Review Article

A Review of Perfluoroalkyl Acids (PFAAs) in terms of Sources, Applications, Human Exposure, Dietary Intake, Toxicity, Legal Regulation, and Methods of Determination

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Per- and polyfluoroalkyl substances (PFASs) are widely distributed across the world and are expected to be of concern to human health and the environment. The review focuses on perfluoroalkyl acids (PFAAs) and, in particular, on the most frequently discussed perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkane sulfonic acids (PFSAAs). In this study, some basic information concerning PFASs is reviewed, focusing mainly on PFAAs (perfluoroalkyl acids). We have made efforts to systemize their division into groups according to chemical structure, describe their basic physicochemical properties, characterize production technologies, and determine potential human exposure routes with particular reference to oral exposure. A variety of possible toxicological effects to human health are also discussed. In response to increasing public concern about the toxicity of PFAAs, an evaluation of dietary intake has been undertaken for two of the most commonly known PFAAs: perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). As summarized in this study, PFAAs levels need further assessment due to the science-based TWI standards laid down by the EFSA's CONTAM Panel regarding the risk to human health posed by the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food (tolerable weekly intakes of PFOA and PFOS set up to 6 ng·kg⁻¹·bw·week⁻¹ and 13 ng·kg⁻¹·bw·week⁻¹, respectively). Current legislation, relevant legislation on PFAAs levels in food, and the most popular methods of analysis in food matrices are described.

1. Introduction and Objectives

PFAAs are ubiquitous in various environmental media and are distributed globally; due to their ability to migrate, they can be transferred from water to soils and taken up by plants and thus enter the food chain. These substances enter the human organism through the digestive and respiratory systems and the skin; moreover, they are not metabolized and instead accumulate in the body [1]. Furthermore, direct and indirect contact with PFAA-containing materials such as oil and water-resistant materials, detergents, paints, and fabrics causes high exposure of humans to their toxic properties [2]. In living organisms, high absorption level and low elimination

rates of perfluoroalkyl substances have been observed [3]. Biomonitoring of perfluoroalkyl substances in the human body started in 2000. Many PFAAs have been detected in human matrices, most commonly in blood samples [4, 5]. In recent years, a number of papers have confirmed the occurrence of these compounds in breast milk [6], seminal plasma [7], umbilical cord blood [8], and liver [9]. However, in contrast to most other POPs, they do not tend to accumulate in fat tissues but bind to serum albumin and other cytosolic proteins and accumulate mainly in the liver, the kidneys, and bile secretion [10, 11].

As chemical contamination is a global food safety issue, this review is mainly focused on current problems related to

PFAAs content in food and growing concern about the effects of their intake. The overarching objective of this study is to unify terms associated with consumer health and food safety. Various points are discussed in response to the issues raised: PFAAs' high persistence, environmental mobility, human toxicity, widespread presence in food of plant and animal origin, and poor removability from contaminated matrices. On the basis of existing scientific research data and a review of current legislative acts, the most important issues related to food contaminated with PFAAs are described and discussed.

2. General Characteristics

Per- and polyfluoroalkyl substances (PFASs) are a group of fluorinated, organic, man-made chemicals; they do not occur naturally in the environment. In recent years, PFASs have commonly been referred to as PFCs (an abbreviation of per- and polyfluorinated chemicals, also known as perfluorocarbons), but this ambiguity in abbreviation may have led to misunderstandings. These groups share multiple common denominators, such as the content of fluorinated carbon atoms in the molecule, their stability in the environment, and their anthropogenic origin. While there are obvious similarities, PFASs differ from PFCs in many significant respects. First of all, PFCs contain only carbon and fluorine atoms, whereas PFAS molecules may also include oxygen, hydrogen, sulfur, and nitrogen atoms. These groups of pollutants are released into the environment from a variety of sources. The PFC group includes compounds which exhibit PFAS-like toxicity; nevertheless, some of them have highly desirable characteristics and are used in medicine and biotechnology [12, 13]. It has been shown that direct exposure to PFASs has a number of adverse health effects in laboratory animals and humans. Perfluoroalkyl compounds (fully fluorinated carbon chain) tend to be more persistent and toxic in the environment in comparison to polyfluoroalkyl compounds (carbon chain with some C-H bonds among C-F bonds) [14].

The family of perfluoroalkyl substances consists of many individual homologous members and isomers. The general classification of per- and polyfluoroalkyl substances relies on their division into polymeric and nonpolymeric chemicals [15]. This synthesis paper focuses mainly on perfluoroalkyl acids (PFAAs), especially perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkane sulfonic acids (PFSAAs), and the potential risks to human health that arises from their high persistency and ability to bioaccumulate in trophic chains (especially in food) and the consequent occurrence of toxic effects. Perfluoroalkyl acids constitute a group of chemicals of the perfluoroalkyl substances family. PFCAs and PFSAAs are the most commonly known and studied components of the perfluoroalkyl substances family. Nevertheless, the family of fluoroalkyl substances covers many individual homologous members and isomers such as fluoropolymers, side-chain fluorinated polymers, fluoropolyethers, ethers, sulfonyl fluorides, sulfonamides, fluorides, iodides, aldehydes, aldehyde hydrates, fluorotelomers, phosphonic acids, phosphinic acids, and sulfinic acids. The general classification of perfluoroalkyl substances into polymeric and nonpolymeric chemicals is described in detail in Buck et al.'s publication [14].

3. Physicochemical Characteristics of PFAAs

Buck et al. and coworkers specified perfluoroalkyl substances as aliphatic chemicals that contain one or more carbon atoms in the carbon chain in which all attached hydrogen atoms (in the nonfluorinated molecule) have been replaced by fluorine atoms; only H atoms whose replacement would change the character of the molecule are an exception. According to this rule, the perfluoroalkyl moiety is C_nF_{2n+1} [14]. The C-F bond in perfluoroalkyl molecules is very strong (~ 485 kJ/mol) due to the differences between hydrogen and fluorine atoms, which stems from their physicochemical properties. Fluorine, in contrast to hydrogen, has higher ionization potential, electronegativity, and electron affinity and lower polarizability [2]. The values of these parameters for both elements are summarized in Table 1.

The high electronegativity (the highest in the periodic table), the high ionization potential, and the simultaneous low polarizability of fluorine make the carbon-fluorine bond very stable with a weak tendency to inter- and intramolecular interactions [16]. PFAAs are a diverse group of compounds with high thermal, chemical, and biological inertness [17, 18].

Perfluoroalkyl substances remain stable in the presence of acids, bases, oxidants, and reductants. Furthermore, PFAAs exhibit high resistance to degradation by photolytic or metabolic processes and by microbial decomposition. These processes are limited by strong carbon-fluorine and carbon-carbon bonds in the molecule [19].

Thermal degradation of PFAAs occurs at very low rates, e.g., common fluoroalkylcarboxylic and fluoroalkane sulfonic acids may be heated to a temperature of as much as 400°C without significant decay [2]. However, according to the studies of Taylor and Yamada conducted in 2003 at the University of Dayton Research Institute, PFOS (perfluorooctane sulfonic acid), which is the most common perfluoroalkyl acid, may have lower thermal stability in contrast to other PFAAs containing C-C and C-F bonds due to the presence of a carbon-sulfur bond [20]. Nevertheless, fluorochemicals are considered to preserve their properties under the presence of both high and low temperatures and UV radiation, thus allowing them to be applied in extreme conditions.

The double amphiphilic nature of PFAAs is due to their molecular structure. These compounds consist of a polar water-soluble (hydrophilic) group attached to a water-insoluble (oleophilic) alkyl chain. Individual PFAAs differ in terms of the perfluorinated carbon chain length and in the functionality of the end group, which can be neutral or positively or negatively charged, thus creating nonionic, cationic, and anionic substances, respectively. Their hydrophobicity, hydrophilicity, and ability to form ions of different charges make them water, oil, grease, and fat repellent and able to reduce surface tension [21–23].

4. Production and Application of PFAAs

Three major large-scale PFAAS manufacturing processes have been distinguished: electrochemical fluorination (ECF), telomerization, and polymerization [3, 24].

ECF technology was first applied in the Simons process by 3M Company in the 1940s [25]. The general synthesis

TABLE 1: Atomic characteristics of fluorine and hydrogen.

Parameter	Fluorine	Hydrogen
Ionization potential ($\text{kJ}\cdot\text{mol}^{-1}$)	1676	1312
Electron affinity ($\text{kJ}\cdot\text{mol}^{-1}$)	328	72.8
Electronegativity (Pauling units)	3.98	2.20
Polarizability α (10^{-24} cm^3)	0.557	0.667

process based on ECF that is used to produce PFOS, PFOA (perfluorooctanoic acid), and their derivatives is shown in Figures 1(a) and 1(b).

In this process, raw materials such as linear alkane sulfonyl fluorides (A) or linear alkane acyl fluorides (B) are transformed into perfluorinated sulfonyl fluorides and acyl fluorides as a result of fluorination in hydrofluoric acid solution. These intermediate products are further converted into final products including perfluoroalkane sulfonic acids (PFSA) (A) and perfluoroalkyl carboxylic acids (PFCA) (B) [2, 14]. This process is highly nonselective, and target chemicals are accompanied with mixture of linear, branched, and cyclic fluorocarbon homologues with different numbers of carbon atoms [24, 26].

Another highly relevant industry process for manufacturing PFAAs is the telomerization process. This technology is most frequently used in the production of fluorotelomer substances, mainly fluorotelomer alcohols (FTOHs), fluorotelomer olefins (FTOs), and acrylates (FTAs) [3, 17]. This technology involves a free-radical reaction between tetrafluoroethylene (TFE) and a perfluoroalkyl iodide substance, mainly pentafluoroethyl iodide (PFEI) in order to yield a mixture of linear perfluoroalkyl iodides (PFAIs). In the second step, a follow-up reaction with ethylene gives rise to fluorotelomer iodides (FTIs), which are starting materials in the further derivatization of final products [2, 14]. The general telomerization process is shown in Figure 2.

Another approach used for industrial manufacturing of PFAAs is polymerization, which is predominantly used to produce fluoropolymers, mainly polytetrafluoroethylene (PTFE), at global scale [3, 17]. This process is based on radical polymerization of monomers of tetrafluoroethylene (TFE) in the presence of an initiator, in accordance with Figure 3 [27].

PFAAs are extensively applied in various industrial and consumer goods. Fluorosurfactants are more effective and more efficient in terms of surface activity than their hydrogenated analogues. Liu and Lee [28] observed that water solubility decreased in line with an increase of the chain length for $n:2$ FTOHs ($n = 4-10$) by about 0.78 log units [28]. This outstanding aptitude of fluorocarbon chains leads to the formation of effective barrier films against non-fluorinated media such as water, grease, fat, dirt, and microorganisms. These and other properties such as high thermal, chemical, and biological stabilities make perfluoroalkyl acids a perfect material for many industrial and domestic applications [29, 30]. Moreover, PFAAs may act as catalysts for various chemical processes such as polymerization and oligomerization and, due to their persistence, they can be successfully applied in any processes carried out under extreme conditions [16]. Typical applications

encompass the automotive and aviation industries (hydraulic fluids, low-friction bearings and seals, and materials for car interiors), construction technology (paints and coating additives and glues), biocides (herbicides and pesticides), electronics (flame retardants, weather resistant coatings, and insulators), household products (wetting and cleaning agents, nonstick coatings, and components of cosmetic formulations), medical articles (stain and water repellents in surgical equipment, raw materials for implants), and packaging materials (oil and grease repellent materials) and textiles (impregnating agents for fabrics, leather, and breathable membranes) [2, 31, 32].

5. Methods of Determining PFAAs

Environmental exposure and growing concerns over food safety associated with the occurrence of PFAAs in trophic levels represent significant reasons for the development of analytical methods. Due to trace levels of PFAAs in the analyzed matrices, there is a strong need to implement the best available techniques with high selectivity and sensitivity. Unrestricted access to advanced equipment and high-purity chemicals make it possible to achieve 70–120% recovery rates of measured analytes with quantitation limits of $1 \mu\text{g}\cdot\text{kg}^{-1}$, as described in Commission Recommendation 2010/161/EU [33]. Nevertheless, difficulties can arise in identifying these substances and achieving reliable measurement because of the wide range of PFAAs, the complexity of matrices, and problems with blanks and sample contamination during analytical procedures. For this reason, analytical chemistry is still focused on improvements in experimental design, the creation of new measurement tools, and optimization and validation of analytical procedures.

Choice of adequate sample preparation procedures in the case of complex biological matrices like food is crucial in preventing the undesired matrix effect. Effective isolation of analytes from the sample matrix and removal of bulk coextracts from the crude extract constitute sample treatment steps which assist in alleviating any negative impact of the interfering components of the matrix. Labelled internal standards are commonly added just before the analytical approach, and further clean-up procedures are applied to decrease the matrix effect [34].

Biological samples are regarded as a very complex matrix, and different kinds of sample preparation and extraction procedures have been used. The most common extraction techniques that are widely used in food safety studies are ionic-pair extraction employing methyl tert-butyl ether (MTBE) as an extraction solvent [35], solid-liquid extraction using methanol or acetonitrile as an extraction solvent [36, 37], solid-acidic liquid extraction with formic or acetic acid as an extraction agent [38, 39], and solid-alkaline liquid extraction utilizing alkaline methanol (with sodium hydroxide or ammonium hydroxide addition) as an extraction medium [40, 41]. The extraction step is usually followed by a purification process. An additional clean-up step is necessary to minimize or eliminate matrix interferences resulting from coextraction of other compounds. In this step, C18, silica, graphitized carbon, or solid-phase

PFSAs (PFOS, corresponding sulfonate salts, sulfonamides, and sulfonamidoethanols):

(a)

PFCAs (PFOA and corresponding salts):

(b)

FIGURE 1: General ECF process: (a) A—PFSAs; (b) B—PFCAs.

Fluorotelomer alcohols (FTOHs), fluorotelomer olefins (FTOs), and acrylates (FTAs):

FIGURE 2: General telomerization process.

Fluoropolymers, by the example of PTFE:

FIGURE 3: Polymerization of TFE.

extraction (SPE) is employed [42, 43]. Of the available SPE procedures in sample preparation techniques, QuEChERS (quick, easy, cheap, effective, rugged, and safe) is one possible alternative which has many environmental advantages, including minimization of solvent usage, simplification of extract clean-up, and material cost reduction. This method was developed by Anastassiades et al. for determination of pesticides in fruit and vegetable matrices [44]. Nevertheless, in recent years, the QuEChERS method has been extended and successfully employed in the determination of other contaminants such as PAHs, acrylamide, or chloropropanols [45–47]. Application of ENV (styrene-divinylbenzene) SPE Bulk Sorbent in the sample treatment step for the determination of PFAAs has been successfully used to carry out rapid purification of different food matrices [48–50]. PFAAs analysis is a challenging task not only because of the low concentration levels expected for these compounds in food samples, but also on account of the complexity of matrices; therefore, efficient sample preparation procedures and very sensitive determination techniques are needed.

The selection of appropriate analytical techniques for monitoring the levels of contaminants in food matrices depends on the physicochemical properties of analytes, the matrix type, the co-occurrence of other substances, and the sensitivity and selectivity of the method. Nowadays, chromatographic separation processes are the most used analytical

techniques for quantitative and qualitative analysis of food contaminants. The most commonly employed analytical method to determine PFAAs is liquid chromatography in combination with other conventional or much more advanced detection methods. Mass spectrometry (MS) detection in various combinations of MS analyzers (e.g., tandem mass spectrometry MS/MS) is regarded as the reference method [51]. The LC-MS/MS technique that uses a triple-quadrupole mass spectrometer (QqQ) with a Multiple Reaction Monitoring (MRM) mode of operation is one of the most frequently applied approaches in trace analysis and is best suited for determination of PFAAs in food samples (along with ion trap (IT) and time of flight (TOF)) [52]. Relatively strong acids, i.e., PFCAs and PFSAs, tend to dissociate to anionic form and therefore negative mode electrospray ionization (ESI-) is widely used for analysis of PFAAs at low levels [53]. Nowadays, one of the most significant techniques for analytical and preparative purposes is micro-HPLC combined with MS/MS, which provides higher peak capacity, greater resolution, increased sensitivity, and higher analysis speed compared to the conventional LC system [54]. The micro-HPLC technique allows analysis time to be reduced without significant losses in separation efficiency; therefore, it has an important role in the monitoring of environmental pollutants.

It is worth mentioning the important role of automated methods of PFAAs analysis. This analytical approach is

based on the modern idea of replacing manual extraction and clean-up procedures, typically associated with low throughput, with automated ones. The benefits of this method include reduction of sample amount, shorter analysis time, and the minimization of manual operations and contamination during sample processing. The application of such techniques ensures maximum recovery ratio of perfluoroalkyls, good reproducibility, and elimination of operational errors. In analytical chemistry, online Turboflow SPE-UHPLC-MS/MS [55] or column switching HPLC-MS/MS [56] have been successfully used to determine PFAAs content in human serum.

Less frequently used but just as effective is gas chromatography with mass spectrometry detection (GC-MS). This technique may be applied to determine anionic and neutral PFAAs; nevertheless, it is mostly used for neutral and volatile PFASs, mainly perfluorooctanesulfonamide (PFOSA), fluorotelomer alcohols, or olefins [57]. ^{19}F NMR [58], Fourier transform infrared spectroscopy (FTIR) [59], and radiochemical methods [60] have been also used in the determination of PFAAs, but in modern laboratories, these methods are less relevant due to their low sensitivity and the time required.

Even though there is significant progress in the development of new methods and technologically advanced equipment, trace analysis of PFAAs in complex matrices is still a challenge. The danger of unexpected contamination, the limited number of commercially available standard solutions, and the lack of certified reference materials make obtaining reliable results difficult. Moreover, it is important to stress the fact that interlaboratory trials on PFAAs analysis in various matrices are available for accredited laboratories. Nevertheless, monitoring trends and changes in human exposure and identifying the environmental risks involved in the global dissemination of PFAAs are still of increasing interest to researchers, as shown by the growing number of papers and scientific meetings devoted to this subject.

6. Sources of PFAAs, Distribution Channels, and Human Exposure

Many PFAAs have been detected globally in various constituents of the environment, such as biota, humans, and food items, even in remote locations. In recent years, a number of studies have reported the various pathways of the distribution of PFAAs. On account of their physical and chemical properties, PFAAs are able to migrate to remote areas using long-range transport such as water currents, atmospheric transport, and deposition of semivolatile precursors in soils [61–64]. Their presence in the natural habitat may affect the ecosystem and public health; therefore, it is essential to develop full knowledge about the direct and indirect sources of emission. PFAAs may enter the environment via various direct and indirect pathways. Direct sources mainly include waste streams from the use of PFAAs in manufacturing, including discharges or emissions of released gases, wastewaters, sludge, and solid waste [65–69]. Moreover, inappropriate treatment procedures of this waste (disposal) [70–74] and the use of products containing

PFAAs (volatilization, washing off, and direct use) [75–78] may contribute to elevated levels of PFAAs in the environment. Transformation of perfluoroalkyl precursors and the breakdown of perfluoroalkyl-based products represent indirect sources of contamination [79, 80]. All of these PFAAs distribution pathways could cause contamination of surrounding air, food, and drinking water and be the primary source of human exposure to these compounds, as depicted in Figure 4.

At this point of our consideration, it is necessary to discuss the distribution of PFAAs in human serum. Our brief description of this issue was based on NHANES data (National Health and Nutrition Examination Survey) which were collected between 1999 and 2016 in the U.S. population [81]. The highest initial concentration and the biggest change over the years was observed for PFOS, whose concentration in the given period changed from $30.4\ \mu\text{g}\cdot\text{L}^{-1}$ to $4.72\ \mu\text{g}\cdot\text{L}^{-1}$. This was probably caused by the phasing out of C8-based chemistry which started in 2000 [82]. PFOA levels in human serum were much lower than those measured for PFOS and in 1999–2000 and 2015–2016 were at a level of $5.21\ \mu\text{g}\cdot\text{L}^{-1}$ and $1.56\ \mu\text{g}\cdot\text{L}^{-1}$, respectively. PFHxS concentrations changed slightly during the NHANES experiment from $2.13\ \mu\text{g}\cdot\text{L}^{-1}$ to $1.18\ \mu\text{g}\cdot\text{L}^{-1}$, while PFNA concentration was almost the same. An EFSA summary report based on results from European studies on general populations collected from 2007 to 2008 and onwards provides detailed information on the prevalence of PFOA and PFOS in human serum and plasma [83]. Yeung et al.'s study was selected to determine the trend in concentrations of PFOA and PFOS in human serum during the years 1982 to 2009 (samples collected in Münster) and 1995 to 2009 (samples collected in Halle) [84, 85]. During the analyzed period for the samples collected in Münster, PFOS concentration changed from $27.5\ \mu\text{g}\cdot\text{L}^{-1}$ to $7.1\ \mu\text{g}\cdot\text{L}^{-1}$, while PFOA changed from $7.59\ \mu\text{g}\cdot\text{L}^{-1}$ to $3.45\ \mu\text{g}\cdot\text{L}^{-1}$. The results obtained in Halle were comparable to those observed in Münster. Evaluated concentrations decreased from 20 to $25\ \mu\text{g}\cdot\text{L}^{-1}$ to $6.9\ \mu\text{g}\cdot\text{L}^{-1}$ and from 5 to $8\ \mu\text{g}\cdot\text{L}^{-1}$ to $2.73\ \mu\text{g}\cdot\text{L}^{-1}$ for PFOS and PFOA, respectively. For both reports, NHANES and EFSA, the results obtained are in good agreement, and in general, PFAAs concentrations in humans follow a downward trend. Nevertheless, the information provided is sufficiently detailed only for several PFAAs.

For the purposes of human risk assessment, three major types of exposure to PFAAs have been distinguished: general human exposure, occupational exposure, and prenatal and neonatal exposure. General human exposure to perfluoroalkyl substances encompasses inhalation of outdoor [86–88] and indoor air including suspended household dust [89, 90], as well as drinking of water [91–93] and food consumption [41, 86, 94, 95]. Nevertheless, the exposure pattern varies according to the nature of PFAAs and the location of their source, the type of consumed food, and eating habits. Ingestion and drinking are classified as oral exposure, and dietary intake is considered as the dominant nonoccupational transfer route of PFAAs [96, 97]. In 2008, the European Food Safety Authority (EFSA) established direct contamination derived from food of animal or plant

FIGURE 4: PFAA distribution route dependency diagram [15].

origin and indirect contamination by food processing and packaging as two main sources of PFAAs in food [98]. In recent years, some research has shown that consumption of fish, dairy products (including milk), and meat is the main source of human exposure, while other sources are of less importance [9, 98, 99]. Seafood and freshwater/marine fish are regarded as an essential component of the everyday diet of humans and are suggested as the most important source of PFAAs [100]. Therefore, many researchers have discussed the level of perfluoroalkyl impurities in different fish species. A cross-sectional study in Poland found significant associations between fish consumption and increased PFHxS (perfluorohexane sulfonic acid), PFOS, PFOSA (perfluorooctanesulfonamide), PFHxA (perfluorohexanoic acid), PFHpA (perfluoroheptanoic acid), PFNA (perfluorononanoic acid), PFDA (perfluorodecanoic acid), PFUnDA (perfluoroundecanoic acid), and PFDODA (perfluorododecanoic acid) and, to a lesser extent, PFOA serum concentrations [101]; this was in agreement with other studies [102–104]. Koponen carried out an investigation of several PFAAs in edible Baltic Sea fish species. The authors observed the presence of PFOS in 100% of the analyzed species, and the concentrations (at $\text{ng}\cdot\text{g}^{-1}$ of fresh weight) were as follows: 0.86–4.8, 2.1–4.9, 0.33–4.6, 1.5–5.6, and 0.60–0.88 for Baltic herring, pike-perch, whitefish, salmon, and vendace, respectively [105]. Svihlikova et al.'s study summarized the levels of 25 PFAAs in 59 fish samples collected in rivers in the Czech Republic [106]. All the samples were contaminated by 6 representatives of PFCAs (PFNA, PFDA, PFUDA, PFDODA, PFTrDA (perfluorotridecanoic acid), and PFTeDA (perfluorotetradecanoic acid)), PFOS and FOSA. The concentration ranges of individual substances in the respective groups of PFAAs ranged from 0.007 to $61.6\text{ ng}\cdot\text{g}^{-1}$ wet weight. Edible fish species have recently been investigated in the USA by Fair and coworkers [107]. Their studies showed that mean $\sum$ PFAS concentrations varied from 12.7 to $33.0\text{ ng}\cdot\text{g}^{-1}$ wet weight in whole fish and $6.2\text{--}12.7\text{ ng}\cdot\text{g}^{-1}$ wet weight in fillets. PFOS was the most abundant compound. As seafood is also regarded as a food of high impact to human health, a number of works have been conducted in this field. Wu et al. investigated the presence of PFAAs in 45 shellfish samples collected in China [108]. PFOA was the predominant compound, for which the highest concentration was found in briny clam and was as much as $7.54\text{ ng}\cdot\text{g}^{-1}$ wet weight. Other research carried out by Hlouskova et al. covered a wider range of food items originating from various parts of Europe [99]. The total PFAS concentrations found in the analyzed samples were established as $1405\text{ ng}\cdot\text{kg}^{-1}$, $3685\text{ ng}\cdot\text{kg}^{-1}$, and $1743\text{ ng}\cdot\text{kg}^{-1}$ for

seafood from Norway, Italy, and Belgium, respectively. Some researchers investigated the effects of the processing of food (mainly fish) on PFAAs content. In 2008, Del Gobbo et al. conducted an experiment to determine the concentrations of PFAAs in raw and cooked fillets (baking, boiling, and frying) of fish species commonly consumed by the Canadian population [109]. Fish samples were obtained from grocery stores, and the PFAAs concentrations were relatively low ($0.21\text{--}1.68\text{ ng}\cdot\text{g}^{-1}\cdot\text{ww}$). This research revealed that all the analyzed cooking methods reduce PFAAs concentrations. The most effective cooking method was baking (15 min at 163°C), as a result of which analyzed perfluoroalkyls were not detected in any of the samples. Studies carried out a few years later gave different results in comparison to the previous experiment: Bhavsar et al. researched the effectiveness of three cooking methods (baking, broiling, and frying) in reducing selected PFAAs levels in fish species sampled from rivers in Ontario, Canada [110]. The authors focused on PFOS as this was the most frequently detected compound. In all the analyzed fish species, PFOS concentrations increased significantly ($p < 0.05$) after cooking, except for broiling and frying of common carp, for which no significant changes ($p > 0.05$) were observed. Nevertheless, the total amount of PFOS largely remained unchanged. Other analyzed PFAAs generally showed little statistically significant change in their amount after cooking. In Vassiliadou et al. and coworkers' study, various fish species and shellfish were analyzed raw and after processing (frying and grilling) and inspected for content of several PFAAs [111]. Heat treatment resulted in elevation of PFAAs concentrations compared to raw samples as a consequence of sample mass changes (water evaporation). The obtained results were in good agreement with Bhavsar and coworkers' study. In conclusion, cooking was generally not effective, and this type of food processing is not applicable to reduction of exposure to PFAAs. Elevated human serum concentrations of PFAAs have been also related to consumption of red meat and animal fat. Experiments carried out by Jogsten showed the presence of PFOS in 8 of 20 items analyzed (e.g., veal steak, pork loin, chicken breast, and black pudding) at levels between <0.001 and $0.330\text{ ng}\cdot\text{g}^{-1}$ fresh weight [22]. Another study on meat and giblets conducted by Hlouskova and coworkers showed that for poultry, canned pork meat, and rabbit samples, no significant contamination by PFAAs was observed, but for the other types of meat (beef, lamb, and pork), $\sum$ PFAAs ranged from 7.51 to $125\text{ ng}\cdot\text{kg}^{-1}$ for bovine meat and lamb, respectively [99]. It should be emphasized that the highest amounts were found in pig/bovine liver. The sum of PFAAs ranged from 286 to $2994\text{ ng}\cdot\text{kg}^{-1}$ for samples from the Czech Republic and Belgium, respectively. Chen et al. reported an even higher concentration of PFAAs in pork liver ($730\text{--}20700\text{ ng}\cdot\text{kg}^{-1}$) [112]. Offal, especially liver, is not a very popular diet component; nevertheless, its consumption (e.g., by pregnant and postnatal women to increase the supply of iron) may pose real health risks. Milk and milk products, as a major component of the human diet, have been studied in depth by many researchers. Wang's studies of milk and derived products provided the concentrations of PFOS in these products, which ranged between <5 and $659\text{ pg}\cdot\text{g}^{-1}$

(wet weight), $<10\text{--}175\text{ pg}\cdot\text{g}^{-1}$ (dry weight) and $<5\text{--}32\text{ pg}\cdot\text{g}^{-1}$ (wet weight) for milk, milk powder and yogurt, respectively [113]. The raw milk examined by Xing et al. was free of PFAAs, with the exception of PFOS [114]. In recent years, similar research has been carried out in Europe by Norwegian [41], Dutch [92], Spanish [9], and German [115] researchers. Milk, cheese, and yogurt were the most frequently examined foodstuffs. Although a wide range of PFAAs was detected, levels were not considered alarming. Another important issue to consider is the fact that PFAAs may be released into the environment at each step of their life cycle and have already been found to be present in various parts of plants. Leaching of these compounds from contaminated soils and further transfer into the aquatic environment and flora highlighted the need to monitor food of plant origin similarly to animal-derived food. In 2009, Stahl et al. studied the process of soil-to-plant carryover of fluoroalkyl substances [116]. Five cultivated plant species (spring wheat, oats, potatoes, maize, and perennial ryegrass) were inspected for selected PFAAs content. Plants were sown or planted under proper controlled conditions and spiked with varying concentration levels of PFOA and PFOS (from 0.25 to $50\text{ mg}\cdot\text{kg}^{-1}$ as aqueous solution). As a result, concentration-dependent carryover of PFAAs from the soil to the plants was observed. PFAAs uptake increased along with increasing PFOA/PFOS concentrations in the spiking mixture. Blaine et al. carried out an experiment on PFAAs uptake into edible parts of strawberry and lettuce irrigated with reclaimed water [117]. The obtained results showed that PFAAs were taken up and accumulated in food crops in an amount proportionate with the aqueous concentration of PFAAs. Recent studies have shown that consumption of plant-based products may be considered an insignificant source of PFAAs in human diet. A cross-sectional study on fruits and vegetables conducted in 2018 showed that the detection frequency was lower than 10% in both groups under investigation [50].

Because of their hydrophobic (water repellent) and lipophobic (fat/oil repellent) properties, PFAAs are commonly used in the food industry as nonstick cooking surfaces, stain- and water-resistant coatings, and oil/fat-resistant food packaging. In recent years, migration of PFAAs from food packaging such as wrapping papers, breakfast bags, baking papers, roasting bags, muffin or ice cups, microwave popcorn bags, fast food boxes, and other specially packaged products to food has been investigated [49, 118]. Studies have shown that fluorochemical additives are common in many types of packaging materials and pass into food during storage. Begley et al. and coworkers described the possibility of migration of PFOA from PTFE-coated cookware [119]. Due to low residual levels of PFOA (at low $\text{ng}\cdot\text{g}^{-1}$ range, $4\text{--}75\text{ }\mu\text{g}\cdot\text{kg}^{-1}$) in PTFE cookware, in spite of favorable conditions, the migration potential into foods was found to be in the very low $\text{ng}\cdot\text{g}^{-1}$ level. Similar studies confirmed that there are no elevated levels of PFAAs related to food preparation in domestic nonstick cookware [120]. In a study of water pollution by PFAAs, Boiteux's study reported that among the investigated chemicals, PFOS, PFHxS, PFOA, and PFHxA were predominant and the detection frequency for PFOS and PFOA was 27% and 11%,

respectively. The highest individual concentration was measured for PFHxA for both raw water samples ($139\text{ ng}\cdot\text{L}^{-1}$) and treated water samples ($125\text{ ng}\cdot\text{L}^{-1}$) [121]. Nevertheless, there have been only a few experiments, and there is little real data on PFAAs levels in consumed food. Due to their stability, bioaccumulation potential, toxicity to living organisms, and ubiquity in the environment, PFAAs represent environmental contaminants of concern and need further detailed regulatory actions.

Prenatal exposure to PFAAs occurs when contaminated umbilical cord blood crosses the placenta during pregnancy [122, 123]. In 2016, Yang investigated placental transfer of several PFAAs during pregnancy. Seven PFAAs (PFHxS, PFOS, PFOA, PFNA, PFDA, PFUnDA, and PFDoDA) and two precursors, 6:2 FTS (6:2 Fluorotelomer sulfonate) and N-methyl perfluorooctanesulfonamidoacetic acid (NMe-FOSAA), were found in maternal serum and cord serum. The highest tested concentration for maternal serum was obtained for PFOS (mean $5.08\text{ ng}\cdot\text{mL}^{-1}$), followed by PFOA, for which the mean concentration was $1.95\text{ ng}\cdot\text{mL}^{-1}$, whilst in cord serum, these concentrations were found at $1.52\text{ ng}\cdot\text{mL}^{-1}$ and $1.32\text{ ng}\cdot\text{mL}^{-1}$ for PFOS and PFOA, respectively [124]. The highest median ratio in fetal versus maternal serum has been shown for PFOA concentration, which is consistent with other worldwide studies [125, 126]. Furthermore, a number of studies confirmed elevated levels of PFAAs in newborns being breastfed by lactating mothers [86, 127, 128]. In recent studies, Lee analyzed 293 Korean women's breast milk samples for 16 PFAAs content and found the total concentration of PFAAs in the range 31.7 to $1004\text{ ng}\cdot\text{L}^{-1}$ [129]. Moreover, Fromme et al. [128] showed that PFOA levels in the serum of infants after six months of breastfeeding were 4.6 times higher compared to maternal blood levels at birth, while in another study, PFOA intake by infants was estimated to be 4.1 ng per kg body weight after six months of breastfeeding [130].

Occupational exposure is directly related to the performance of duties in plants where PFAAs are used or manufactured. Serum concentration levels have also been extensively investigated for occupational environments and for the general population. Exposure to contaminants decreases as follows: occupational workers are at risk the most, followed by populations in identified local exposure areas, including those affected by long-range transport to remote regions (e.g., Arctic), and lastly the general population, which is exposed to PFAAs via background exposure, is least at risk [4]. For occupationally exposed humans (retired workers), serum concentration has been assessed at $0.6\text{ mg}\cdot\text{L}^{-1}$ and $0.4\text{ mg}\cdot\text{L}^{-1}$ for PFOS and PFOA, respectively [131]. In turn, background exposure levels of the U.S. population from the National Health and Nutrition Examination Survey have been estimated to be $3.1\text{ }\mu\text{g}\cdot\text{L}^{-1}$ serum and $9.3\text{ }\mu\text{g}\cdot\text{L}^{-1}$ serum for PFOA and PFOS, respectively [132]. Biomonitoring data provided by DuPont and 3M has shown that occupationally exposed workers have higher PFAAs serum concentrations in comparison to a non-occupationally exposed group [86]. Moreover, potential exposure to PFAAs in the workplace by professional ski wax technicians has been confirmed because of the presence of

high concentrations of several PFAAs in aerosol fractions in ambient air and humans [133, 134].

Of the exposure pathways mentioned above, exposure to PFAAs may occur in various ways as the result of use of consumer-related products such as textiles, upholstery, waxes, sealing lubricants, and paints. Washburn et al. [135] studied exposure to PFOA through these treated products, and no significant risk involved with this source of PFAAs was concluded.

7. Dietary Intake of PFAAs

Oral exposure, including food and water consumption, represents one of the primary routes of human exposure to PFAAs. Everyday diet consisting of diverse food products such as fish, seafood, meat, dairy products, and vegetables represents a potential risk to human health [43, 98]. Contamination sources of food are complex; nevertheless, in recent years, researchers have identified aquatic bioaccumulation, soil/groundwater uptake, and animal feed as the most significant origins of PFAAs [71, 87, 136]. PFAAs are regarded as challenging contaminants whose levels need to be determined in order to assess the real risk involved in food consumption. In 2012, EFSA recommended controlling the presence of PFAAs with a chain length between 4 and 15 carbon atoms and their precursors in a variety of foodstuffs within the EU [94]. A report published by EFSA in the same year provided data on the occurrence and dietary exposure to perfluoroalkyl substances in Europe. Among 27 PFAAs under investigation, PFOS and PFOA were quantified with the highest frequency, respectively, 29% and 9%. The presence of other perfluoroalkyl substances was less frequent at a level equal to or less than 7%. Another report, which included only the 3 most widely researched PFAAs (PFOA, PFOS, and PFHxS), prepared on the basis of recent literature and published by FSANZ (Food Standards Australia New Zealand), was in good agreement with the EFSA 2012 report. PFOS, PFOA, and PFHxS were identified in a similar range of food items at similar levels. It was also confirmed that fish, shellfish, meat, and other products of animal origin such as giblets are major contributors of PFAAs in the human diet [137]. Studies conducted by Yamada supported the thesis that fish and seafood are highly contaminated by PFAAs [138, 139]. Freshwater fish consumers were the most exposed to PFOS at a level of $7.5 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$, and to a lesser extent to PFUnDA, PFDA, and PFHpS (perfluoroheptanesulfonic acid), whilst seafood consumers were the most exposed to PFOA ($1.2 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$), followed by PFNA and PFHxS.

A number of researchers have attempted to estimate dietary intake of PFAAs. Noorlander et al.'s study evaluated intake of PFOS and PFOA on the basis on quantities detected in foodstuffs purchased in the Netherlands [92]. The long-term intake was estimated to be $0.3 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ and $0.2 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ for PFOA and PFOS, respectively. Similar studies have been conducted within other European Union countries, namely Spain, France, Sweden, and Norway. Domingo et al. and coworkers estimated the intake of PFOS and PFOA based on data obtained from analysis of

40 different food products from Catalonian retail stores [9]. The dietary intake levels for adults were estimated to be $1.84 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ and $5.05 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ for PFOS and PFOA, respectively. In France, the dietary intake of selected PFAAs was determined within the framework of the Total Diet Study 2 (TDS 2) [140]. A variety of foodstuffs were checked for 16 PFAAs content. The dietary intake was estimated to be 0.66 and $0.74 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ for PFOS and PFOA, respectively. In Sweden, studies were spread over time due to the analysis of archived food samples (sets archived in 1999, 2005, and 2010) [141]. In a summary report published by Vestergren in 2012, the dietary intake of PFOA was assessed to be 0.35 , 0.50 , and $0.69 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ in 1999, 2005, and 2010, respectively. For PFOS these amounts were relatively higher in comparison to PFOA and were 1.44 , 0.86 , and $1.00 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ in 1999, 2005, and 2010, respectively. In Norway, studies were conducted within the A-TEAM project (Advanced Tools for Exposure Assessment and Biomonitoring) and included measuring daily PFAAs intakes in 1-day duplicate diet samples of 61 Norwegian adults [142]. The median daily intakes were estimated to be $86 \text{ pg}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ and $163 \text{ pg}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$, for PFOA and PFOS, respectively. Scientists from South Korea have also published studies on the issue. The dietary intakes reported by Heo and coworkers were estimated for adults within the range 0.47 – $3.03 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ and 0.17 – $1.68 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ for PFOA and PFOS, respectively [143]. These values were estimated based on the content of PFOA and PFOS measured in 397 food items purchased in Korea. These data are summarized in Table 2.

In general, results published after 2010 are comparable to previously assessed exposure estimates. For PFOS, dietary exposure was estimated to be $1.07 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ in Spain [148], $1.4 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ in Germany [149], and 0.1 – $0.5 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ in Canada [150]. Dietary exposure to PFOA was calculated to be $1.1 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ and $2.9 \text{ ng}\cdot\text{kg}\cdot\text{bw}\cdot\text{day}^{-1}$ for the Canadian [151] and German [149] population, respectively. For Canadian Inuits, dietary exposure to PFOA was 0.1 – $0.5 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ [150].

With regard to the existing standards of TWIs laid down by EFSA in the minutes of the expert meeting of 24 September 2018 (tolerable weekly intakes of PFOA and PFOS defined as $6 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{week}^{-1}$ and $13 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{week}^{-1}$, respectively), PFAAs levels are becoming a global concern and need further assessment [152]. More details about PFAAs concentrations in food and related dietary intakes are summarized and reviewed in Domingo and Nadal's paper [153]. There is very little information on dietary exposure to other PFAAs. Ostertag and coworkers estimated dietary exposure to PFNA for Inuits as 1.5 – $4.4 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ [150]; exposure for the Canadian population was calculated by Fromme as $1.1 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ [151]. Nowadays, there is a growing need to extend the scope of research to completely assess the scale of exposure to perfluorinated compounds.

8. Toxicological Studies of PFAAs

Due to the presence of PFAAs in ambient air, various consumer products, drinking water, and food, it has become

TABLE 2: Summary of recent estimates of dietary intake of PFOA and PFOS in various countries.

Location	Dietary intake (ng·kg ⁻¹ ·bw·per-day)		Year	References
	PFOA	PFOS		
Sweden	0.35	1.44	1999	[144]
	0.50	0.86	2005	
	0.69	1.00	2010	
The Netherlands	0.2	0.3	2011	[48]
Spain	5.05	1.84	2012	[56]
France	0.74	0.66	2014	[145]
Norway	0.086	0.163	2017	[146]
South Korea	0.47–3.03	0.17–1.68	2014	[147]

necessary to accurately assess their potential impact on human health. The occurrence of highly fluorinated compounds in human matrices has been reviewed by researchers in recent years, and there is indisputable evidence that their bioaccumulation potential in tissues is high [154, 155]. However, there is uncertainty regarding the accumulation processes themselves and the acute or chronic toxicity effects due to variation of observed toxic response to PFAAs between species as well as between genders within tested species.

Varieties of PFAAs have been detected in human blood (both in serum and plasma) [5, 39, 148, 156–158] as well as in umbilical cord [38, 159] and maternal [160, 161] blood. Besides blood, some PFAAs have also been found in other human tissues. The presence of PFAAs was predominantly found in the liver [162, 163]. Furthermore, existing studies show that there is some accumulation potential with regard to lungs, kidneys, bones, and the brain [11]. Numerous recent studies have confirmed their presence in seminal plasma [7], the breast milk [164] of lactating mothers, and umbilical cord blood, all of which draws attention to their influence on the human reproductive system.

The most frequently detected compounds of perfluoroalkyl substances are PFOS and PFOA, for which elimination half-life ($t_{1/2}$) was estimated as 5.4 years and 3.8 years, respectively [165]. As opposed to these compounds, PFBA, PFBS, and PFHxA are considered short-chain alternatives with shorter elimination periods as follows: 3 to 4 days for PFBA, 24 to 46 days for PFBS, and below 28 days for PFHxA [15, 166]. For PFHxS, the elimination half-life is 8.8 years [131]. With regard to other compounds, the relatively long half-life period in humans has been explained by the occurrence of enterohepatic circulation and renal reabsorption processes [167, 168].

These long half-lives, in conjunction with the bioaccumulation and biomagnification potential of PFAAs, can give rise to various processes within the living cell and lead to concern over their potential hazard to human health. Because of their capacity to modify surface properties, even on the molecular level, it is essential to elucidate their toxicity and toxicokinetic activity [145]. PFOA and PFOS are the most common of the perfluoroalkyl family, and therefore they have been thoroughly examined to understand their environmental fate and toxicity. Their adverse health effects have been confirmed by many researchers [4, 144, 146] and authorities [147, 169]. Both PFOA and PFOS have shown

moderate acute toxicity via ingestion. The oral LD50 levels assessed for PFOS were 230 and 270 mg·kg⁻¹ bw for male and female rats, respectively [170]. In contrast to PFOS, PFOA is moderately toxic. The LD50 value in rats ranged from 430 to 680 mg·kg⁻¹·bw [171]. The suspected toxic effects of PFAAs include the following: liver toxicity, including liver hypertrophy [172, 173]; liver cancer [174]; disruption of lipid metabolism due to their effect on serum cholesterol and triglyceride levels [4, 175]; function of the immune system, causing atrophy of the thymus and spleen or suppressed antibody responses [144, 176, 177]; function of the endocrine system due to their effects on thyroid hormone levels (triiodothyronine (T3) and thyroxine (T4)) [178, 179]; induction of adverse neurobehavioral reactions [180]; tumor formation [181]; prenatal and neonatal toxicity [4]; decreased birth weight and size [182]; and even obesity [183].

A number of studies cover the putative modes of action of PFAAs on a cellular level, but these mechanisms are still not fully defined. Nevertheless, due to the structural similarities of PFAAs to endogenous fatty acids, these reactions can be partly attributed to their morphology, more precisely to activity resulting from their chemical structure. PFAAs are characterized by high tendency to noncovalent, intracellular binding to β -lipoproteins, albumin, and other plasma proteins, such as fatty acid-binding protein (L-FABP) [10]. Kerstner-Wood et al. and coworkers showed that PFOA, PFOS, and PFHxS were bound to human albumin at physiological concentrations above 99.7% [184]. Moreover, the high tendency to bind bovine serum albumin (BSA) to other short- and long-chain PFAAs such as PFBS, PFHxS, PFPeA (perfluoropentanoic acid), PFHxA, PFHpA, PFNA, PFDA, and PFUnDA was confirmed by Bischel in 2011, but their binding affinity with BSA decreases as the carbon chain length of the perfluoroalkyl compound increases [185]. Absorbed PFAAs can be freely transferred from plasma into soft tissues. PFAAs are identified as ligands of peroxisome proliferator-activated receptors (e.g., PPAR α). PFOS and PFOA are the most widely studied in terms of describing their specific toxicological characteristics and adverse effect on human health [98]. PFOA and PFOS have been shown to activate the peroxisome proliferator-activated receptor alpha (PPAR α) in a number of in vitro studies conducted in recent years [186, 187]. The effect of PFOA and PFOS on PPAR α also occurs via the COS-1 human cell line transiently transfected with a luciferase reporter gene [188]. Because PPARs are

transcription factors responsible for controlling lipid modulation, gene expression, glucose homeostasis, cell proliferation, and inflammation processes, their activation contributes to the proliferation of peroxisomes and the catabolism of fatty acids and cholesterol [189]. Proliferation of peroxisomes is one of the main reasons for liver toxicity observed in laboratory animal studies. In 2008, Wolf found that increasing activity of PPAR α is correlated to increasing chain lengths of PFAAs and perfluorinated sulfonates are weaker activators of PPAR α than perfluorinated carboxylates [190]. Moreover, PFOA induces cytochrome enzymes P450 (Cyp2b2, Cyp3a4, and Cyp4a1) in liver microsomes and may also interact with xenobiotic receptors such as constitutive androstane receptor (CAR) and pregnenolone X receptor (PXR), which are relevant in the regulation of hepatic metabolism [191]. Exposure to PFOS also caused activation of the CAR/PXR nuclear receptors [192]. Ten-fold increases in expression and three-fold increases in expression have been observed for CAR (Aldh1a7 and Cyp2b) and PXR (Cyp3a) target genes, respectively. Gallo et al. investigated the correlation between PFOS and PFOA concentration levels in human serum with typical liver function biomarkers such as alanine transaminase (ALT), γ -glutamyltransferase (GGT), and direct bilirubin [193]. Liver malfunction has been confirmed on the basis of a positive association being demonstrated between the investigated perfluoroalkyl substances and serum ALT level.

9. Regulatory Actions regarding PFAAs

Per- and polyfluoroalkyl substances have been in use on an industrial scale since the 1950s as raw materials, ingredients, intermediate products, and finished products in many technical and consumer applications. Their widespread use became popular due to their fire- and oil-resistant and stain-, grease-, and water-repellent qualities; thus, PFAAs are commonly found in a range of industrial and consumer goods. Because of their persistency, toxicity, and ability to bioaccumulate, many long-chain PFAAs are found globally in different trophic levels in biota, food items, and humans [194, 195]. Nowadays, it is essential to reduce the risk associated with the global impact of these chemicals on the environment and human health and to support worldwide progress towards safer alternatives.

The review of available research data and scientific opinions showed that existing risk assessment activities mainly concern perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA). Other compounds belonging to the PFAAs group tend to be omitted from estimates or are discussed only briefly. Nevertheless, there is an increased awareness of the risks involved with the occurrence of PFAAs in surrounding matrices. Risk assessment activities include not only humans, also but other elements of the trophic chain. Contamination of aquatic organisms, plants, and other living organisms is analyzed in a broad extent. Moreover, monitoring of PFAAs content in surface water, groundwater, soils, and surrounding air is an inherent part of overall risk assessment. Current regulations mainly

impose restrictions for the manufacturing, use, and distribution of long-chain PFAAs and specify safe concentration limits for their dietary intake (food and drinking water). Crucially, increased understanding of the potential health effects and environmental impact of PFAAs has resulted in the implementation of increasingly stringent regulations.

9.1. Legal Acts and Current Trends. Substantial changes in the management model of PFAAs were launched in 2000, when 3M Company, the main large-scale manufacturer of PFOS, in agreement with the US Environmental Protection Agency (USEPA), started the voluntary phasing out of C8-based production. By the end of 2000, 3M had reduced its PFOS production by 90 percent; in 2002, 3M completely withdrew from the production of products based on POSF (perfluorooctanesulfonyl fluoride) [82]. In December 2002, the Organisation for Economic Co-operation and Development (OECD) classified PFOS as a persistent, bioaccumulative, and toxic chemical (PBT) at the 34th OECD Chemical Committee meeting [196]. In 2006, restrictions on the marketing and rules of further use of perfluorooctane sulfonates in the nonfood area were laid down by EU Directive 2006/122/EC of the European Parliament and of the Council of 12 December 2006, amending annex I to directive 76/769/EEC [197]. The first government stewardship program, “2010/15 PFOA Stewardship Program”, involving a risk reduction strategy for manufacturers and downstream users of PFAAs was implemented in 2006 by USEPA in collaboration with eight dominant PFAAs producers: Arkema, Asahi, Ciba (now BASF), Clariant (now Archroma), Daikin, DuPont, 3M, and Solvay Solexis. These companies undertook to phase out global emissions and residual product content of long-chain PFAAs, mainly PFOA, by 95 percent by 2010 and committed to work towards the total elimination of PFOA and its precursors and related higher homologues by the end of 2015 [198]. These targets were met by 2015, as reported in the Final Progress Reports [199]. Originally, PFOS was added to the REACH annex XVII restricted substances list, which defines limitations on the manufacturing, selling on the European market, and use of certain dangerous substances, preparations, and products. In 2009, PFOS and its salts and PFOSF (perfluorooctanesulfonyl fluoride) were added to the Annex B list of the Stockholm Convention as persistent organic pollutants (POPs) for limiting global production and use [200]. Furthermore, PFOS and its derivatives were registered in Annex I of Regulation (EC) No 850/2004 of the European Parliament and of the Council on persistent organic pollutants [201]. At present, PFOS- and PFOS-related substances are regulated as persistent organic pollutants (POPs) within the European Union. PFOA and its salt (APFO) and other related substances have been identified as substances of very high concern (SVHCs) because of their CMR (carcinogenic, mutagenic, or toxic for reproduction) and PBT (persistent, bioaccumulative, and toxic) properties; they were included in the Candidate List of Substances of Very High Concern (SVHC) under the EU Chemicals Regulation REACH in 2013 [202]. In 2017, perfluorooctanoic acid

(PFOA) and its salts and PFOA-related substances were added to the REACH Annex XVII restricted substances list (entry 68) by Commission Regulation (EU) 2017/1000 [203]. Poland generally applies EU legislation on PFAAs. Additionally, Poland has taken action under the HELCOM Baltic Sea Action Plan (2007), which is focused on the Baltic Sea environment and supports the sustainable development and good environmental and ecological status of this area. PFOS and PFOA constitute two of eleven substances deemed as substances of specific concern to the Baltic Sea which need to be subjected to special supervision [204]. Between 2009 and 2012, the COHIBA (Control of Hazardous Substances in the Baltic Sea Region) program was introduced to assess pollution levels in the Baltic Sea and raise awareness of perfluoroalkyl substances in this area [205]. In summary, many different research programs implemented in the United States, Canada, Asia, Australia, and the European Union are focused on the distribution, toxicity, production hazards, processing, and use of PFAAs and are intended to minimize this risk [206].

Since 2000, when 3M Company announced the phasing out of C8-based chemistry and the 2010/15 PFOA Stewardship Program was implemented, global manufacturers started to design technologies based on alternatives to long-chain PFAAs. In this regard, diverse approaches are applied, namely, the currently used chemicals are being replaced with substances containing shorter chains, using non-fluorine-containing substitutes, or developing nonchemical processes. In view of the growing threat, a wide range of fluorinated alternatives are being developed and commercialized globally [14, 207]. Usually, homologues containing 6 or less carbon atoms in the carbon chain are used as substitutes because they are considered to be less toxic and bioaccumulative than long-chain PFAAs. The main transition paths are shown in Table 3.

Nevertheless, greater emphasis is placed on long-chain perfluoroalkyl acids, mainly PFOA, PFOS, and related substances. The most significant alternatives to PFOS are perfluorobutane sulfonic acid (PFBS) and perfluorohexane sulfonic acid (PFHxS), which also exist as various salts, as well as other chemicals like N-Methyl perfluorobutane sulfonamidoethanol (MeFBSE) and N-methyl perfluorohexane sulfonamidoethyl acrylate (MeFOSEA), which may be used as precursors of short-chain alternatives [208]. In PFOA chemistry, the substances of utmost technological importance are perfluorobutanoic acid (PFBA), perfluorohexanoic acid (PFHxA), and precursors, most frequently the short-chain fluorotelomer alcohols (4:2 FTOH or 6:2 FTOH) [208].

Although the industry regards these alternatives as safe, sustainable, and well-tested [209], implementation of PFAAs substitutes is still in the research stages. This is illustrated by the fact that there are some concerns over the long-term effectiveness of the alternatives at a global level [17]. Replacement chemicals, because of their similar structure to PFAAs (the same building blocks, highly fluorinated carbon chain) present a potential risk to human health and the environment due to their persistency and ability to accumulate [210]. The accumulation level of short-chain

substitutes in human tissues like the kidney, liver, brain, and lungs has been estimated to be higher than that for long-chain PFAAs, and their level is considered worrying [11, 208]. For example, data submitted by Pérez and co-workers showed that PFHxA concentration in liver was about 8 times higher than that measured for PFOA, and PFBA concentration in lung tissue was about 10 times higher than that measured for PFOA and PFOS. Moreover, adverse health effects (e.g., impact to hormone system, toxicokinetic activity) occurring as a result of exposure to PFOA and PFOS are similar to those caused by exposure to the long-chain compounds [211, 212]. Although short-chain PFAAs are considered to have properties of very high concern, these compounds are increasingly used [213].

9.2. Law Regulations regarding PFAA Content in Food.

Perfluoroalkyl substances are regarded as chemically stable and resistant to processes such as hydrolysis, photolysis, microbial degradation, and metabolic action. Therefore, they pose a risk to humans due to their ability to bioaccumulate in tissues, which occurs with the greatest intensity in the liver. The main route of exposure to PFAAs is the consumption of food products and drinking water. Concerns about potential adverse health effects have led authorities and non-governmental organizations to take appropriate measures to assess the threat of PFAAs in food and drinking water.

Because diet has been indicated as the most relevant route of exposure, in 2008, the European Food Safety Authority Scientific Panel issued an opinion on the health risk associated with PFOA and PFOS and estimated the tolerable daily intakes (TDIs) to $150 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ and $1500 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ for PFOS and PFOA, respectively [98]. Moreover, in 2010, the European Commission published a document to oblige EU member states to monitor PFAAs levels in a variety of foodstuffs reflecting actual dietary preferences, thereby allowing an accurate estimation of exposure [33]. On the basis of the data collected during the 2006–2012 period in 13 European countries, a summary document assessing dietary exposure was drafted by EFSA [94]. In 2018, the EFSA Scientific Panel on Contaminants in the Food Chain replaced existing TDI levels of PFOA and PFOS with TWIs (tolerable week intakes) of PFOA and PFOS, which were set at $6 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{week}^{-1}$ and $13 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{week}^{-1}$, respectively [83]. These actions highlighted the complexity and scale of the problem of the presence of PFAAs in various food items [152]. Cross-sectional studies showed that PFAAs were found with higher frequency in fish and other seafood and meat and meat products, especially in liver. In terms of the newest regulatory legislations, PFAAs levels in food are of concern and TWI limit values for PFOA and PFOS are exceeded. Collected data enabled the Commission to estimate the mean exposure for adults to be 5.2 and $4.3 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$, while for infants it is 14 and $17 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{bw}\cdot\text{day}^{-1}$ for PFOS and PFOA, respectively. A few significant documents concerning the risk arising from oral exposure to PFAAs in drinking water have since been published. In 2016, EPA published a Lifetime Health Advisory (LTHA)

TABLE 3: Main transition paths in fluorochemical-based industry [15].

End products	Starting substances
Fluorosurfactants	From $\geq$ C6- to C4-based sulfonate chemistry From $\geq$ C8- to C6-based fluorotelomer chemistry From C8, C9 perfluorocarboxylic acids (PFOA/PFNA) to mono- and polyperfluoroethers or other substances
Fluorosurface property modification agents	From $\geq$ C6- to C4-based sulfonate chemistry From $\geq$ C8- to C6-based fluorotelomer chemistry
Nonfluorinated surfactants	Hydrocarbon-based chemicals such as propylated naphthalenes or biphenyls, sulfosuccinates, hydrocarbon surfactants, naphthalene derivatives, polypropylene glycol ether, amines, sulphates Siloxanes Silicone polymers

recommending the limit value for PFOA and PFOS (at individual or combined concentrations) for drinking water samples to 70 parts per trillion [214]. In recent years, many researchers have carried out studies on PFAAs levels in drinking water [215, 216]. Furthermore, the EU Water Framework Directive has been established to regulate environmental quality standards (EQS). For perfluorooctane sulfonic acid and its derivatives, EQS in inland surface waters is $0.65 \text{ ng}\cdot\text{L}^{-1}$ [217].

Due to the growing threat resulting from the increased use of short-chain alternatives and the highly variable presence of PFAAs in food and drinking water, there is also a need for further detailed research on PFAAs concentration levels in the human diet.

10. Conclusions

PFAAs are highly stable, man-made chemicals which are ubiquitous in the environment globally. As shown in this review, dietary exposure to PFOA and PFOS is lower than their respective TDIs; therefore, the probability of negative health effects from these compounds is not very high. Nevertheless, the increased consumption of fish and seafood may lead to exceedance of intake limit values. Due to the increasing use of short-chain PFAAs, the scope of research into their presence in food matrices urgently needs expanding. In addition, large-scale research resulting in additional data on PFAAs levels in foodstuffs is essential to monitor human exposure trends and is a future challenge for scientists. Many methods of analysis are available which claim to be able to detect PFAAs, but reliable trace analysis of such a broad group of compounds is still a challenge.

Disclosure

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Conflicts of Interest

The authors declare no conflicts of interest.

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