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Reviews

Perfluoroalkylated substances – an endocrine disruptor with reprotoxic effects

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Abstract

This Perfluoroalkylated substances (PFAS) are persistent organic pollutants. They are subject to restriction to specific production and uses according to the Stockholm Convention 2009, implemented also by the Romanian Government in 2012. The main concerns related to PFAS are the effects on the reproductive system, affecting fertility and the development of the fetus. PFAS can pass through the placenta and in the breast milk and can affect the development of the newborns. Therefore, the possible occupational exposures need to be assessed for couples who want to become parents and before the decision to return to work of a breastfeeding mother is taken. It is also important to identify this exposure, as PFAS and they have other negative effects on health, such as the carcinogenic and the endocrine disrupting ones.

This article reviews the main sources of exposure to PFAS, the means of regulating their use in the European Union and the effects on the reproductive system in people exposed to PFAS. It also describes the occupations in which this exposure exists and the studies on the effects of this exposure in workers.

Keywords: *perfluoroalkylated substances, reprotoxic substances, endocrine disruptors*

Introduction

The decrease in natality in Romania raised serious concerns on the exposure to endocrine disruptors from the general or the occupational environment. As many countries in the European Union, Romania have implemented policies to increase natality, but also women's participation in the labor market and reduce gender inequalities. The impact of motherhood is reflected in the employment rate of women with children under the age of 6. For example, in the European Union, the employment rate of women in this category is on average more than 8% lower than the employment rate of women without children.

Some Member States have introduced specific measures to encourage women to re-enter the labor market while the child is still very young. For example, in April 2014, Malta introduced a free childcare scheme for children under the age of 3 to incentivize more parents, especially mothers, to return to or remain in the workforce. In 2017 Bulgaria adopted a measure whereby mothers with children under 1 year of age who return to the labor market receive a childcare allowance [1]. Similarly, in Romania, these benefits were increased in 2017 (the incentive is granted until the child turns 3, if the parents start working at least 60 days before the child turns 2)[2].

Return to work after giving birth has to be safe to

the mother and for the child. More and more mothers follow the WHO recommendation for exclusive breastfeeding for the first 6 months of life and continue breastfeeding with the gradual introduction of complementary feeding until the child is 2 years old. For mothers who decide to return to work before the end of the breastfeeding period, employers are obliged to support them by assuring breaks, reduction of normal working time, provision of special rooms for breastfeeding, the possibility of not working night shifts, or in unhealthy or unbearable conditions [3]. This obviously includes the non-exposure to dangerous substances which might be transferred to the toddlers. As perfluoroalkylated substances (PFAS) are such hazards, we will review the current knowledge regarding their effects on the reproductive system of the adults and their offsrings.

General considerations

Perfluoroalkylated substances (PFAS) are a group of man-made chemicals that are manufactured and used in a variety of industries around the world (electrical and electronics, photo workshops, mining, chemical processing, industrial textiles, furniture, automotive, textiles, detergents, etc.).

PFAS are organic substances with surface-active properties classified as persistent organic pollutants (POPs) and are subject to specific production and use restrictions [4]. In 2021, the Organization for Economic Cooperation and Development (OECD) defines PFAS as "any chemical substance with at least one methyl perfluorinated (-CF 3) or one methylene perfluorinated (-CF 2 -) group". According to the OECD, there are at least 4,730 distinct PFASs known that contain at least three perfluorinated carbon atoms. The most widespread PFAS are perfluorooctansulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) [5].

The 2009 Stockholm International Convention decided to eliminate the use of PFOS and its derivatives due to their classification as possible human carcinogens [6]. PFOA has been banned under the POPs Regulation on July 4, 2020 as a human carcinogen; by derogation it can be used in photolithography or etching processes in semiconductor manufacturing, in photographic coatings applied to films, for invasive and implantable medical devices, as a component of firefighting foam already installed in mobile and fixed systems, for liquid fuel vapor suppression and for extinguishing fires caused by liquid fuels (Class B fires) until July 4, 2025 [7]. The EU Drinking Water Directive, which entered into force on January 12, 2021, includes a limit of 0.5 μg/l for all PFAS in the environment. In addition, in September 2020, the European Food Safety Authority (EFSA) set a new safety threshold (4.4 nanograms/kilogram of body weight /week) for the group composed by perfluoroalkyl substances: perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA), perfluorohexane sulfonic acid (PFHxS)[8]. There are also some specific recommendations of the European Commission about the maximum amount found in different types of foods [9].

One of the main characteristic of PFAS is due to their strong carbon-fluorine bonds, which make them stable to metabolic and environmental degradation. PFAS are not easily eliminated and may have a long half-life in humans and animals. However, the toxicokinetic profile and the underlying mechanism for the long half-life of the chemical are not completely understood. Animal studies indicate that PFAS is well absorbed orally and is mainly distributed to the blood and liver.

PFAS is known to activate the peroxisome proliferator activated receptor (PPAR) pathways by increasing transcription of mitochondrial and peroxisomal lipid metabolism, as well as sterol and bile acid biosynthesis. This is based on transcriptional activation of many genes in PPARα-null mice, involving more than just PPAR receptor activation (Andersen et al. 2008) [10].

Human exposure to PFAS occurs mainly through oral intake of contaminated food and water, as well as inhalation and, to a lesser extent, dermal exposure.

The absorption process requires transport across the tissue interface with the external environment. PFAS exhibits both hydrophobic and oleophobic properties, indicating that movement across the membrane surface is likely to be associated with transporters rather than by simple diffusion. Unfortunately, no information on the interaction of PFAS with intestinal, pulmonary or cutaneous transporters in mammals has been identified.

There are currently no studies available on the uptake of PFAS in humans quantifying the amount absorbed. PFAS are distributed within the body by non-covalently binding to plasma proteins, most commonly albumin. Stein et al. (2012) compared PFAS levels in maternal serum and amniotic fluid paired samples from 28 females in their second trimester of pregnancy. PFOS (0.0036–0.0287 μg/mL) were detected in all serum samples and in nine amniotic fluid samples (0.0002–0.0018 μg/mL). The Spearman correlation coefficient between the serum and amniotic fluid levels was 0.76 ($p = 0.01$), indicating a direct relationship between the levels in blood and

amniotic fluid. The median ratio of maternal serum: amniotic fluid concentration was 25.5:1. PFOS was rarely detected in amniotic fluid unless the serum concentration was ≥ 0.0055 μg/mL [11].

No studies on the metabolism of PFAS were identified and, apparently it these compounds, once absorbed, are not further metabolized. However, electrostatic interactions with biopolymers were indicated [12] and data on binding to plasma proteins, such as albumin were also described [13, 14]. PFAS binding to other serum and intracellular proteins also occurs.

Weiss et al. (2009) [15] screened the binding of PFOS to the thyroid hormone transport protein transthyretin (TTR) in a radioligand-binding assay to determine if it could compete with thyroxin (T4), the natural ligand of TTR. Human TTR was incubated with 125I-labeled T4, unlabeled T4, and 10–10,000 Nano moles (nmol) competitor (PFOS) overnight. The unlabeled T4 was used as a reference compound, and the levels of T4 in the assay were close to the lower range of total T4 measured in healthy adults. PFOS had a high binding potency to TTR. The 50% inhibition concentration was 940 nmol. The authors concluded that PFOS demonstrates an affinity to TTR and had a greater affinity than the compounds with shorter chain lengths.

Urinary excretion of PFAS in humans is impacted by the isomeric composition of the mixture present in blood and the gender/age of the individuals. The half-lives of the branched chain PFAS isomers are shorter than those for the linear molecule, an indication that renal reabsorption is less likely with the branched chains[16] levels, the elimination times being around 3–5 years for PFAS and 5–8 years for PFHxS [17, 18].

Menstruation appears to be a crucial pathway of elimination for many PFAS, potentially explaining about 30% of the discrepancy between serum PFAS levels in men and women. (Zhou and colab., 2017) [19], as 90-99% of PFAS in the blood are bound to serum albumin [20, 21]. For example, Park et al. (2019) [22] showed that for the majority of PFASs studied, serum PFAS concentrations decreased in women who had recent menstrual bleeding compared with those who reported no bleeding [23]. Breastfeeding may be another important route of PFAS excretion in women. Studies have shown that PFAS levels, particularly PFOS and PFOA, are higher in women who have never breastfed [24]. It is important to underline that the level in breastfed children is higher than in the maternal plasma [25].

Sources of exposure

The sources of exposure to PFAS can be classified as:

2.1. Non occupational

- Consumption of contaminated food, most commonly fish from contaminated aquatic environments, meat and meat products.
- Use of products such as: paper and cardboard packaging, upholstery, fabrics, leather goods treated with water-repellent additives, insecticides and pesticides, detergents, medical devices. Although considered "non-occupational", some of these products might be used also in office buildings, cleaning services or agriculture work, situations where they become an occupational hazard.

2. 2. Occupational

There are few occupational medicine studies on occupational exposure to PFAS although these substances are present in several industries.

2.2.1. Firefighters

Firefighters are exposed through the use of aqueous film-forming foam (AFFF- aqueous film-forming foam) in fire rescue operations and through firefighting equipment that is made of PFAS-treated materials. AFFFs used to fight Class B oil fires contain longer-chain PFAS such as PFOA and PFOS.

The use of PFOS in new AFFFs and other products was banned in the European Union in 2011 and Canada in 2013, and major U.S. AFFF manufacturers have indicated that they will no longer produce PFOA-based fluorosurfactant foams after 2015. However, AFFFs typically have a long shelf life of up to 25 years. In addition, current fluorinated AFFFs contain shorter-chain PFAS chemicals, about which less is known about potential toxicity. Epidemiologic studies have associated fire-fighting with an increased risk for a variety of cancers, including testicular and kidney cancer, among others, but the exposures responsible for these increased rates have not been identified [26].

2.2.2. Professional ski waxers

In this occupation, the usage of solid ski waxes and ski wax powders, necessary for the preparation of equipment in different winter sports such as cross-country skiing, downhill skiing and biathlon is the main source. A study conducted in Norway in 2010 showed the presence of 11 perfluorinated carboxylic acids (PFCA) and 8 sulfonic acids (PFSA) in the serum of 13 professional ski waxers. These compounds were also identified in the workroom air and in the composition of solid ski waxes and ski wax powders [27].

2.2.3. Other workplaces

Chemical factories, ammonium perfluorooctanoate manufactures [28], textile manufactories using coating agents such as water repellents and surfactants [29], custodial maintenance (e.g. waxing of the floors), construction industry (roofing coatings, some types of paints, flooring materials, adhesives, and even glass fixtures).

The reprotoxic effect of PFAS

Studies have linked exposure to PFAS to a number of health problems, such as developmental effects, immune system dysfunction, metabolic disorders and an increased risk of certain cancers [30-32]. PFAS are endocrine disrupting chemicals (EDCs) defined as "exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action" [33]. In the latest statement of the Endocrine society on this issue the main health effects were categorized in a) obesity, diabetes and cardiovascular disease, b) female reproductive health c) male reproductive health d) Hormone-Sensitive Cancers in Females e) Prostate Gland Disruption f) Thyroid Disruption g) Neurodevelopmental and Neuroendocrine Effects of EDCs [34].

The effects of the PFAS on the reproductive function might by direct or indirect.

The direct ones refer to the consequences on the reproductive system of women and men and on the immediate, medium and long term effects on the offspring. They also cover the transmission and possible influence of these chemicals on breastfeeding.

The indirect effects refer to their relation with obesity, dyslipidemia and diabetes which all might affect fertility in both sexes [35-37]. or lead to higher risk of pregnancy complications [38, 39].

3.1. Direct effects

3.1.1. Reproductive effects on women

Numerous studies have shown that some PFAS have the potential to affect endogenous hormone metabolism and the production or secretion of steroid hormones, including that of estradiol (E2), progesterone, testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) [40], [41-45], reducing fecundity [46] damaging the development of oocytes [47] or the corpus luteum function [48].

A reduction in fecundity by 11% for one standard deviation increase in PFOA and of 9% for a standard deviation increase in PFHxS was found in a large cohort including 1743 participants. The odds of infertility were even higher: increase by 31% per one SD increase of PFOA and by 27% per one SD increase of PFHxS [49]. In this study PFOS had no statistical significant association neither to fecundity nor to infertility. Another study identified that primary ovary insufficiency was also more prevalent in women with higher circulating levels of PFAS and PFOA [50], in line with the infertility data described above.

The risk of miscarriage seems also to be higher in those exposed to PFOA or perfluoroheptane sulfonate (PFHpS) in case–control study nested within the Danish National Birth Cohort [51]. Others have shown that exposure to PFAS early in life can disrupt placental growth and function [52] such as induction of apoptosis of the placental syncytiotrophoblasts, reduction the secretion of estradiol, human chorionic gonadotropin and progesteron [53] modification of epigenetic loci, influencing genes involved in fetal growth, neurodevelopment and cardiometabolic health [54]. In another case-control study, the level of PFOA and PFAS in the placenta was correlated with pregnancy complications such as preterm birth, preeclampsia, gestational diabetes or small-for-gestational age, independent of other possible confounders [55].

Some of the negative on the reproductive system are mediated by the deregulating of the thyroid-stimulating hormone (TSH), triiodothyronine (T3) and/or thyroxin (T4) axis [56-63], which is essential for the female reproductive system: it mediates the gonadotropin releasing hormone (GnRH) secretion [64], increase the Follicle Stimulating Hormone (FSH) action on the ovary follicles [65], and maintain the normal uterine growth [66]. As consequence, both hypo- and hyper-thyroidism are associated with infertility [67].

3.1.2. Reproductive effects on men

An extensive review of the epidemiological data showed many inconsistent results in studies which has analysed semen volume or quality (sperm motility, proportion of morphologically normal spermatozoa) and sex hormones that regulates spermatogenesis (total or free testosterone, FSH, LH) [68]. Both positive and negative correlations were found, probably due to the different effects of certain compounds considered in these studies; there was however, a tendency to a more likely positive correlation in younger populations. For example, a study conducted in Italy in men (average age = 18 years) identified significant differences in those with higher environmental exposure. In this research not only the blood samples contained significantly more PFOA and PFOS but also the semen samples. The main differences noticed referred to anthropometric measures (testicular

volume, penis length), to sperm concentration, motility and morphology of the spermatozoa [69], and to the significantly higher levels of testosterone and LH. To explain the apparently less physiological effects, the authors designed an experiment on HeLA cells and on Leyding MA cells. In the first one, the presence of PFOA reduced the binding of testosterone to the androgen receptor. Leiding MA cells incubated with testosterone and PFOA showed a reduced internalization of the androgen receptor, therefore diminishing its nuclear action.

It is not in the scope of this review to present detailed experimental data. However, we have to underline that they are many (either on female or on male reproductive system) and well designed studies are needed in particular in the occupational were exposure can not avoided.

3.1.3. Effects on breastfeeding

One of the main effects of maternal exposure to perfluoroalkylated substances is a decrease in the total duration of breastfeeding, whether breastfeeding is exclusively or mixed (breast and formula feeding). Timmermann C.A.G. et al. analysed the serum levels of 5 PFAS - in the blood of 1092 mothers during pregnancy and 2 weeks after birth. Breastfeeding duration was assessed by questionnaire and clinical interview. In adjusted linear regression models, a doubling of maternal serum PFAS was associated with a reduction in breastfeeding duration. A doubled serum PFOS level reduced total breastfeeding duration by 1.4 months for multiparous women and by 1.3 months for primiparous women, and a doubled serum PFOA level reduced exclusive breastfeeding duration by 0.5 months for multiparous women and 0.4 months for primiparous women [70].

There is a strong correlation between maternal serum PFAS levels and the number of months of breastfeeding. In a study in a population of 1716 mostly nulliparous women, the association between plasma concentrations of nine PFAS during pregnancy and discontinuation of breastfeeding before 3 and 6 months of age, respectively, was assessed. Samples were collected from women between 17-20 weeks gestation. Thirteen PFAS were measured, of which only 7 met the >50% threshold values above the limit of quantification (LOQ set at 0.05 ng/mL): PFOA (perfluorooctanoic acid), PFNA (perfluorononononanoic acid), PFDA (perfluorodecanoic acid), PFUnDA (perfluoroundecanoic acid), PFHxS (perfluorhexanesulfonic acid), PFHpS (perfluorheptane sulfonate) and PFOS (perfluorooctansulfonic acid). The two outcomes of interest were: breastfeeding was discontinued before the end of 3 full months of breastfeeding by approximately 11.18% of the study population (n = 192 women) and discontinuation of breastfeeding before 6 full months, recorded in a total of 362 women (approximately 21.09%). In the analyzed samples PFOS had the highest median concentration (12.9 ng/ml), followed by PFOA (2.56 ng/ml).

Increased concentrations of PFNA, PFDA and were associated with a reduced risk of breastfeeding cessation at both 3 and 6 months, indicating longer breastfeeding durations. This suggested that at least from the perspective of the duration of breastfeeding, these compounds would have a less harmful effect [71].

3.1.4. Effects on the fetus and newborn

As mentioned above, PFAS/PFOA pass through the placenta in the fetal circulation. The levels of these chemicals in the fetal circulation and organs were similar to those in the placenta and tended to accumulate in highest quantity in the lungs in the first trimester and afterwards in the liver. The heart had intermediate values in the second and third trimester. The concentrations of PFOA were higher than those of PFAS [72]. The parity decreased and by the fish consumption increased the maternal and PFAS concentrations at week 18 of pregnancy, independent of age and BMI [73]. As there is a certain equilibrium between serum maternal concentrations and the fetal concentrations, these factors also affect their bioavailability in the offspring circulation.

There are short term (first 1-2 years after birth), medium term (after the first years till puberty) and long term effects (adults) described in association with the prenatal exposure.

3.1.4.1. Short term effects

In different cohorts of new born child, PFOA [74] or PFAS [75] were associated with low birth weight. A synthesis of 11 prospective prenatal cohorts confirmed this association and found that perfluorodecanoic acid (PFDA) explained the highest percentage (40%) of these effects [76]. In breastfed babies, PFAS exposure alter the phospholipid composition of breast milk [77]. This modification increase the size of milk fat globules, which were associated with slowed growth and increased markers of intestinal inflammation in infants.

The neurological development was assessed at 6 months of age in child born by 114 healthy women, with normal BMI recruited at week 18 of pregnancy [78]. None of the mothers was exposed to occupational pollutants, 55% were primipare, 2/3 had higher education, all had an omnivorous diet and 90% reported serving fish for dinner at least once a week.

All babies were healthy, born at term. At 6 months of age, the infant's gross motor development was assessed by a pediatrician using the Alberta Infant Motor Scale (AIMS) considering both quantitative (e.g., motor skill emergence) and qualitative (e.g., motor performance mode) characteristics. The mean duration of exclusive breastfeeding was 3.8 months, but 98 infants (86%) were breastfed for up to six months. Infant serum concentrations of all PFAS were closely correlated with maternal levels throughout pregnancy and in the postpartum period. In the study, a strong correlation was demonstrated between poorer gross motor development and higher PFAS concentrations in very young infants. Parity and fish consumption were strong predictors of maternal PFAS status, while maternal PFAS concentrations at 18 weeks of gestation and months of exclusive breastfeeding determined infant PFAS concentrations at six months [79].

3.1.4.2. Medium term effects

In line with the low adiposity at birth, a meta-analysis found that the prenatal exposure to exposure to PFHxS was inversely and significantly associated with BMI z-scores in pediatric population [80], despite large studies supporting a dose relation association [81, 82]. As for the adult population, the medium term effect of the intrauterine exposure to PFAS/PFOA on adiposity remain rather uncertain.

In a cohort of 967 mothers and children, the prenatal and early postnatal exposure to PFAS was correlated with the neurocognitive development at 7 years of age of the children [83]. The evaluation of the neurocognitive development was comprehensive, including vocabulary, similarities, block design, and matrix reasoning. A possible confounder in this type of studies is the longer duration of breastfeeding which increases child's level of PFAS/PFOA but has a positive impact on the neurocognitive development. In an US study, positive association was found between prenatal PFAS exposure and the cognitive outcome at 4 years of age, with sex specific differences according to the instrument used for the cognitive evaluation. For example, using Bayley Scales of Infant Development index, the relation with PFOS was negative for boys and positive for girls [84].

Prenatal exposures to PFNA, PFDA, PFOS, PFHpS, and PFHxS were associated with earlier age at onset of puberty. The dose-effect was, as for other endocrine disruptors, non-monotonic for the majority of these substances in girls [85]. In the same cohort exposure to PFHxS and PFHpS decreased the age of puberty in boys, as well. On the contrary, PFDA and PFNA exposure delayed to age of puberty in boys. Other studies reported also later age of menarche [86] or level of testosterone compatible to a pubertal sexual maturation [87] or no influence [88].

PFOA are listed as class I carcinogens by the International Agency for Research on Cancer based on the well documented effects on animal experiments and on a demonstrated mechanistic effects in humans [89]. Enough evidence from epidemiological studies are still missing. An interesting report about acute lymphoblastic leukemia (ALL) diagnosed in children younger than 15 years old, found a more than doubled risk in those who were highly exposed intrauterine to N-methyl-perfluorooctane sulfonamidoacetic acid [90]. The relation was independent on child's gender, but was stronger for the first born and for children diagnosed with ALL in the first 5 years of life.

3.1.4.3 Long term effects

In a long term follow up of young men with known prenatal exposure to PFAS, the perfluoroheptanoic acid was identified as main contributor to the lower sperm concentration, lower total sperm count and to the higher proportion of nonprogressive and immotile sperm [91].

There is also a nested case control study in a cohort 19,044 live births with a follow up of 54 years that benefited from their mothers' samples which were analysed for a variety of PFAS and PFOA. There were 137 daughters of these mothers who were diagnosed with breast cancer before the age of 52 years. The analysis showed that there was statistically significant association (OR=3.1, CI: 1.2,8.2 in quartile 4 compared to quartile 1) between exposure in utero to a precursor to PFOS (EtFOSAA), and risk of breast cancer in the presence of high maternal perinatal total cholesterol [92]. This is not a conclusive result of the long term exposure, as the association was not maintained if mothers had low cholesterol levels.

3.2. Indirect effects

Obesity is a high matter of concern for the reproductive function in both sexes, but the association between exposure to PFAS and PFOS obesity is still controversial. No association [93], positive [94] and negative association were found [95] in different studies, maintaining a high level of uncertainty on this issue.

Epidemiological studies also found that some PFAS impair the free levels of leptin in circulation, which might explain a higher food intake [96]. PFAS/PFOA exposure were also related to elevated plasma lipid levels and dyslipidemia [97]. In this Chinese representative sample the strongest associations were found for: PFHpS, PFUnDA, PFNA and PFOS,

even the dose-response relationship was not linear. The association between PFAS and the abnormal plasma lipoprotein profile was stronger in people with diabetes mellitus [97].

An interesting metabolomic study provided supplementary arguments about the relation between PFOS, obesity, lipid metabolism and the altered response to oral glucose [98]. High exposure to PFOS associated higher levels of glycerol. As it is well known, glycerol results from the breakdown of triglycerides in adipocytes. Indeed, in this study, glycerol was linked to obesity. But glycerol is also a substrate for gluconeogenesis in the liver, contributing to the high hepatic glucose output and diabetes. Another finding of this study was the association with phenylalanine, an amino acid which exacerbates the lipid accumulation in the liver [99].

There are few occupational studies on PFAS and PFOA and lipid metabolism and one of them, conducted on fire-fighters, revealed the complexity of the relation. In this occupation, the longer duration of fire fight work increased the blood levels of PFAS and PFOS. In young fire-fighters, the level of blood free fatty acids (stearic acid, oleic acid) was directly associated with the PFAS concentration [100], while after longer exposure this relation was reversed. The authors explained this finding as a probably abnormal adaptive response to the exposure, with more retention of lipids in the liver and increased peroxisome and β-oxidation. In regard of these results, longer versus shorter duration of exposure to highly persistent toxic substances might have different metabolic effects. If this finding is confirmed in other occupational cohorts, it might be translated in a recommended limit of years of exposure.

In what concerns the relation with diabetes, moderate occupational exposure to ammonium perfluorooctanoate, a product which is transformed by the human body in PFOA, the incidence of diabetes was significantly higher than the one expected from general population data [101]. Mortality from diabetes was higher in workers from a polymer production plant [102].

A longitudinal study also supported a role of these toxicants in the etiology of diabetes. This study included overweight and obese persons, randomized for lifestyle intervention median, during 8.9 years of follow up, the risk of diabetes increased by 14% with a doubling in baseline concentration of the branched perfluorooctanoic acid if no lifestyle intervention was provided during. Each doubling in N-ethyl-perfluorooctane sulfonamido acetic acid or perfluorodimethylhexane sulfonic acid was associated with 17% and, respectively, 18% greater odds of prevalent microvascular disease (neuropathy, retinopathy or kidney disease) disregard of the intervention [103]. There are all human data that higher levels of PFAS act to decrease the beta-cells function [104].

Take-away messages for the occupational medicine doctors

The reproductive toxicology is not sufficiently developed in occupational medicine practice and there are few guidelines on how to assess this issues. In the American Association of Occupational and Environmental Medicine (ACOEM) guideline [105] the followings are underlined. First, the recognize of the hazard and the risk characterization should be the result of a multidisciplinary team which includes besides the occupational medicine specialist, toxicologists, occupational hygienists, obstetrician/gynecologists and other health professionals, if necessary. The occupational medicine doctor should take a detailed medical and reproductive history, including the one of the partner, and should consider other elements from the working environment which might contribute to adverse effects on the reproductive function or evolution of the pregnancy such as: heavy lifting or strenuous physical effort, chemical, physical or biological hazards. Nonoccupational factors such as personal habits (alcohol, smoking, exercise), hobbies, drugs, non occupational usage of chemicals (personal care products, cleaning agents) need to be assessed as well. The risk characterization implies an estimation of the intensity, duration and frequency of exposure. All these elements should be communicated including the uncertainties due to the insufficient scientific data if applicable.

The Romanian legislation requires a risk assessment during pregnancy and avoidance of any hazard which might influence the pregnancy and the affects the offspring. PFAS/PFOA are included in the reprotoxic list and any exposure should be avoided. This includes also the environmental one, and information about this risk should be provided also. For returning to work while breastfeeding, the same precaution is to be taken.

Conclusion

Limiting the use of PFAS/PFOA should be achieved through policy and business practices changes but also through individual measures, particularly for

future parents, pregnant and breastfeeding women. In this latest approach the occupational medicine doctor should take an active role in identifying the risk, education, and limitation of exposure.

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