Buck RC. Are PFCAs bioaccumulative? A critical review and comparison with regulatory criteria and persistent lipophilic compounds. Environ Sci Technol 2008;42:995–1003.
24. External peer review draft: proposed approaches to the derivation of a draft maximum contaminant level goal for perfluorooctanoic acid (PFOA) (CASRN 335-67-1) in drinking water. U.S. EPA (U.S. Environmental Protection Agency). EPA-822-D-21-001. Washington, DC: EPA, Office of Water; 2021a. Available from: https://sab.epa.gov/ords/sab/f?p=100:18:16490947993:::RP,18:P18_ID:2601.
25. External peer review draft: proposed approaches to the derivation of a draft maximum contaminant level goal for perfluorooctane sulfonic acid (PFOS) CASRN 1763-23-1 in drinking water. U.S. EPA (U.S. Environmental Protection Agency). EPA-822-D-21-002. Washington, DC: EPA, Office of Water; 2021a. Available from: https://sab.epa.gov/ords/sab/f?p=100:18:16490947993:::RP,18:P18_ID:2601.
26. Procedure for polytetrafluoroethylene (PTFE) registration. Helsinki: European Chemicals Agency (ECHA); 2023. Available from: https://echa.europa.eu/et/substance-information/-/substanceinfo/100.120.367.
27. Drohmann D, Sales J, Hernández F, Dickens L. Regulatory management option analysis for fluoropolymers. Fluoropolymers group (FPG) of plastics Europe Brussels; 2021. Available from: https://fluoropolymers.plasticseurope.org/application/files/5416/5104/8333/20211104_FP_RMOA_Final_3.pdf.
28. Consonni D, Straif K, Symons KM, Tomenson JA, van Amelsvoort LG, Sleeuwenhoek A, et al. Cancer risk among tetrafluoroethylene synthesis and polymerization workers. Am J Epidemiol 2013;178:350–8.

29. European Chemicals Agency (ECHA). Submitted restrictions under consideration. Helsinki; 2023. Available from: https://echa.europa.eu/en/restrictions-under-consideration/-/substance-rev/72301/term.
30. Mulkiewicz E, Jastorff B, Skladanowski AC, Kleszczyński K, Stepnowski P. Evaluation of the acute toxicity of perfluorinated carboxylic acids using eukaryotic cell lines, bacteria and enzymatic assays. Environ Toxicol Pharmacol 2007;23:279–85.
31. Proposed designation of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) as CERCLA hazardous substances. Washington D.C.: United States Environmental Protection Agency (EPA); 2022. Available from: https://www.epa.gov/superfund/proposed-designation-perfluorooctanoic-acid-pfoa-and-perfluorooctanesulfonic-acid-pfos.
32. Proposed restriction of 200 PFAS intended to prevent regrettable substitution. ChemSec 2018. Sweden, European Union, Germany. Available from: http://mm.chemsec.org/proposed-restriction-of-200-pfas-intended-to-prevent-regrettable-substitution/.
33. Registry of restriction intentions until outcome. Helsinki: European Chemicals Agency (ECHA); 2023. Available from: https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e18195edb3.
34. Health science summary: long-chain perfluorocarboxylic acids (PFCAs), their salts and related compounds. Seventeenth meeting of the Persistent Organic Pollutants Review Committee (POPRC-17); 2021. Available from: https://www.canada.ca/en/health-canada/services/chemical-substances/chemicals-management-plan/initiatives/health-science-summary-long-chain-perfluorocarboxylic-acids-salts-related-compounds.html.
35. Per- and polyfluoroalkyl substances (PFAS) proposed PFAS national primary drinking water regulation. Washington D.C.: United States Environmental Protection Agency (EPA); 2023. Available from: https://www.epa.gov/sdwa/and-polyfluoroalkyl-substances-pfas.
36. Margerrison E, Argentieri M, Lucas SR, Kommala D. Medical device material performance study. PTFE safety profile. Report details. Prepared for U.S. FDA Center for devices and radiological health. Emergency care research institute (ECRI) Corporate Governance Project; 2021. Available from: https://www.fda.gov/media/158495/download.
37. MedTech Europe position on the proposal for A REACH universal PFAS restriction; 2023. Available from: https://www.medtecheurope.org/resource-library/medtech-europe-position-on-the-proposal-for-a-reach-universal-pfas-restriction/.