A review: Effects of prenatal exposure to perfluoroalkyl substances (PFAS) in humans

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Abstract

Perfluoroalkyl substances (PFAS) are man-made, persistent, aliphatic compounds that have been widely manufactured and used since 1950s. Due to their water, oil and heat resistant properties these compounds have been used for example, in textiles, food-packaging materials and cooking utensils. Although nowadays the use and manufacturing of PFAS, especially of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), have been widely restricted, general population can still be exposed to mixtures of PFAS mainly through consumption of PFAS contaminated food or drinking water. Exposure to these chemicals is universal and found to be more in infants than in adults. PFAS have also been found to cross placenta, thus creating a route of prenatal exposure to the mixtures of PFAS throughout the gestation period. Concerningly, the exposure to PFAS has been associated with adverse health effects in humans. Prenatal phase is a critical time for development and exposure to harmful chemicals can lead to adverse health effects at birth as well as in later life. In this review, we provide an overview of the effects found to be associated with prenatal exposure of PFAS on different developmental parameters measured at birth.

Keywords: perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluoroalkyl acids (PFAAs), fetal exposure, thyroid, anthropometric measurements, *in utero* exposure

Introduction

Perfluoroalkyl substances (PFAS) are man-made, persistent, aliphatic compounds in which all the hydrogen atoms attached to the carbon atoms of the alkyl chain are replaced by fluorine atoms (**Figure 1**) (OECD 2018). Due to the fluorine substitution, the perfluoro-chemicals are resistant to degradation, and are hydrophobic as well as hydrophilic. Because of their water, oil and heat resistant properties, they have been widely manufactured and used since 1950s in firefighting foams, textiles, paints, food-packaging materials, cooking utensils, etc. (Mudumbi *et al.* 2017). There are more than 4 700 chemicals in the family of PFAS which include both poly- and perfluoro-chemicals (EEA 2019). Of these, perfluoroalkyl acids (PFAAs) are considered to be of particular importance due to their highly persistent nature and because they were extensively manufactured and used in the past (Buck *et al.* 2011).

The two PFAAs, perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) are the most widely used, extensively studied, and ubiquitously detected PFAS (Mudumbi *et al.* 2017, EEA 2019). According to the OECD classification, the PFAAs are divided into four groups: perfluoroalkyl carboxylic acids (which include PFOA), perfluoroalkane sulfonic acids (which include PFOS), perfluoroalkyl phosphonic acids and perfluoroalkyl phosphinic acids (**Figure 1**) (OECD 2018). Perfluoroalkyl carboxylic acids with ≥ 7 and perfluoroalkane sulfonic acids with ≥ 6 perfluoroalkyl carbons are referred to as "long-chain" PFAS (OECD 2018). Hence, both PFOA and PFOS, with eight carbons, are long-chain PFAS. Long-chain PFAS were found to bioaccumulate and to be more toxic than short-chain ones (Mudumbi *et al.* 2017). Unfortunately, the novel short-chain PFAS manufactured to replace the long-chain ones, were also found to be persistent and highly mobile in the atmosphere and the aquatic environment, raising serious environmental and health concerns (EEA 2019, Johansson and Undeman 2020).

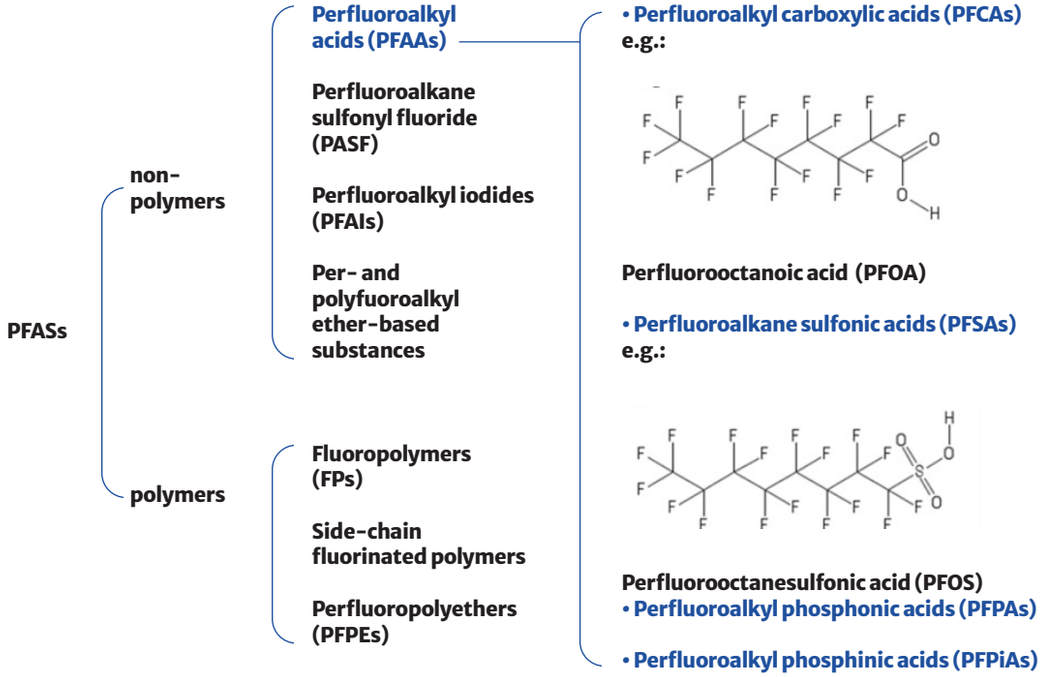

Figure 1. Classification of per- and polyfluoroalkyl substances (PFAS), and examples of perfluoroalkyl carboxylic acids and perfluoroalkane sulfonic acids (Modified from Buck *et al.* 2011, OECD/UNEP 2013, Johansson and Undeman 2020).

Regulation of perfluoroalkyl substances

As the adverse environmental and health effects of PFOA and PFOS became apparent, initiatives were taken to globally restrict their production and use. In Europe, particularly PFOS have been strictly restricted since early 2000 (Buck *et al.* 2011). In 2009, PFOS and its derivatives were included in the Stockholm Convention, which is an international treaty to restrict or eliminate the production and use of persistent organic pollutants (POPs) (ECHA 2021). Consequently, PFOS and its derivatives were restricted in the EU under the EU POPs regulation, Regulation (EU) 2019/1021, through which the commitments made in Stockholm Convention are implemented. PFOA and its derivatives were already restricted in EU under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation (EU) 2017/1000. Since July 2020, PFOA and its derivatives are also restricted under the EU POPs Regulation. Recently, another long-chain PFAA, perfluorohexane sulfonic acid (PFHxS) and its salts have also been proposed to be included in the Stockholm Convention (ECHA 2021). Since September 2020, under the Toxic Substances Control Act, the manufacture (including import) or processing of certain PFAS including PFOA are prohibited in the United States until reviewed by the Environmental Protection Agency (EPA 2020). Even though the use and manufacture of the PFAS, particularly, PFOA and PFOS have been largely restricted, their use continues in some developing countries.

Exposure to perfluoroalkyl substances

Due to their persistent nature, environmentally released PFAS form an important source of human and animal exposure (EFSA 2018, Johansson and Undeman 2020). Environmental release may occur through industrial emissions or leakage from manufacturing or industrial user sites, directly from PFAS products and release due to inappropriate treatment of PFAS-containing wastes (OECD/UNEP 2013, EFSA 2018). PFAS, particularly PFAAs being water soluble, environmental water acts as an important reservoir of these compounds. Oceanic distribution spreads the dissolved PFAAs across the world from their sites of origin (Johansson and Undeman 2020). It has been reported that PFAAs can be transported from ocean water to the atmosphere through aerosols formed on ocean surfaces (Johansson and Undeman 2020). Hence, it is not surprising that some PFAS have been detected globally, even in remote areas (EEA 2019). The PFAS present in atmosphere, soil and water tend to bioaccumulate in aquatic and terrestrial food chains (EFSA 2018). They are taken up by crops grown on contaminated soil which eventually may be consumed by humans or grazing livestock (OECD/UNEP 2013, THL 2021). In adult human population, exposure to various PFAS can occur following their environmental release, during handling of PFAS or their precursors in occupational settings, and through PFAAs containing products in end-users (OECD/UNEP 2013, THL 2021).

In occupational setting, exposure can be through inhalational and dermal routes (EPA 2020). For the general population, although inhalation forms an important exposure route, approximately 70 % of the total PFAS exposure occurs via diet (THL 2021). Food contaminated from the PFAS containing packing material has been considered as one of the most important sources (Trudel *et al.* 2008). Other dietary sources include fish, meat, fruits and eggs (THL 2021). In Finland, domestic Baltic and freshwater fishes were found to be sources of PFAAs (Koponen *et al.* 2015), although substantial variations in PFAA concentrations were observed between species and sampling locations. Drinking water is another important source of PFAA exposure as chronic intake of even a small quantity of the compounds through drinking water can result in substantial exposure (Schrenk *et al.* 2020). In Finland, the Drinking Water Directive (Directive (EU) 2020/2184) implemented on January 2021, set a limit of 0.5 µg/l for all PFAS (ECHA, 2021).

Also, a new safety threshold of "a group tolerable weekly intake" (TWI) of 4.4 ng/kg bw/week was set in September 2020 by European Food Safety Authority (EFSA) for the main PFAAs that accumulate in the body (PFOA, PFOS and PFNA, PFHxS). The limit value was based on the effects of these chemicals on the immune system (Schrenk *et al.* 2020). However, as reported by EFSA (2018), the general population is estimated to be exposed to 1.47-18.27 ng/kg of PFOA and 1.26-20.86 ng/kg of PFOS via diet within one week, which raises concerns.

After birth, a child can also be exposed to PFAS through lactation (Schrenk *et al.* 2020). Exposure in infants is greater than in adults due to their higher consumption of food and water with respect to their body weight (Trudel *et al.* 2008). Also, their closeness to the ground, their crawling and hands-to-mouth activity, increases their exposure (Trudel *et al.* 2008). However, independent of the age and sex of the exposed individuals, both PFOA and PFOS are found to be absorbed quickly, distributed mainly to plasma, liver, and kidneys, and eliminated poorly (Mudumbi *et al.* 2017). In a report by EFSA (Schrenk *et al.* 2020), findings from studies measuring serum concentrations of some PFAS from general European populations between 2007 and 2018 were summarized. The median serum concentrations of PFOS and PFOA in adults were reported to be 7.7 ng/mL and 1.9 ng/mL, respectively. In case of children, the medium serum concentrations of PFOS and PFOA were found to be 3.2 ng/mL and 3.3 ng/mL, respectively (Schrenk *et al.* 2020).

Mechanism of toxicity of perfluoroalkyl substances

Exposure to PFAS has been associated with several adverse health effects in humans (EEA 2019). It is known that PFAS are involved e.g. in dysregulation of mitochondrial bioenergetics, altering plasma membrane potential, inflammatory signaling and lipid homeostasis (Szilagyi *et al.* 2020). However, the exact mechanism of toxicity is still unclear (Szilagyi *et al.* 2020). Activation of peroxisome proliferator-activated receptor alpha (PPARα) is often considered to be responsible for the adverse health effects caused by PFOA and PFOS. PPARα is a nuclear receptor that is responsible for cellular growth and differentiation, maintaining homeostasis, whereas activation of PPARα has been associated with altered gene regulation which are involved in lipid metabolism (Behr *et al.* 2020, Szilagyi *et al.* 2020). PPARα is linked to the pathophysiology of intrauterine growth restriction, gestational diabetes mellitus and preeclampsia (Szilagyi *et al.* 2020). These observations may explain the adverse effects of PFAS after prenatal exposure. Apart from PPARα, other lipid-regulated nuclear receptors, such as the pregnane X receptor, farnesoid X receptor, liver X receptor, and constitutive androstane receptor, have also been proposed as potential targets of PFAS (Szilagyi *et al.* 2020).

Prenatal exposure to perfluoroalkyl substances and their effects

Human exposure to PFAS already begins in womb, as these compounds have been found to cross placenta (OECD/UNEP 2013, EFSA 2018). Mamsen and co-workers (2019) found six different PFAS in human embryonic and fetal organs during different fetal developmental stages confirming that fetuses are exposed to a mixture of PFAS throughout gestation. The human embryos and fetuses studied were derived from elective pregnancy terminations and cases of intrauterine fetal death (Mamsen *et al.* 2019). Of the six measured PFAS, the most abundantly detected compounds in the organs were PFOS, PFOA and PFNA (perfluorononanoic acid). Highest concentrations of the compounds were found in two highly perfused fetal organs – liver and lungs. The central nervous system was found to have the least concentration of PFAS, which according to the authors, may be due to the protective role of the blood brain barrier. They also observed higher concentrations of PFAS in placentas with male fetuses compared to placentas with female fetuses, indicating a gender difference in placental accumulation of PFAS (Mamsen *et al.* 2019).

Prenatal exposure to chemicals has been found to affect the critical phase in development which eventually may impact the health of the individual in later life. Apart from affecting the survival of the newborns, prenatal toxic exposure has been reported to be associated with the development of certain diseases such as diabetes and cardiovascular diseases in adulthood (Chen *et al.* 2012). In the following paragraphs, we will discuss some of the developmental parameters that were studied in relation to prenatal PFAS exposure (summarized in **Table 1**). In these studies, prenatal exposure was determined by measuring the concentrations of specific PFAS in the child's cord blood at delivery or in the corresponding maternal serum during the pregnancy or both. It is to be noted that several PFAS are ubiquitously detected in human serum although the levels may vary. Hence, to find possible association of the adverse outcomes with the PFAS exposure, the studies compared the observed effects with different concentrations of these chemicals.

Anthropometric measurements

At birth, the anthropometric measurements are carried out to estimate the growth and developmental status of the baby. These measurements commonly include body weight, body length, and head circumference. Also, the ratio of weight to length is noted at birth as ponderal index or body mass index (BMI) (Bertino *et al.* 2007). In case of anthropometric measurements, prenatal exposure to PFOA (e.g., Apelberg *et al.* 2007, Li *et al.* 2017, Minatoya *et al.* 2017) and PFOS (e.g., Apelberg *et al.* 2007, Chen *et al.* 2017, Li *et al.* 2017, Wang *et al.* 2019) have been strongly associated with low birth weight. However, few studies have also reported a lack of association of different PFAS exposures, including PFOA and PFOS, to birth weight (Kim *et al.* 2011, Lee *et al.* 2015, Shi *et al.* 2017). Some PFAS were associated with increased fat percentage in childhood (Chen *et al.* 2019).

Association of PFAS exposure and birth length has also been studied. Chen *et al.* (2017) observed that PFOS decreased birth length, but no such association was found with PFOA or other measured PFAS. In another study, Cao *et al.* (2018) reported a negative association of birth length in girls with PFOA but not with PFOS. Almost five times higher mean serum PFOS level in the study by Chen *et al.* (2017) as compared to that measured by Cao *et al.* (2018) may have affected the outcomes. On the other hand, Apelberg *et al.* (2007) failed to find any association of birth length with either PFOS or PFOA exposure. However, they found negative association of ponderal index with PFOA and PFOS concentrations in the cord blood. In the same study, negative association was also found between the PFOA and PFOS concentrations in cord blood to the head circumference (Apelberg *et al.* 2007). Also, Wang and co-workers (2019) found a significant negative association between PFOA concentration in cord blood and head circumference in female babies. Head circumference has been shown to be a measure of brain volume and reduced head circumference has been associated with cognitive deficits (Lindley *et al.* 1999).

Some studies have used small for gestation age (SGA) as a measure of adverse birth outcome, which is defined as "birth weight and/or length at least 2 standard deviations (SDs) below the mean for gestational age (≤-2 SD)" (Lee *et al.* 2003). For example, Govarts *et al.* (2018) had studied the association of PFOA and PFOS in samples obtained from different European countries, with SGA of the respective countries. According to them, PFOA was positively associated with SGA. However, PFOS was found to be positively associated with SGA only in mothers who smoked during pregnancy. Also, Minatoya *et al.* (2017) found significant dose response relationships between prenatal exposures to PFOA and PFOS and the birth size. In another study, where effects of prenatal exposure to PFOA, PFOS and PFHxS were studied only in girls, higher maternal concentrations were found to be associated with smaller size at birth and increased weight at 20 months (Maisonet *et al.* 2012). Similarly, Wang *et al.* (2019) also found negative association of PFOA and PFOS exposure to birth size indices which included body weight, body length, head circumference, and ponderal index.

Impact of perfluoroalkyl substances on hormonal levels

In addition to a strong association to birth weight, PFAS have been discussed to have a possible impact on hormonal levels of the infants, particularly those related to the thyroid organ (EFSA 2018, EEA 2019). However, the exact mechanism behind the effects of PFAS on thyroid hormone levels is still

under debate (Shah-Kulkarni *et al.* 2016, Tsai *et al.* 2017, Preston *et al.* 2018). In several studies, altered levels of the hormones secreted from thyroid gland, i.e., triiodothyronine (T3) and thyroxine (T4), as well as the level of thyroid-stimulating hormone (TSH) secreted from the pituitary gland, were associated with prenatal PFAS exposure. It is well established that T3 and T4 hormones are responsible for critical body functions, e.g., thermoregulation, neurodevelopment, movement of nerve impulses and growth regulation (Sand *et al.* 2014). Therefore, disruption of the thyroid hormone functions could impact overall growth and development of an infant. To maintain homeostasis, raised T3 and T4 levels send negative feedback to pituitary to reduce TSH secretion (Sand *et al.* 2014). According to Preston *et al.* (2018) normal or elevated T3 levels could result in unstable or decreased TSH levels. Consistently, according to the observations made by Tsai and the co-workers (2017), prenatal exposure to PFOS was associated with higher TSH levels and with lower T4 levels (Tsai *et al.* 2017). Also, maternal TSH levels were inversely associated with fetal T4 levels but, not with fetal TSH levels (Kato *et al.* 2016).

However, the effect of PFAS on T4 level, as observed by different authors, is not consistent. An association of decreased T4 level in infants due to prenatal exposure to PFOS (Kim *et al.* 2011, Tsai *et al.* 2017) and PFOA (de Cock *et al.* 2014, Preston *et al.* 2016) was reported. Also, less common PFAS, such as PFTrDA (Kim *et al.* 2011) were shown to decrease infant T4 levels. Particularly in case of PFAAs, their binding to thyroid binding proteins like albumin and transthyretin has been suggested thereby increasing the free T4 level in blood which is then excreted faster from the body compared to the bound T4 (Kim *et al.* 2011, de Cock *et al.* 2014). On the contrary, associations of increased T4 hormone levels due to PFOS (Shah-Kulkarni *et al.* 2016), PFOA (de Cock *et al.* 2014) and less common PFPeA (Shah-Kulkarni *et al.* 2016) exposures have also been noted. Similar inconsistencies were noted in association with TSH levels. PFOS has been observed to increase TSH levels (Kato *et al.* 2016, Tsai *et al.* 2017). However, PFOA has been associated with both increased (Kim *et al.* 2011), as well as decreased TSH level (Kato *et al.* 2016, Shah-Kulkarni *et al.* 2016, Preston *et al.* 2018), In case of T3, exposure to both PFOS (Kim *et al.* 2011) and PFOA (Shah-Kulkarni *et al.* 2016) were associated with a decreased T3 level.

Gender seems to also affect the PFAS association with thyroid hormone levels. Kato *et al.* (2016) found that increased TSH levels after PFOS exposure were more pronounced in male infants than in female infants. Similarly, Preston *et al.* (2014) found reduced T4 levels only in male infants following prenatal PFOA exposure. Shah-Kulkarni and co-workers (2016) observed that PFOA increased T4 and T3 levels in girl infants but decreased T3 levels in boy infants. The reasons for sex-specific results are still unclear (Preston *et al.* 2014), although Shah-Kulkarni and co-workers (2016) suggested that the sex-specificity could be due to estrogen-induced increase of T4 levels. Even though majority of the studies focused on the PFAS associations with thyroid hormones, some studies focused on the effects of PFAS on other hormones, such as sex hormones (Itoh *et al.* 2016), including estrone, estradiol, estriol, progesterone, prolactin, testosterone, dehydroepiandrosterone and inhibin B, and cortisone and cortisol hormone levels (Goudarzi *et al.* 2017). However, no clear associations were reported because of the prenatal PFAS exposure to the levels of these hormones.

Impact of exposure to perfluoroalkyl substances on other parameters

Compared to the strong association to birth weight and levels of thyroid hormones, there are much less evidence to support clear associations of PFAS exposure to other parameters, such as, neurodevelopment and immune functions (EFSA 2018, EEA 2019). The studies that have explored effects of prenatal PFAS exposure on neurodevelopment, have found associations with poorer gross-motor, fine-motor and self-help domains (Chen *et al.* 2013), and better impulse control with higher prenatal exposure to PFOA (Voung *et al.* 2018). In addition, PFOA exposure was associated with slight increase in ADHD diagnosis, whereas PFOS was associated with decrease in ADHD diagnosis (Ode *et al.* 2014). Studies finding associations between prenatal PFAS and immune parameters, also

Table 1. Summary of the developmental parameters studied in relation to prenatal PFAAs exposure.

Parameters	Effects observed	References
Anthropometric effects	Decrease in birth weight	Apelberg *et al.* 2007 Chen *et al.* 2012 Li *et al.* 2017 Minatoya *et al.* 2017
	Decrease in head circumference	Apelberg *et al.* 2007 Chen *et al.* 2012 Wang *et al.* 2019
	Decrease in birth length	Maisonet *et al.* 2012 Chen *et al.* 2017 Minatoya *et al.* 2017
Hormonal effects	Decrease in thyroid hormone level and TSH level	Kim *et al.* 2011 de Cock *et al.* 2014 Kato *et al.* 2016 Preston *et al.* 2016 Shah-Kulkarni *et al.* 2016 Tsai *et al.* 2017
	Increase in thyroid hormone level and TSH level	Shah-Kulkarni *et al.* 2016 de Cock *et al.* 2014 Kato *et al.* 2016 Tsai *et al.* 2017
	Alteration in sex hormone level	Itoh *et al.* 2016 Goudarzi *et al.* 2017
	Decrease in cortisol and cortisone levels	Goudarzi *et al.* 2017
Parameters	**Effects observed (limited evidence)**	**References**
Neurodevelopment	Reduced gross-motor, fine-motor, self-help domains	Chen *et al.* 2013
	Varied observations related to ADHD	Ode *et al.* 2014
Immune system	Varied observations in IgE levels	Ashley-Martin *et al.* 2015 Okada *et al.* 2012
Malformations	No associations with cases of cryptorchidism	Jensen *et al.* 2014

varied in their observations. For example, Ashley-Martin and co-workers (2015) failed to observe any impact on the IgE levels of the infants but based on the study performed by Okada *et al.* (2012), cord blood IgE levels were found to be decreased in girls by PFOA. IgE level in cord blood is considered as an important marker for allergic reactions, as raised IgE level has been found to indicate higher incidence of allergic manifestations in childhood and also in adult life (Pesonen *et al.* 2009). In addition, prenatal exposure to PFAS has been associated with some effects on leukocyte telomere length and formation of reactive oxygen species (Liu *et al.* 2018), levels of leptin and adiponectin (Minatoya *et al.* 2017, Buck *et al.* 2018) and lipids and liver enzymes (Mora *et al.* 2018). Also, PFAS association to malformations have remained inconclusive. In a study, no association was found between PFOA and PFOS and the cases of cryptorchidism in male newborns (Jensen *et al.* 2014). However, a positive association between increased risk of sporadic miscarriage and first trimester PFOA exposure was reported by Wikström and co-workers (2021).

Conclusions

General population is still being exposed to PFAS despite the restrictions on their use and manufacturing since the beginning of this millennium due to their adverse effects on health and environment. PFAS have the ability to cross placenta, thereby exposing fetuses during the critical phase of prenatal development. Based on a number of studies, a strong association of prenatal exposure to PFAS and decrease in birth weight has been observed. Similarly, prenatal exposure to PFAS has been associated with changes in hormonal levels of the infants, especially related to thyroid hormones and thyroid-stimulating-hormone in many studies. Some studies have also pointed towards the effects of prenatal PFAS exposure on other developmental parameters, such as neurodevelopment and immune system. This review is not exhaustive and provides only a brief overview of the topic. However, it is evident that more studies are needed to know the extent of toxicity caused by prenatal exposure to PFAS and, to elaborate the underlying mechanisms.

Tiivistelmä

Katsaus: Perfluoroyhdisteiden raskauden aikaiset vaikutukset ihmisessä

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Perfluoratut alkyyliyhdisteet (PFAS-yhdisteet) ovat ihmisen kehittämiä, pysyviä ja alifaattisia yhdisteitä, joita on kehitetty ja käytetty laajasti 1950-luvulta lähtien. Hyvän veden-, rasvan- ja lämmönkestävyytensä ansiosta kyseisiä yhdisteitä on käytetty esimerkiksi tekstiileissä, elintarvikkeiden pakkausmateriaaleissa ja keittiövälineissä. Vaikka nykyään PFAS-yhdisteiden, erityisesti perfluoro-oktaanihapon (PFOA) ja perfluoro-oktaanisulfonaatin (PFOS), käyttöä ja valmistusta on rajoitettu, väestö voi edelleen altistua PFAS-yhdisteiden seoksille erityisesti kontaminoituneen ruoan ja juomaveden kautta. Altistuminen näille kemikaaleille on yleistä, ja on havaittu, että pikkulapset altistuvat näille kemikaaleille aikuisia enemmän. Tämän lisäksi näiden yhdisteiden on myös havaittu kulkeutuvan istukan läpi, mahdollistaen raskausaikaisen prenataalisen altistumisen näiden yhdisteiden seoksille. PFAS-yhdisteille altistuminen on yhdistetty huolestuttavasti haitallisiin terveysvaikutuksiin. Raskausaika on kriittistä aikaa ihmisen kehitykselle, ja altistuminen haitallisille kemikaaleille voi johtaa haitallisiin terveysvaikutuksiin myös myöhemmin elämässä. Tässä katsauksessa annamme yleiskuvan PFAS-yhdisteiden prenataalisen altistumisen vaikutuksista syntymähetken kehitysparametreihin.

Avainsanat: perfluoro-oktaanihappo (PFOA), perfluoro-oktaanisulfonaatti (PFOS), perfluoroalkyylihapot (PFAA-yhdisteet), sikiöaikainen altistuminen, kilpirauhanen, antropometriset mittaukset, kohdunsisäinen altistuminen

Conflicts of interest

No conflicts of interest.

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