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Review

Exposure to per- and polyfluoroalkyl substances and premature skin aging

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ABSTRACT

Per- and polyfluoroalkyl substances (PFASs) are a ubiquitous group of persistent chemicals distributed globally in the environment. Skin aging is a notorious process that is prematurely induced by the interaction between endogenous and exogenous factors, including exposure to environmental chemicals. The existing evidence suggests that skin absorption of PFASs through dermal contact may be an important route of exposure to these chemicals in humans. On the other hand, PFASs intake by other routes may lead to PFASs bioaccumulation in the skin via tissue bio-distribution. Additionally, the presence of PFASs in consumer and cosmetic products combined with their daily close contact with the skin could render humans readily susceptible to dermal absorption. Therefore, chronic low-dose dermal exposure to PFASs can occur in the human population, representing another important route of exposure to these chemicals. Studies indicate that PFASs can threaten skin health and contribute to premature skin aging. Initiation of inflammatory-oxidative cascades, induction of DNA damage such as telomere shortening, dysregulation of genes engaged in dermal barrier integrity and its functions, signaling of the mitogen activated protein kinase (MAPK) pathway, and last but not least the down-regulation of extracellular matrix (ECM) components are among the most likely mechanisms by which PFASs can contribute to premature skin aging.

1. Introduction

Since the 1940s, per- and polyfluoroalkyl substances (PFASs), a large group of persistent organic pollutants (POPs), have been extensively dispersing in the environment worldwide (Nakayama et al., 2019). These chemicals are categorized into two main subgroups, including perfluoroalkyls and polyfluoroalkyls. The former encompasses an enormous family of the fluorinated compounds within which the carbon chains are fully occupied by fluorine atoms. These chains commonly

terminate with a carboxylate (e.g. perfluorooctanoic acid (PFOA), perfluorodecane sulfonic acid (PFDS)), or sulfonate group (e.g. perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFH₆S)). On the contrary, in polyfluoroalkyls, the carbon chains are not fully fluorinated. Plenty of fluoropolymers and fluorotelomers fall into this subset. They are eventually transformed or metabolized to perfluoroalkyl acids and carboxylates (Li et al., 2019).

Thanks to the perfluoroalkyl moiety (C_nF_{2n+1}-), these highly bio-accumulative compounds benefit from prominent physico-chemical

Abbreviations: AD, atopic dermatitis; APFO, ammonium perfluorooctanoate; arNOX, age-related NADH oxidase; CE, cornified envelope; DSBs, double-strand breaks; ECM, extracellular matrix; EDCs, endocrine-disrupting chemicals; EDI, estimated daily intake; EpiDermFT, EpiDerm full thickness; GST, glutathione S-transferase; HSE, human skin equivalent; MARK, mitogen activated protein kinase; MDA, malondialdehyde; MMP, matrix metalloproteinase; NFKB1, nuclear factor of kappa light polypeptide gene enhancer in B-cells 1; PFASs, per- and polyfluoroalkyl substances; PFBS, perfluorobutanesulfonic acid; PFDA, perfluorodecanoic acid; PFDS, perfluorodecane sulfonic acid; PFH₆S, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; P-p38 MAPK, phosphorylation of p38 MAPK; POP, persistent organic pollutants; PPARα, peroxisome proliferator-activated receptor alpha; ROS, reactive oxygen species; SA-β-gal, senescence-associated β-galactosidase; SC, stratum corneum; VDES, vitamin D endocrine system.

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features such as stronger acidity, higher surface activity, chemical and thermal stability, and water- and oil-repellency compared with their hydrocarbon counterparts (Wang et al., 2017). Such unique properties make them unusually exceptional (if not incomparable) to be utilized in a very wide spectrum of industries and products. There is a myriad of these fluoroalkyl compounds all of which have considerable similarities in structure, behavior, and effects (Barzen-Hanson et al., 2017). Extensive application and resistance to natural decomposition have dispersed PFASs throughout the globe. As can be seen in Fig. 1, all the steps from production, consumption, to waste treatment and disposal of PFASs have the potential to release these chemicals or their precursors into the environmental compartments, including the atmosphere, hydrosphere, and lithosphere. Environmental distribution of PFASs in turn, leads to their exposure to living organisms and their bioaccumulation through the trophic chains. This is an indirect route of exposure affecting humans and other forms of life. On the other hand, exposure to consumer products containing PFASs is considered a direct route of exposure increasing the risk of health effects.

Due to the ubiquity of PFASs and the serious threats that they continuously pose to the environment and people, the attention to the environmental fate and transport, as well as the toxicity of these

chemicals has been continuously increasing over the last few decades. Based on findings obtained from growing epidemiological and toxicological studies on PFASs, exposure to these long-lasting chemicals participates in a wide range of adverse health outcomes, including endocrine disruption, immunotoxicity, developmental disorders, and some types of cancers (ATSDR, 2018; Temkin et al., 2020). That is why an issue of high importance turning into a priority is lowering the use and exposure to long-chain PFASs through the innovation and development of fluorine-free alternatives. It is worth noting a recent growing concern is related to exposure to some short-chain PFASs which have been considered as a replacements for long-chain PFASs (Wang et al., 2013, 2015).

Encompassing the tremendous growth of industrialization, an increasing number of pollution sources release hazardous chemicals into the environment. For this reason, measuring exposure to environmental pollutants, under the umbrella term of “exposome”, has recently turned into an ineluctable constituent of epidemiological analysis assessing the linkage between environmental exposure and individual health and pathogenesis of a large number of human diseases. However, the influence of environmental chemicals on skin health is less studied compared with other health endpoints. During the last two decades, the

Fig. 1. Presence and dispersion of PFASs in the environment. After the production of PFASs by fluorochemical manufacturers, they distribute across the environment via the integrated cycles in which atmosphere, hydrosphere, and lithosphere are interconnected. Besides, the leachate and gaseous emissions from landfills, the effluent of wastewater treatment plants, and the release of fire-fighting foams render the environment much more susceptible to PFASs. Air, water, and soil interact with each other in an interconnected way and transfer PFASs to the biosphere, including macro- and micro-organisms. As a result, these non-biodegradable compounds penetrate the biosphere and accumulate across the trophic chains. Such a chain of events results in indirect exposure of humans to PFASs via air, dust, food, and drinking water. Humans are additionally exposed to consumer products containing PFASs and their precursors. The other, but considerably less frequent, direct route of exposure is by dermal contact and inhalation of fire-fighting foams.

detrimental effects of environmental contaminations on the human skin emerged as a new domain of environmental medicine. Specifically, a special emphasis has been placed on the contribution of air pollution-induced skin diseases and skin aging. Furthermore, toxic impacts of dermal exposure to POPs, especially in the workplace, have been studied substantially. Concerning PFASs exposure, although numerous experimental and epidemiological studies have been conducted for understanding the possible contributions of these chemicals to the pathogenesis of a broad array of diseases, the interaction between PFASs and the skin has received less attention as their dermal toxic effects may have been underestimated.

Of all the environmentally-induced skin disorders, skin aging is a prevalent global health challenge requiring serious attention. In this regard, the term “extrinsic skin aging” has been proposed to cover the cutaneous aging stemmed from environmental stressors. It is worth mentioning that the dermal absorption of pollutants is capable of triggering skin damage and bringing about undesirable structural changes. Within the last decade, some experimental studies have been designed to consider dermal exposure to PFASs. For the first time, this review aims to critically and mechanistically examine existing evidence related to dermal effects induced by exposure to PFASs and to figure out potential pathways that may accelerate the process of skin aging.

2. Methodology

Briefly, the authors performed a literature review over PubMed Database on April 10th, 2020 using a combination of the following keywords: (“Fluorinated hydrocarbons”, per- and polyfluoroalkyl substances”, “PFASs”, “perfluorooctanoic acid”, “perfluorooctane sulfonic acid”) AND (“skin”). Rayyan, a review web application, has been employed for making decisions in compliance with following exclusion and inclusion criteria (Ouzzani et al., 2016).

Original human and animal studies were included if meeting one of the following requirements: (1) reporting absorption, distribution, and

accumulation of PFASs in the skin; (2) evaluating the toxic effects of PFASs under dermal exposure.

Studies were excluded if (1) Toxic endpoints of PFASs alternatives were investigated. (2) Toxic impacts of fluorinated hydrocarbons other than PFASs were examined. (3) Referred to non- dermal exposure. (4) Were written in languages other than English. (5) Referred to in-silico investigations.

To compile all available relevant studies, Google Scholar was used as an additional source to check the first 200 results for all possible combinations of the foregoing keywords. Although only original articles were included, the reference lists of relevant review articles were checked thoroughly to prevent missing any relevant items. Gray literature and research from governmental organizations and authorities published in journals other than academic ones, were excluded. The search strategy is presented in online [Supplementary File 1](#).

3. Results and discussion

The following sections present findings extracted from the retained articles and are presented in a logical and interconnected order. Firstly, dermal exposure pathways to PFASs are considered, then their tissue distribution and bioconcentration are discussed with an emphasis on the skin. Finally, experimental and epidemiological evidence are examined to elucidate the most outstanding mechanisms triggering the procedure of skin aging under dermal exposure to PFASs.

3.1. Dermal exposure pathways to PFASs

Fig. 2 depicts the most significant exposure pathways to PFASs. In the case of dermal uptake of PFASs, direct contact of the skin surface with consumer products is the main route. PFASs exist in a myriad of consumer products that have direct contact with the human skin. Thanks to their versatility, PFASs are widely used to render shoes, clothes, carpets, sofa, to name but a few, water, soil, and stain-resistance. They

Fig. 2. Human exposure to PFASs. Human exposure pathways to PFASs mainly consists of air and dust inhalation, food and water ingestion, and dermal absorption.

are utilized to prevent food sticking onto cookware and food packaging. Using long-chain PFASs -and recently their short-chain alternatives- in varnishes, lubricants, detergent products, textiles, paper, ink, waxes, and fire-fighting foams make the human health in general and the skin in particular frequently susceptible and vulnerable to these chemicals (Figs. 1 and 2).

PFASs are low molecular weight surfactants that easily penetrate the skin. Such a key feature is exploited in manufacturing cosmetic products as well. According to a comprehensive risk assessment carried out by the Danish Environmental Protection Agency, PFASs are found at high concentrations in roughly one-third of cosmetic and personal care products (Danish, 2018). It has been reported that exposure to PFOA and PFOS can interfere with membrane and barrier permeability in mitochondria (Hagenaars et al., 2013), brain (Chang et al., 2009), and skin (Fasano et al., 2005). Increasing dermal permeability may develop to dermal penetration and consequently dermal absorption of the chemicals. There are a very limited number of studies that have estimated the human exposure to PFASs through skin contact. Su and colleagues measured several perfluoroalkyl acids (PFAAs) in outdoor and indoor dust around a mega fluorochemical industrial park and assessed their estimated daily intake (EDI) for the local residents (Su et al., 2016). Dermal exposure to PFASs is estimated according to Eq. (1) (Poothong et al., 2019, 2020).

$$EDI_{\text{dermal}} = \frac{Q_{\text{hw}} \times t_{\text{exp}} \times F_{\text{uptake-dermal}}}{BW} \quad (1)$$

where EDI_{dermal} is the estimated daily exposure to the target PFASs via dermal absorption ($\text{pg} \cdot \text{kg} \cdot \text{bw}^{-1} \cdot \text{day}^{-1}$), Q_{hw} is the total mass present of the target PFASs (pg), t_{exp} is the exposure duration (day), $F_{\text{uptake-dermal}}$ is the uptake fraction of PFASs absorbed via the skin, and BW is the bodyweight of an exposed individual (kg). Su et al. (2016) study reported that the EDI ($\text{ng}/\text{kg} \cdot \text{bw}/\text{day}$) of PFAAs via dermal absorption and ingestion of dust contaminated with PFAAs was dependent on the age group and the distance between the population and the industrial park. Additionally, EDIs through the dust ingestion was evaluated to be roughly 4–14 times larger than that through skin contact (Su et al., 2016). Similarly, other studies indicated the dermal route, restricted to the hand's skin, was the least significant exposure to PFASs (Poothong et al., 2019, 2020). Nonetheless, dermal exposure to PFASs could be more substantial than what has been reported provided the whole surface of an individual's skin is considered. Moreover, attention should be paid to the fact that the skin is the only tissue that can be exposed to PFASs both externally and internally. On the one hand, PFASs can enter the body through ingestion and inhalation and transfer to the skin by the circulatory system and accumulate there during tissue distribution. On the other hand, skin can be exposed directly to PFASs through dermal contact. Therefore, despite initial estimations implying that exposure to PFASs through the skin is not comparable to other routes (dietary, inhalation, and dust ingestion), this issue is not incontrovertible. Developing more reliable and holistic methods are recommended to offer an actual and precise assessment of dermal exposure to PFASs.

3.2. PFASs exposure and tissue distribution

PFASs, by nature, are markedly stable and resistant to chemical reactions. In spite of being metabolically inert, these compounds can exert negative influences on endogenous metabolic processes. Disturbance in metabolism may induce biochemical alterations that are interconnected to systemic toxicity (DeWitt, 2015). Since PFASs are not metabolized in humans and animals, they are excreted with different half-lives through different routes. The half-life of PFASs in human serum has been estimated to be 8.3 yr, 5.4 yr, and 3.8 yr for PFHxS, PFOS, and PFOA, respectively (Olsen et al., 2008).

Tissue distribution refers to a process in which a chemical, primarily a drug, transfers from one site to another within the body. During this

process, different doses of a chemical are delivered to each target organ by the vascular system. The residence time, distribution level, and elimination rate of a chemical is a complicated equation influenced by several variables, including but not limited to species, sex, and age (DeWitt, 2015). Assessment of tissue distribution of environmental contaminants in animal models is a pivotal factor required for determining their distribution and magnification or of their metabolites as well as evaluating their potential toxic responses. A growing body of experimental evidence presents the skin as one of the main target tissues for PFASs distribution.

The pervasive influences of PFOA have been detected in human communities, animals, and the general environment. Male and female rats, mice, hamsters, and rodents were exposed to a single oral dose of 10 mg/kg ammonium [^{14}C] PFOA by Hundley and colleagues (Hundley et al., 2006). The experimental analysis showed that almost all of the salt administrated was absorbed by the gastrointestinal tract. The recovery of radioactivity indicated that the highest levels of [^{14}C] were accumulated in blood, liver, and kidney followed by lung, skin, and testis. It is of note that the elimination of PFOA was reported to be sex and species-dependent (Hundley et al., 2006). Sex-dependent plasma clearance half-life has been observed by Gannon et al., when they studied tissue clearance of [1– ^{14}C]-PFHx in rats and mice dosed orally at 2 or 100 mg/kg (Gannon et al., 2011). 24 h after a single dose of 100 mg/kg, PFHx was quantifiable only in the skin as its concentrations were above the limit of quantification (LOQ) levels in the skin of both genders of the two species. Authors deduced from these findings that humans may eliminate PFHx as rapidly as rats and mice.

Bogdanska and colleagues conducted a series of experiments to evaluate the tissue distribution of PFASs in mice (Bogdanska et al., 2011, 2014, 2020). In their earliest study, the tissue distribution of PFOS in C57/BL6 mice was assessed following dietary exposure. Mice were exposed to 0.031 mg/kg/day of ^{35}S -PFOS for 1–5 days. The analysis of radioactivity revealed that skin was among the significant compartments containing the largest amount of PFOS. The distribution of PFOS in the skin was homogeneous and dose-dependent (Bogdanska et al., 2011). Perfluorobutanesulfonic acid (PFBS), a four-carbon perfluorobutanesulfonate, was labeled by ^{35}S and administrated to adult male mice in the same molar concentration of the former study (Bogdanska et al., 2014). Bogdanska et al. (2014) observed that most of ^{35}S -PFBS was localized in tissues, including liver, whole bone, blood, skin, and muscle, similar to the observations of PFOS in their previous study (Bogdanska et al., 2011). The tissue concentrations of PFBS, however, were substantially lower than those of its eight-carbon homolog (PFOS). In the most recent study, Bogdanska and colleagues characterized the tissue distribution of ^{14}C -PFOA in mice in the same manner that they assessed in the cases of PFOS and PFBS (Bogdanska et al., 2020). They carried out the experiment using two different doses; a high experimental dose (22 mg/kg/day) and a lower one (0.06 mg/kg/day) similar to those detected in exposed humans. Results revealed that the concentrations of PFOA measured in the blood are in the same range of those reported in humans. Moreover, the distribution profile had a good agreement with the previous findings (Bogdanska et al., 2011, 2014). Interestingly, the level of PFOA in the skin after low-dose exposure was nearly a third of that in the blood. This suggests that PFOA, even at lower doses, leaves the bloodstream and is distributed homogeneously throughout the skin. This suggests that the presence of PFOA in the skin, a tissue with 15–20% body weight, may play a major part in the whole-body burden.

In agreement, experiments on fish (Goeritz et al., 2013; Falk et al., 2015; Pignotti et al., 2017; Meng et al., 2017), and frog (Cui et al., 2018) corroborated the aforementioned findings and indicated the skin as one of the main areas for localization and recovery of PFASs. Fisheries products are a source of exposure to fluorinated chemicals as shown by the positive correlation between seafood consumption and human exposure to PFASs (Christensen et al., 2017). Market-size rainbow trout (*Oncorhynchus mykiss*) was exposed to PFHxS, PFOA, PFOS, and PFBS via

their diet for 28 days. Goertiz et al. identified the skin of fish as one of the main preferential destinations for PFASs deposition (Goeritz et al., 2013) in accordance with findings by another study on this species (Falk et al., 2015). The accumulation of PFASs in the skin was deemed as an intermediate step for subsequent excretion via the skin (Goeritz et al., 2013). However, recent evidence suggests that body surface mucus is responsible for the elimination mechanism of PFOS (Honda et al., 2018). The contribution of edible parts of seafood (skin and muscle) to PFASs exposure is expected to be significant because of their high proportion of the whole weight of the body. In this respect, PFASs uptake by fish dietary intake would reduce with the consumption of fillet without skin (Goeritz et al., 2013).

Remarkable concentrations of PFASs, especially long-chain ones, are magnified in a host of aquatic organisms as a result of bioaccumulation along trophic chains, which are more likely to terminate in humans (Pérez et al., 2014). Despite the ban on the production of PFOS, Pignotti and colleagues detected it as the most abundant perfluoroalkyl compound in a couple of seawater fish species (Pignotti et al., 2017). They evaluated the distribution of several PFASs in the skin and muscles of

fishes in different positions of the food chain. Surprisingly, although the concentrations of PFASs were below the method limit of quantification (mLOQ) in water and sediment, a very high amount of PFASs in general, and PFOS in particular, was reported in the fishes (Σ PFASs range from 63.8 ng/g ww to 938 ng/g ww), with a relatively more disposition in the skin. It is of relevance that a specific type of PFOS, perfluorooctanesulfonamide, was only detected in predators such as *Cyprinus carpio* and *Silurus glanis*, which are at the top of the ecological food chain. Such solid evidence led authors to infer that biomagnification of PFASs continually occurs in aquatic food chains (Pignotti et al., 2017). Similar results have been found in farmed *Trachinotus ovatus* exposed to PFOS and PFOA. Unlike the abovementioned works, the highest fraction of PFOS was measured in the skin (18.100 mg/kg ww) and its distribution declined in the descending order: skin > gill > kidney > liver > flesh (Meng et al., 2017).

There is further evidence confirming the skin as one of the particular spots for the tissue distribution and bioconcentration of PFASs whether alone (Cui et al., 2018; Honda et al., 2018) or in co-exposure with other chemicals (Li et al., 2017). Many amphibians utilize cutaneous gas

Fig. 3. Tissue distribution and accumulation of PFASs. PFASs leave the bloodstream and enter the target tissues. This flow direction can be reversed and returns PFASs to the vascular system. Skin is among the main destinations for the accumulation of PFASs after the ingestion of contaminated food, water, and dust.

exchange as a mode of respiration. Their skin has a high permeability to small molecules affecting the distribution and accumulation of PFASs (Brühl et al., 2013). Recently, it was proven that PFASs bioconcentration in dermally exposed post-metamorphic amphibians depends on the species and the chemical (Abercrombie et al., 2020). For the first time, this influence was examined in frogs collected from Chinese cities with large-scale fluorochemical plants. Cui et al. (2018) observed fairly similar patterns of tissue distribution in frog and fish. More than one-third of the total body burden of PFASs (mainly PFOS and chlorinated polyfluorinated ether sulfonic acid) was found in the skin of males whereas the greatest proportion of the chemicals in females accumulated in the ovary (Cui et al., 2018). Such gender-related differences were also reported in the case of rodents by Hundley et al., (2006). It is expected that the considerable distribution of PFASs in the female sexual organs results in early-life exposure and induces developmental toxicity during pregnancy and infancy.

Investigating the tissue distribution of PFASs shows their capability to leave the bloodstream and enter tissues. The distribution profile of PFASs, according to the findings of the included experimental studies, has been shown in Fig. 3. It is well-known that PFASs exhibit a high binding affinity to serum proteins and fatty acid-binding proteins and this might be the reason why PFASs transfer and accumulate in the target tissues (liver, kidney, lung, muscle, bone, and skin; Goeritz et al., 2013). PFASs have been reported to largely leave the bloodstream and accumulate considerably in tissues in a dose-dependent manner after exposure to high PFASs doses (Bogdanska et al., 2011). The patterns of tissue distribution of contaminants like PFASs in the mentioned animal models indicate general trends and similarities that would be observed in mammals, including probably in humans. As a result, the skin is a potential target tissue for the distribution and accumulation of PFASs through diet, inhalation, and dust dermal exposure.

3.3. Potential role of PFASs in skin damage

3.3.1. Dermal penetration and absorption of PFASs

Having surfactant properties, PFASs are mostly able to change dermal permeability and break down the skin barrier. Ammonium perfluorooctanoate (APFO) is the ammonium salt of PFOA which can enhance skin penetration in the human and animal skin (Fasano et al., 2005; Kennedy, 1985). APFO was administrated to rats and rabbits to investigate its dermal toxicity. Kennedy Jr (1985) reported that sufficient quantity of APFO had penetrated the skin for the initiation of histomorphologic and physiological changes (Kennedy, 1985). In a similar study, the dermal penetration rate of APFO was evaluated in vitro in rat and human skin. After 48 h, the permeability coefficient for rat and human skin was 3.25×10^{-5} cm/h and 9.5×10^{-7} cm/h, respectively (Fasano et al., 2005). Only a small percentage of applied APFO (1.44% in rats and 0.048% in humans) penetrated the skin after 48 h of exposure. The estimates provided for absorbed dose via dermal exposure demonstrated that the threshold limit value (TLV) may be exceeded under uninterrupted exposure (Fasano et al., 2005). Another study by Franko et al. measured the dermal absorption and penetration of PFOA in mouse and human skin (Franko et al., 2012). The serum level of PFOA significantly increased following dermal exposure in BALB/c mice, which implies its absorption through the skin. In vitro dermal penetration of PFOA indicated that approximately 24% of applied dose penetrated both full-thickness and epidermis samples of the human skin after 24 h. The total absorbable amount of PFOA (i.e. the sum of the total amount that had penetrated plus the amount originally available in skin samples) for these samples was 69% and 48%, respectively. In the case of the mice, more than one-third of the administrated dose passed into the skin, and nearly 50% absorption occurred. It turned out that the ionization state is a determining factor in the absorption degree of PFOA. The less acidity or non-ionized PFOA (pH = 5.5) yields more permeability and easy penetration compared with its ionized form (pH = 2.25) (Franko et al., 2012).

The potential of a chemical for inducing skin irritation and sensitization has a direct correlation with its capability of dermal penetration. Some evidence shows that some PFASs potentially are skin irritant and sensitizer (Kennedy, 1985; Gordon, 2011; Han et al., 2020). Moreover, synthesis and release of cytokines such as interleukin-1 α (IL-1 α) and interleukin-8 (IL-8), two appropriate parameters for screening chemicals for their sensitizing/irritating potential (Coquette et al., 2003), have been reported under exposure to PFASs, strongly suggesting dermal absorption and penetration of these chemicals (Han et al., 2020; Lunardi et al., 2016). Based on the abovementioned research on dermal penetration and absorption of PFASs, the dermal pathway is suggested to be a potential route of exposure to these chemicals.

3.3.2. Dermal exposure to PFASs and immunotoxic effects

It is generally known that PFASs, especially longer-chain congeners, have a markedly potential for triggering inflammatory and oxidative reactions. Hue et al. (2020) evaluated the levels of a pro-inflammatory factor (IL-1 α) and two oxidative stress biomarkers, including malondialdehyde (MDA) and 8-hydroxydeoxyguanosine (8-OHdG) under topically dermal exposure to perfluoroalkyl carboxylic acids (PFCAs) with 5–8 carbons (Han et al., 2020). They used a human skin equivalent (HSE) model entitled EpiDerm Full Thickness (EpiDermFT) composed of constituents such as collagen and human fibroblasts and keratinocytes. This model is used for a variety of experimental analyses on the skin. MDA and 8-OHdG are well-known markers for lipid peroxidation and DNA damage, respectively. The HSE samples were topically exposed to 0.25 and 2.5 mM of the chemicals. In accordance with results from previous studies performed on dermal exposure to different doses of PFOA (Franko et al., 2012), the concentrations under study were non-corrosive. In fact, the concentration, repeat, and period of the exposure were to a great extent similar to those that may occur for the human skin. The measurements revealed that the production of MDA and the release of IL-1 α have significantly increased in tissues treated with 2.5 mM PFASs compared with the control group whereas the level of 8-OHdG in the EpiDermFT skin model did not show any meaningful increase (Han et al., 2020). In a study on the immortal human skin keratinocyte (HaCaT) cells, however, exposure to 50 μ M resulted in a remarkable growth of 8-OHdG-positive staining after a recovery period of 8 days (Peropadre et al., 2018). The discrepancy between these two studies regarding the levels of 8-OHdG could originate from the different human skin models and methodologies applied. Immunological changes in a murine model, including a significant increase of pro-inflammatory cytokines interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) have been reported under dermal exposure to 0.5–2% w/v, or 12.5–50 mg/kg/dose of PFOA (Shane et al., 2020). The positive immunofluorescence staining of IL-6 in HaCaT, a reliable human skin model, was also detected in a significant number of the cells (Peropadre et al., 2018).

Immunotoxicity of PFASs following dermal exposure has been demonstrated by animal studies via the alteration of immune responses and the expression of pro-inflammatory cytokines (Shane et al., 2020; Fairley et al., 2007). In vitro test models (Han et al., 2020; Peropadre et al., 2018) and in-utero studies (Wen et al., 2019a, 2019b) underscore the immunomodulatory role of PFASs. A wealth of evidence suggests that PFOA can act as an immunosuppressive agent. Fairley et al. (2007) demonstrated that dermal exposure to 1–1.5% PFOA is capable of significant augmentation of IgE antibody and airway hyperreactivity response to ovalbumin, a stimulator of allergic reactions, and probably environmental allergens. This action has been attributed to peroxisome proliferator-activated receptor alpha (PPAR α), a ligand-activated transcription factor that plays a pivotal role in the skin homeostasis. This nuclear factor regulates inflammatory responses in the skin, and it is expressed in keratinocytes, T-lymphocytes, and macrophages (Dubrac and Schmuth, 2011). PPAR α agonists are applied in pharmaceuticals to treat inflammatory skin diseases (Hawkins et al., 2010). With this anti-inflammatory role of PPAR α in mind, any environmental factor with the capability of decreasing the expression of PPAR α nuclear factor can

disrupt skin homeostasis and jeopardize skin integrity (Shane et al., 2020). Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (NFKB1) is a transcription factor that similar to PPAR α fights against inflammation, senescence, and carcinogenesis (Cartwright et al., 2016). Down-regulation of these two anti-inflammatory proteins has been reported in the murine model administrated dermally to PFOA during 14-days (Shane et al., 2020).

Exposure to PFASs exacerbates allergic responses (Fairley et al., 2007) and has been associated with atopic diseases (AD) (Wen et al., 2019a; Dubrac and Schmuth, 2011). Wen and colleagues shed light on the association between PFOA exposure and atopic dermatitis (Wen et al., 2019a, 2019b). AD, also known as atopic eczema, is the most common type of skin disease that typically starts at childhood and is characterized by the occurrence of a long-term skin inflammation (TUVW, 2016). Through a 5-year follow-up study, prenatal exposure to PFOA was positively associated with earlier onset of AD since higher prenatal PFOA exposure enhanced the risk of AD development (Wen et al., 2019b). The combined effect of exposure to PFOA and glutathione S-transferase (GST) T1/M1 genotype on childhood AD has been explained using a 2-year follow-up birth cohort study in Taiwan (Wen et al., 2019a). GST is an enzyme catalyzing the conjugation of glutathione (a powerful antioxidant) to xenobiotics such as PFASs in order to detoxify these. Therefore, it is expected that individuals with null types of GST may be less equipped to overcome the oxidative situation due to having dysfunctioned enzymatic activity. Subsequently, reactive oxygen species (ROS) overproduction can initiate and elicit the activation of inflammatory cells and the expression of pro-inflammatory cytokines. It was revealed that the gene-environment interaction in the form of in-utero PFOA exposure and GSTT1/M1 null phenotype might synergistically heighten the risk of AD in children (Wen et al., 2019a). Likewise, prenatal exposure to other PFASs such as PFHxS and perfluorodecanoic acid (PFDA) substantially increases the risk of AD in female children (Chen et al., 2018). Overall, PFASs have the potential to elicit inflammation and oxidative responses in the skin leading to skin inflammation and oxidative damage.

3.3.3. DNA damage under exposure to PFASs

Telomeres in mammal cells consist of a non-coding region of DNA with repetitive sequences of 5'-TTAGGG-3' found at each end of eukaryotic chromosomes. Steady telomere shortening probably acts as a mitotic clock that regulates DNA replication and restricts cell proliferation. Typically, they are shortened over the cell life as every cell division moves telomeres further toward a critical length where programming cell self-destruction occurs (Møller et al., 2018). Therefore, it is speculated that telomere shortening would be a mechanism for preventing carcinogenesis through the induction of cellular aging and senescence. Some epidemiological studies have associated the length of this single-stranded overhang with environmental and occupational pollutants (Zhang et al., 2013). On top of that, toxicological investigations have considered telomere shortening and decreasing telomerase activity as hallmarks of premature cellular senescence induced by exposures to halogenated contaminants such as PFASs (Møller et al., 2018; Liu et al., 2018). Nevertheless, a few numbers of studies reported the positive association between exposure to chemicals and telomere elongation (Zhang et al., 2013; Blévin et al., 2017). The elongation of telomeres takes place in proliferating cells by the mediatory role of the telomerase enzyme adding tandem repeats of 5'-TTAGGG-3' to DNA (Zhang et al., 2013). Increasing telomere length under exposure to chemicals has been ascribed to environmental and nutritional conditions, which carry more weight by comparison (Blévin et al., 2017); thus, such environmental conditions stimulate regulated telomerase activity which is growth-modulated. It is worth mentioning that telomerase is detected in somatic tissues with high proliferation capacity (e.g. skin, intestines, and bone marrow) and proliferating normal stem-like cells such as human T cells. In fact, not only telomerase is expressed in tumor tissues, but also accumulating evidence suggests that it is

expressed in a variety of normal human tissues in a controlled level (Shay and Wright, 2019).

Inflammatory responses and oxidative stress are two effective factors playing a destructive role in the regulation of telomere length and telomerase activity. On the other hand, the increment of free radicals as well as telomere shortening rate are key elements in the aging process. ROS may attack DNA nucleobases and form products that substantially put telomeres in danger. Although the exact influence of ROS on telomere is not fully understood, it is stated that both chronic and acute exposure to oxidizing free radicals may give rise to DNA strand breaks leading to telomere loss (Møller et al., 2018). Measuring concentrations of PFASs, ROS, and leukocyte telomere length in umbilical cord blood of 581 newborns have demonstrated that telomere length has an inverse association with the level of ROS and concentration of PFASs, especially PFOS and PFDA in female newborns (Liu et al., 2018).

Likewise, in the case of skin cells, telomeres are of high importance in their life cycle and play a part in skin aging. Skin is susceptible to premature telomere shortening through agents such as inflammatory mediators, free radicals, and chemicals which interfere in the cell proliferation. DNA damage, cell cycle arrest, and senescence of skin cells can be triggered by telomere attrition (Buckingham and Klingelutz, 2011). HaCaT, a cell line from adult human skin, is a suitable candidate to assess dermal toxicity and irritancy (van de Sandt et al., 1999). Exposure of HaCaT to bioaccumulative and degradable-resistant organic pollutants shortens the telomere length and declines telomerase activity (Senthilkumar et al., 2011; Senthilkumar et al., 2012). Peropandre et al. (2018) evaluated cytotoxic indices such as cell proliferation, DNA damage, oxidative stress, and cell senescence in epidermal HaCaT keratinocytes under exposure to PFOA. The proliferation ability of HaCaT cells was impaired during 24 h after a single dose of the chemical and did not restore within the recovery period. Treatment of HaCaT cells with 50 μ M of PFOA for 24 h resulted in a significant increase of nuclear γ -H2AX foci, a marker of DNA double-strand breaks (DSBs). Moreover, significant positive staining for acidic β -galactosidase has been reported (Peropandre et al., 2018). Senescence-associated β -galactosidase (SA- β -gal) activity and the number of γ -H2AX foci are well-known biomarkers involved in the development of senescence-associated secretory phenotype (Herbig et al., 2006; Debacq-Chainiaux et al., 2009).

3.4. Biological mechanisms involved in PFASs exposure and premature skin aging

During natural skin aging, the skin ability to heal and rejuvenate diminishes, dermal collagen and elastin are fragmented, and undesirable aesthetic signs like uneven tone, wrinkling, and loss of elasticity, and thinning develop (Farage et al., 2007). Both intrinsic and extrinsic skin aging are accompanied by underlying mechanisms such as reduction of skin integrity, impairment of immune responses, the increment of oxidative stress, degradation of extracellular matrix (ECM), dramatic up-regulation of matrix metalloproteinases (MMPs), disruption of vitamin D endocrine system, and signaling of the mitogen activated protein kinase (MAPK) pathway (Elsner et al., 2009; Krutmann et al., 2017). Chronic dermal exposure to PFASs would occur directly via consumer products and indirectly by their bioaccumulation in the skin (Figs. 2 and 3). The role of PFASs exposure in skin aging is summarized in Fig. 4 and discussed in detailed below.

3.4.1. Production of free radicals and reactive oxidative species

It is generally acknowledged that PFASs induce the overproduction of free radicals, including ROS, resulting in a significant decrease in total antioxidant capacity, which in turn puts target tissues in an oxidative state (Wielsoe et al., 2015). Based on the experimental studies on a human skin model, exposure to PFASs initiates oxidative stress through the production of MDA, with values 1.3–2.1 times higher than the control group, with the exception of those treated with perfluorohexanoic acid (Han et al., 2020). The increase of MDA levels has

Fig. 4. Exposure to PFASs and premature skin aging. PFASs trigger interconnected mechanisms where immunotoxic and genotoxic responses work together synergistically and establish inflammatory-oxidative cascades. Reinforcing these reactions by compromised skin integrity results in premature skin aging.

been reported in tissues of animal models exposed to PFOA (Yang et al., 2014; Liu et al., 2007). MDA is one of the most prominent products of peroxidation of polyunsaturated fatty acids which reacts with macromolecules and forms protein and DNA adducts, major contributors to the aging process (Popoola et al., 2015; Calyniuk et al., 2016). Recently, a novel mechanism of aging explained how MDA could engage in skin senescence. The mechanism is activated by age-related NADH oxidase (arNOX) and propagates ROS production at the cell surface to surrounding cells, similar to the mechanisms of natural skin aging (Morre and Morre, 2014). It was shown that the formation of MDA-like adducts involved in the oxidation of lipoproteins correlates with arNOX (Morre and Morre, 2014). Going into the depth, individuals with higher activity of arNOX suffers from skin characteristics that make them appear older than their chronological ages. Accordingly, MDA is capable of strengthening the production and dissemination of free radicals in the skin by the help of this ROS generator (Peres et al., 2011). Fig. 4 depicts the chain of events through which the generation of oxidative agents contributes to the process of skin aging.

3.4.2. Production of pro-inflammatory cytokines

Pro-inflammatory cytokines play an indispensable part in skin aging process as an imbalanced production of these proteins produces discernible changes in the skin appearance (Borg et al., 2013). The skin is an immunologically active organ, and therefore would modulate and synchronize pro- and anti-inflammatory responses (Farage et al., 2009). PFASs have the potential to considerably lower the levels of leukocytes, lymphocytes, and neutrophils in the skin (Shane et al., 2020) and to

increase the mRNA levels of pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor- α (TNF- α) in different tissues (Shane et al., 2020; Qazi et al., 2009; Dong et al., 2011). The age-associated cutaneous pigmentation may originate from the production of endothelin-1 (ET-1) by keratinocytes triggered via the increased secretion of IL-1 α (Okazaki, 2009). Under normal circumstances, IL-1 α is stored in keratinocytes but it is released after membrane breakdown or cell damages. The levels of IL-1 α were markedly enhanced in EpiDermFT treated with 2.5 mM PFOA suggesting that PFOA can induce keratinocyte membrane perturbation (Han et al., 2020). Besides, significant expression of cytokines such as IL-1 β (Shane et al., 2020) and IL-6 (Peropadre et al., 2018) was reported in the skin after dermal exposure to PFOA. IL-1 and IL-6 stimulate the expression of collagen-degrading enzymes such as MMPs leading to the decreased production of collagen and disruption in collagen homeostasis (Maggio et al., 2006; Baugé et al., 2007). IL-1 α , IL-1 β , IL-6, IL-8 are well-known components of the senescence-associated secretory phenotype as they are upregulated in aged skin leading to skin inflammation (Chung et al., 2008; Coppé et al., 2010). Transcriptomic analysis of bottlenose dolphin skin biopsies cultured and treated with PFOA revealed variations in the expression of genes involved in the immune system. For instance, IL-8, an inflammatory cytokine engaged in neutrophil activation, showed a 6.8-fold increase (Lunardi et al., 2016). The overproduction of oxidative agents activates NF- κ B leading to the up-regulation of IL-1, IL-6, and IL-8 (Maggio et al., 2006). Shane et al. (2020) reported that exposure to PFOA has also been associated with the increase of gene expression of T helper cell type 2 (Th2) skewing cytokines, involved in allergic reactions

and atopic skin conditions (Berger, 2000), and with a reduction of gene expression of peroxisome proliferator-activated receptor alpha involved in the anti-inflammatory response (Dubrac and Schmuth, 2011). The oxidative stress produces the expression of pro-inflammatory factors leading to further dermal inflammation. Based on the reciprocal connection between oxidative stress and inflammation; and on the occurrence of these conditions in human skin models under chronic exposure to PFASs on the other hand, it can be hypothesized that the formation of inflammatory-oxidative cascades upon PFASs exposure may be plausible mechanism producing skin aging (Fig. 4). This mechanism would be consistent with observations from other exogenous factors involved in the skin aging process (Ahuja et al., 2017).

3.4.3. Production of DNA oxidative damage

As summarized in Fig. 4, increased secretion of pro-inflammatory molecules and free radicals potentiate skin aging by their structurally detrimental impacts on DNA, including but not limited to single-stranded and double-stranded DNA breaks, telomere shortening, and damages to the DNA repair system (Victorelli and Passos, 2020; Ahsanuddin et al., 2016). In a narrow-age cohort of older adults, particular skin aging features such as wrinkles, facial sagging, and pigmented spots were positively associated with high concentrations of 8-OHdG, a critical biomarker of oxidative stress (Allerhand et al., 2011). PFASs are capable of inducing oxidative stress and oxidative DNA damage via the production of 8-OHdG (Peropadre et al., 2018; Zhao et al., 2019; Yahia et al., 2016). For example, exposure of epidermal HaCaT keratinocytes to 50 μ M PFOA for 24 h resulted in the moderate increase of 8-OHdG concentrations observed 8 days after exposure cessation (Peropadre et al., 2018). On the other hand, the excessive formation of oxidative stress (8-OHdG) may in turn accelerate telomere shortening rate (Fouquerel et al., 2019). Likewise, premature telomere shortening would be another possible mechanism through which 8-OHdG may contribute to skin aging.

Phosphorylation of H2AX, the minor histone H2A variant, produces γ -H2AX which is another hallmark of DNA damages. It is taken into consideration as a cellular reaction to DSBs, one of the worse forms of DNA lesions (Redon et al., 2002; Mah et al., 2010). Formation and accumulation of irreparable DSBs, indicated by the persistent presence of γ -H2AX foci, has an essential role in starting cellular senescence (Fumagalli et al., 2012). A significant increase in γ -H2AX foci under exposure to PFOS and PFOA represents another mechanistic pathway in which PFASs can exert genotoxic impacts mediated by oxidative stress (Peropadre et al., 2018; Wang et al., 2015). The possibility of DSBs induction in HaCaT cells treated with 50 μ M PFOA was indirectly assessed by using γ -H2AX immunofluorescence. PFOA exposure in epidermal HaCaT keratinocytes has displayed a marked increase of γ -H2AX-positive cells and significant positive staining for acidic β -galactosidase (SA- β -gal) (Peropadre et al., 2018). Notably, telomere shortening strongly correlates with SA- β -gal and the number of γ -H2AX foci (Bernadotte et al., 2016). These observations in the lower layers of the HaCaT cells are associated with the features developing senescence-associated secretory phenotype. As a result, mild exposure to PFOA has the potential to induce DNA damages and senescence in dermal HaCaT cells (Peropadre et al., 2018). In summary, the evidence suggests that oxidative DNA damages induced under exposure to PFASs produces 8-OHdG, γ -H2AX as well as activates β -galactosidase providing a plausible mechanism by which dermal exposure to PFASs may increase telomere shortening and consequently produce premature skin aging.

3.4.4. Disruption of vitamin D endocrine system

The skin acts both as the main generator and as a target tissue for the biologically active metabolites of vitamin D₃, especially 1,25-dihydroxyvitamin D [1,25(OH)₂D]. The latest evidence suggests that the vitamin D endocrine system (VDES) exerts considerable influences over the aging process in different tissues, including the skin (Reichrath, 2012; Chang et al., 2010). Mechanistically speaking, VDES contributes to skin health

via several biochemical pathways. These are the down-regulation of genes responsible for oxidative damage, inflammation, and cellular aging, the preservation of telomere biology, the inhibition of UV-B-induced cleavage of the Poly-(ADP-Ribose)-Polymerase, and the induction of synthesis of metallothionein, an antioxidative protein (Reichrath, 2012). In vivo studies suggest the modulatory role of vitamin D and its analogs in the biology of keratinocytes and melanocytes of the skin (Piérard-Franchimont et al., 2007). Through a mechanistic insight, Mousavi et al. (2019) meticulously elucidated how endocrine-disrupting chemicals (EDCs) disturb VDES and trigger the insufficient and deficient serum levels of biologically active forms of vitamin D. Since PFASs are also categorized as EDCs, it is expected that these persistent chemicals alter circulating levels of active metabolites of vitamin D. Limited epidemiological evidence exists to examine this association (Pearl et al., 2018; Etzel et al., 2019). A cross-sectional analysis investigated the relationship between four abundant PFASs, including perfluorononanoic acid (PFNA), PFOS, PFHxS, and PFOA, with the serum concentrations of 25-hydroxyvitamin D [25(OH)D] (Etzel et al., 2019). PFASs were detected in 98% of participants' samples and two different patterns were observed regarding the correlation between PFASs exposure and serum 25(OH)D levels. In the adjusted model, each 2-fold increment of PFOS was associated with lower levels of 25(OH)D (0.9 nmol/L, 95% CI: 0.2, 1.5). The association was statistically significant in the case of PFHxS (0.8 nmol/L, 95% CI: 0.3, 1.3 per each 2-fold increment), while no association was observed for PFOA or PFNA (Etzel et al., 2019). In another study by Pearl et al. (2018), 2-(N-Ethyl-perfluorooctane sulfonamide) acetate (Et-PFOA-AcOH) was inversely associated with the level of 25 (OH)D measured in serum of pregnant women. Concentrations of serum Et-PFOA-AcOH were associated with increased odds of 25(OH)D insufficiency (OR = 1.3, 95% CI 1.0, 1.7 per nmol/L), whereas elevated maternal serum concentration of PFNA was associated with decreased odds of vitamin D insufficiency (OR=0.6, 95% CI 0.4, 0.9) (Pearl et al., 2018). Although there is inconsistency in the direction of the observed results, both studies report alterations in the serum levels of vitamin D triggered by PFASs exposure. These results are of interest as VDES plays an underlying part in the aging process through signaling pathways in which tumor protein p53 and fibroblast growth factor 23 (FGF-23) are involved in mechanisms resulting in damages to DNA and telomere shortening (Reichrath, 2012; Pusceddu et al., 2015). Due to the capability of PFASs disturbing VDES and the association of vitamin D level with the aging process, PFASs-originated disruption of normovitaminosis D could potentially accelerate premature skin aging, which in turn could perturb the synthesis of cutaneous vitamin D (Fig. 4).

Sufficient levels of vitamin D decelerates skin aging through the prevention of UV-derived skin and DNA damage, the increase of collagen levels, and the maintenance of skin integrity (Raj et al., 2017). Skin integrity plays a determining role in maintaining its homeostasis and normal functions. Skin integrity is associated with factors including vitamin D concentration and maintenance of acidic pH (Farage et al., 2013). Accordingly, inasmuch as PFASs exposure could interfere VDES, it could deteriorate skin integrity due to decreased levels of vitamin D. Moreover, a breach in the epidermal barrier facilitates the dermal absorption of environmental chemicals as well as the skin penetration by allergens (Hughes, 2017). Consequently, environmental insults, including pathogenic microorganisms, pollutants, toxic chemicals, and UV radiation could penetrate into the damaged skin potentially leading to persistent inflammatory-oxidative cascades. Such a situation could represent a negative loop between the quality and quantity of vitamin D and skin integrity potentially worsening skin conditions and accelerating skin aging.

3.4.5. Downregulation of components that contribute to skin integrity

Aging imposes profound impacts on the epithelial barrier's structures and functions (Parrish, 2017). In aging skin, the permeability barrier and its structural integrity are significantly disrupted as a result of the activation of MMPs and subsequent ECM degradation (Farage

et al., 2014). Although not in cutaneous cells, tight junction disruption, barrier integrity breakdown, and MMPs upregulation have been reported as a response to PFASs exposure (Yu et al., 2020; Qiu et al., 2016; Zhang et al., 2014; Saejia et al., 2019). Moreover, the decrease of overall thickness in the EpiDermFT skin model caused by exposure to 2.5 mM PFOA may be partially interpreted as the loss of ECM which can in turn be attributed to the activation of epidermal MMPs (Han et al., 2020). The metabolism of collagen, one of the most principal proteins of dermal ECM, is vital for maintaining skin barrier function and integrity (Genovese and Sibilla, 2015). Exposure of epidermal cell cultures of bottlenose dolphins to 13 ppm PFOS caused alterations in the expression of genes associated with the decrease of cell proliferation and activation of stress responses. Most importantly, significantly decreased expression of collagen type XII has been observed after 1 or 25 h of exposure (Mollenhauer et al., 2009). This type of collagen is expressed in dense connective tissues primarily composed of collagen type I. Collagen XII takes part in tissue remodeling and the organization of ECM architecture of the skin whilst mutations of genes expressing collagen XII leads to a disruption of the matrix structure (Reichenberger et al., 2000). No sign of the decreased level of collagen type I was observed in the human skin model exposed to 2.5 mM of several PFASs (Han et al., 2020). The deductive reasoning of Han and colleagues puts an emphasis on the possible role of PFASs on skin senescence. However, two major components of the skin integrity (collagen type I and filaggrin) which are affected in the aging process, were strongly stained (i.e. immunohistochemical staining technique) throughout the dermal layer in all groups treated with the examined PFASs. Such a seemingly dichotomy between normal filaggrin expression and other microscopic observations (epidermal vacuolization, necrotic tissues, and decreasing skin thickness) could be the result of insufficient exposure duration, or due to the lack of an observable effect. In addition to the exposure period, collagen type I and filaggrin may require slightly higher concentrations of PFOA to be down-regulated in a short-time exposure. Hence, evaluating the chronic effects of PFASs on the constituents of dermal ECM is one area that requires further research.

Filaggrin is a structural filament-associated protein binding to keratin fibers in epithelial cells and plays an essential role in the formation and maintenance of the epidermal skin barrier, particularly stratum corneum (SC), the outmost layer of the skin (Sandilands et al., 2009). It fulfills many significant functions in the skin, including the regulation and maintenance of skin hydration, skin pH, SC barrier integrity, and probably skin buffering capacity (Rinnerthaler et al., 2013). Hence, the down-regulation of filaggrin in aged skin participates in the pathogenesis of inflammatory skin diseases, breaking down the epidermal barrier integrity, and increasing water loss (Sandilands et al., 2009). Recently, two studies measured filaggrin expression in two different *in vitro* human skin models following exposure to two different dosages of PFASs (Han et al., 2020; Shane et al., 2020). Dermal administration of 0.5–2% PFOA in a murine model led to a decrease of filaggrin and loricerin, both of which are structural proteins found in the cornified cell envelope (CE) in epidermal cells (Shane et al., 2020). Importantly, CE is the frontline defense against environmental stimuli and, therefore, it is effectively involved in the skin aging process where its protein composition changes drastically (Rinnerthaler et al., 2013). It is of note that the decreased levels of PPAR α and NFKB1 under PFOA exposure were concomitant with the declined levels of filaggrin and loricerin. Therefore, PFOA could potentially disturb the immunological functions of the skin and damage the skin barrier. The reduced amount of filaggrin and loricerin is associated with poor skin integrity, and it is a hallmark of the rebuilt of CE observed in aging skin as well as in a couple of skin disorders such as AD, ichthyosis, etc (Streubel et al., 2017). On the contrary, the study by Han and colleagues (2020) did not reported reduced expression of filaggrin and collagen type 1 in HSE treated with 0.1% of PFOA and short-chain PFCAs (Han et al., 2020). It should be noted that neither the concentrations of PFASs used nor the exposure duration in the HSE model was similar to that applied in the murine model.

Nevertheless, the decrease of overall skin thickness, necrotic keratinocytes and fibroblasts, and intracytoplasmic vacuolation in the epidermal granulosum layer were observed in PFOA-treated tissues (Han et al., 2020). These structural observations are among the visual phenotype and degenerative changes of skin cells undergoing aging *in vitro* (Farage et al., 2017; Rattan, 2017).

3.4.6. Signaling of the mitogen activated protein kinase (MAPK) pathway

Elevated ROS was associated with the activation of the MAPK pathway downstream of TNF α , including the p38 pathway responsible for the ROS-mediated cell apoptosis (Yu et al., 2015) and in autophagy regulation (Gu et al., 2020). Lu et al. (2016) reported that PFOA exposure induced p38 MAPK signaling in the blood-testis barrier. In turn, p38 MAPK signaling is related to the induction of apoptosis through a p53-dependent mechanism (Ge et al., 2016). p53 is a tumor suppressor protein that plays vital roles in the regulation of cellular processes, such as modulating the cell cycle and the inducing apoptosis (Harris and Levine, 2005). On the other hand, the activated form of p38 MAPK, the phosphorylation of p38 MAPK (P-p38 MAPK) has been reported to be elevated in cancerous cells (e.g. breast cancer cells) (Esteve et al., 2004).

P-p38 MAPK pathway can be signaled in response to external stressors, such as ultraviolet irradiation and chemicals (Dérjard et al., 1994). Lu et al. (2016) reported a dose-dependent increase of the p-p38 MAPK/p38 MAPK ratio in the testes of male mice after PFOA administration, with the group exposed to 20-mg/kg/d PFOA being statistically significantly different from the control group. In addition, the P-p38 MAPK pathway can also be activated in response to endogenous stressors such as growth factors and cytokines, which are overexpressed after exposure to PFOS (Peropadre et al., 2018; Shane et al., 2020). The p38 MAPK plays a dual role as a regulator of cell death. It can mediate cell survival but also cell death depending on the type of stimulus and type of cell (Koul et al., 2013). Therefore, the activation of the p38 MAPK pathway upon exposure to PFOS could result in skin cell apoptosis, senescence, and autophagy leading to skin aging, or alternatively, could promote cell proliferation potentially leading to skin cancer.

4. Future research

To ascertain the role of direct dermal exposure and/or indirect exposure through skin bioaccumulation of PFASs in accelerated skin aging, the following research is recommended:

- Investigation of PFASs exposure on the expression, release, and activation of antioxidant enzymes (e.g. superoxide dismutases), ROS-generator enzymes (e.g. NADH oxidases, nitric oxide synthases), and the antioxidant reservoir of the skin tissue.
- The contribution of PFASs in the formation of inflammatory-oxidative cascades in skin tissue, especially in connection with the mediatory role of transcription factors such as NF- κ B, PPAR α , and activator protein 1 (AP-1).
- Induction of DNA damage biomarkers, e.g. examining the formation of DNA adducts under dermal exposure to PFASs.
- The associations between PFASs exposure with telomerase activity and telomere shortening rate in a population chronically exposed to PFASs.
- The possible relationship between exposure to PFASs and the disruption of VDES functions, and their effect on skin senescence.
- Expression and activation of enzymes involved in the degradation of components that contribute to epidermal integrity, MMPs in particular, under long-term dermal exposure to PFASs.
- Elucidation of the conditions in which exposure to PFASs activates MAPK signaling pathway leading to apoptosis, autophagy, and senescence of skin cells.

5. Conclusion

The existing evidence suggests that skin absorption of PFASs through dermal contact may be an important route of exposure to these chemicals in humans. On the other hand, PFASs intake by other routes may eventually increase dermal exposure via tissue bio-distribution leading to PFASs bioaccumulation in the skin. Additionally, the presence of PFASs in consumer and cosmetic products, combined with their daily close contact with the skin could render humans readily susceptible to dermal absorption. Therefore, chronic low-dose dermal exposure to PFASs could occur in the human population, representing another important route of exposure to these chemicals. Further research requires a holistic approach to investigate the importance of PFASs exposure across several routes of exposure.

To the best of our knowledge, PFASs exposure can exert detrimental effect on skin health and could accelerate skin aging. The plausible biological mechanisms through which PFASs could accelerate skin aging include oxidative DNA damage, overproduction of ROS, up-regulation of pro-inflammatory cytokines, the disruption of VDES, the down-regulation of genes involved in establishing epidermal integrity and cohesion, and signaling of the MAPK pathway. These events may participate in the formation of inflammatory-oxidative cascades resulting in the activation of MMPs, degradation of ECM, and telomere shortening; all of which accelerate the process of skin aging. Further research is required to evaluate the plausibility, importance and synergic effects of the aforementioned mechanisms on skin damage associated with PFASs exposure.

CRediT authorship contribution statement

Sayed Esmaeil Mousavi: Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Visualization, Project administration, Writing - review & editing. **Juana Maria Delgado-Saborit:** Validation, Writing - review & editing. **Lode Godderis:** Validation, Writing - review & editing.

Declaration of Competing Interest

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

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.jhazmat.2020.124256](https://doi.org/10.1016/j.jhazmat.2020.124256).

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