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Perfluoroalkyl substances (PFAS) and their effects on the placenta, pregnancy and child development: A potential mechanistic role for placental peroxisome proliferator-activated receptors (PPARs)

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Abstract

Purpose of review.—This review summarizes studies highlighting perfluoroalkyl substances (PFAS) and their effects on the placenta, pregnancy outcomes, and child health. It highlights human population-based associations as well as *in vitro*-based experimental data to inform an understanding of the molecular mechanisms underlying these health effects. Among the mechanisms by which PFAS may induce toxicity is via their interaction with the peroxisome proliferator-activated receptors (PPARs), nuclear receptors that regulate lipid metabolism and placental functions important to healthy pregnancies, as well as fetal and child development.

Recent findings—*In utero* exposure to prevalent environmental contaminants such as PFAS is associated with negative health outcomes during pregnancy, birth outcomes and later in life. Specifically, PFAS have been associated with increased incidence of gestational diabetes, childhood obesity, preeclampsia, and fetal growth restriction. In terms of placental molecular mechanisms underlying these associations, studies demonstrate that PFAS interfere with trophoblast lipid homeostasis, inflammation, and invasion. Moreover these effects could be mediated in part by the interaction between PFAS and PPARs, as well as other biological mechanisms.

Conflicts of Interest

The authors have no conflicts of interest to disclose

Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

Summary—This review summarizes how PFAS, critical environmental contaminants, may contribute to diseases of pregnancy as well as early and later child health.

Keywords

PPAR; placenta; PFAS; preeclampsia; *in utero*; pregnancy; development

Introduction

The placenta is a temporary organ that connects the fetus with the maternal blood supply through the endometrium. The primary function of the placenta is to ensure that the fetus develops properly throughout pregnancy (1). To accomplish this, the placenta performs endocrine, immune, and chemical exchange functions that maintain optimal conditions for fetal development (1). The placenta regulates the flow of nutrients in and waste out of the fetal compartment, thereby meeting the high metabolic demand of the developing fetus (2). Because of its role in fetal development, disturbances to placental homeostasis, such as those induced by exposure to chemical substances, can negatively influence neonatal outcomes and increase disease risk later in life (3). It is therefore crucial to understand the contaminants that impact the human placenta and the molecular mechanisms by which these may negatively impact pregnancy and fetal health.

Perfluoroalkyl substances (PFAS) are widely used in commercial products and serve a diverse array of functions as resistant coatings, lubricants, and aqueous film forming foams (4, 5). As a result of their chemical stability and extensive use, PFAS are ubiquitous and persistent in the environment and are detectible in >97% of human serum samples in the United States (6, 7). The effects of PFAS exposure include lipid accumulation in the blood and liver, immunotoxicity, and certain cancers (8). *In utero* exposure may lead to increased health risks to the mother during pregnancy, and to the child at birth as well as later in life (8). While the precise cellular mechanisms underlying the effects of PFAS are not well understood, they include dysregulation of mitochondrial bioenergetics, plasma membrane potential, intracellular pH, calcium signaling, lipid homeostasis, cellular mobility, and inflammatory signaling (9-12). Although PFAS likely exert these effects through multiple molecular targets, there exists strong evidence across studies to suggest that PFAS toxicity is driven, in part, by their interactions with peroxisome proliferator-activated receptors (PPARs) (8, 13-23).

PPARs are nuclear receptors activated by endogenous fatty acids and certain lipid-like xenobiotics and include three isoforms: α, β/δ, and γ (24). They are classically recognized for their role in regulating fatty acid disposition and metabolism and have been recognized as a contributing factor to metabolic and cardiovascular diseases (24). In the placenta, all three PPAR isoforms are expressed and regulate critical and tightly regulated functions that contribute to placental and fetal homeostasis (25, 26). While the role of each PPAR in placental function has not been fully characterized, both unique and common functions between the isoforms have been observed. For example, all three isoforms regulate placental lipid, hormone, and glucose metabolism (27). However, the strongest evidence exists to support that PPARγ is a regulator of placentation and controls trophoblast differentiation,

inflammatory response, oxidative pathways and barrier formation (28, 29). Moreover, dysregulation of both PPARα and γ in the placenta has been implicated in the pathophysiology of gestational diabetes mellitus, intrauterine growth restriction, and preeclampsia (30). It is therefore likely that environmental exposure to PPAR-activating chemicals contributes to placental dysfunction and diseases of pregnancy.

PFAS have been shown to interact with all three PPAR isoforms. Perfluorooctanoic sulfate (PFOS) and perfluorooctanoic acid (PFOA), for instance, have been shown to activate human and PPARα and β/δ but not γ in a luciferase reporter cell line (19). PPARα is generally supported as the targeted isoform for PFAS activation. Still, some of the effects of PFAS *in vivo* are persistent even in Pparα$^{-/-}$ mice, suggesting that other PPARs play a role (13, 18, 31). There is some evidence of PFAS interaction with PPARγ; PFOA binds to PPARγ in adipocytes and increases fatty acid accumulation and differentiation (22). It is therefore possible that PPARγ can compensate in the absence of the PPARα, but other lipid-regulated nuclear receptors, such as the pregnane X receptor, farnesoid X receptor, liver X receptor, and constitutive androstane receptor have been proposed as potential targets of PFAS (18, 32). Moreover, while PPARα may be the preferential target for PFAS above the other PPAR isoforms (15, 16, 19, 20, 23, 32), consideration must be given to each individual PFAS in combination with tissue type and effect observed to elucidate the precise mechanisms driving PFAS toxicity.

By summarizing both human population-based observational studies and mechanistic *in vitro* data, this review highlights putative molecular mechanisms underlying the interactions between PFAS and the placenta and how this may influence maternal/child health. Specific outcomes addressed in this review include metabolic disease, both during pregnancy and in children, pregnancy hypertension and fetal growth. Reviews have been previously published detailing comprehensive descriptions of the outcomes of *in utero* PFAS exposure (Reviewed in 33, 34-36). Specifically described in the present review are these health outcomes in the context of the interaction between PFAS and placental PPARs. By understanding the potential connections between PFAS exposure, placental PPAR signaling, and health during pregnancy, early life and later life, it may further be possible to identify genetic risk factors and preventative measures against the toxic effects of *in utero* exposure.

Metabolic diseases during pregnancy and in children

Metabolic disease includes maternal obesity during pregnancy, gestational diabetes mellitus (GDM), and childhood obesity among others (37). Metabolic disease is a concern to pregnant women and the developing fetus as it can have both immediate and long-lasting effects on both. The causes of metabolic dysfunction are likely multi-factorial, and evidence supports that environmental obesogens are involved (38). Moreover, strong evidence supports the role of PPARs as a molecular target for metabolic disease, as they are known to regulate cellular energy and lipid homeostasis (24). While PPARs also regulate energy and lipid balance in trophoblasts (26), it is not currently understood how aberrant placental PPAR signaling influences the development of maternal and fetal metabolic disorders.

Gestational diabetes

Gestational diabetes mellitus is classified as a condition in which women without a previous diagnosis of diabetes exhibit abnormally high blood glucose levels during pregnancy and affects 1 in 7 births worldwide (39). Although the precise causes of GDM are unknown, exposure to environmental contaminants may contribute to the disease. For example, in a multi-center prospective cohort study of healthy US women with a family history of type II diabetes, PFOA, perfluorononanoic acid (PFNA), perfluoroheptanoic acid (PFHpA), and perfluorododecanoic acid (PFDoDA) were positively associated with GDM (40). In metabolically vulnerable pregnant women it was found that perfluorohexanoic sulfonate (PFHxS) and PFNA concentrations were associated with impaired glycemic status, evidenced by higher fasting glucose, insulin, fasting insulin, insulin resistance and beta-cell function (41). Evidence also supports the role of PPAR and PPAR agonists as a contributing factor (27, 42, 43).

In considering the toxicological mechanisms involved in GDM, evidence supports the role for placental PPAR dysfunction potentially through epigenetic mechanisms. Placentas from pregnancies affected by GDM have decreased expression of PPARα and PPARγ driven in part by altered DNA methylation and miRNA expression (27, 42, 43). It should be noted that reverse causality is an issue in the interpretation of these findings as it is not clear whether placental PPAR dysfunction is a cause or effect of GDM. Nevertheless, these data highlight the involvement of PPAR and, by association, lipid dysregulation in GDM.

Childhood obesity

Obesity affects up to 18.5% of children under the age of 19 in the United States (44). Although the causes of childhood obesity are not fully understood, *in utero* exposures to various environmental contaminants including PFAS have been strongly associated with obesity later in life (45-48). Childhood obesity is likely influenced by a combination of factors. It is worthwhile to understand how environmental contaminants affect the developing fetus in a lasting way and through what biological mechanisms.

A clear positive association is evident between PFAS exposure *in utero* and obesity later in life as detailed in at least six separate studies. For instance, in a prospective birth cohort study in Shanghai, China, prenatal exposure to perfluorobutanesulfonic acid (PFBS), as measured in cord blood, was positively associated with adiposity at 5 years of age in girls (49). Likewise, in the Project Viva cohort, a prospective pre-birth cohort study in Massachusetts, maternal plasma PFOA, PFOS, PFHxS, and PFNA were associated with indicators of obesity at seven years old in girls but not boys (48). Specifically in that study, each interquartile range increment of prenatal PFOA concentrations was associated with 0.21 kg/m^2 higher body mass index, 0.76 mm higher sum of subscapular and triceps skinfold thickness, and 0.17 kg/m^2 higher total fat mass index (48). Similar associations were observed for PFOS, PFHxS, and PFNA (48). In a prospective cohort in Cincinnati, OH, maternal PFOA during pregnancy was positively associated with adiposity in children at 8 years of age where the highest PFOA tercile had an average 4.3 cm increase in waist circumference (50). In a longitudinal cohort study in Colorado, sex-dependent differences were observed in the association between maternal PFAS concentrations and offspring

adiposity at 5 months (51). In male infants, maternal PFOA and PFNA were associated with a 1.5–1.7% fat mass increase, whereas in females, maternal PFHxS and PFOS were associated with lower weight z-scores (−0.17 and −0.26 respectively) (51). In a longitudinal study in the UK, maternal PFOA concentration was associated with body fat of girls at age 9, an association that was dependent on maternal education status (52). In the lower educated group, body fat in girls was 1.4% higher for each ng/mL PFOA increase (52). In contrast with these data, a study on a cohort of Spanish children found no significant association between maternal PFAS and weight gain at 6 months, 4 years, or 7 years (53). These conflicting results may be explained by dietary or genetic differences between the populations under study.

While experimental evidence supports the role of PPAR in the obesogenic activity of toxicants (22, 54), challenges remain in understanding the molecular mechanisms connecting *in utero* toxicant exposure to obesity later in life. The development of obesity in an individual is the result of interrelated factors beyond toxicant exposure including diet, activity level, ethnicity, genetics, and stress. Nevertheless, the placenta, being a central regulator of fetal programming, has itself been considered as a target that can impact later in life health outcomes including obesity (Reviewed in 55). Understanding how PPAR-related toxicants interact with the placenta in the context of metabolic disease and the biological processes involved may therefore provide much needed insight into their mechanisms of action.

Placental lipid dysfunction and metabolic disease

In vitro data mechanistically support the connection between PFAS, placental PPAR, and metabolic disorders during pregnancy. Specifically, PFAS cause lipid dysfunction across several *in vitro* trophoblast models. For instance, treatment of JEG3 trophoblast cell line with a mixture of eight PFAS was associated with increased plasmalogen phosphatidylcholine, and lyso plasmalogen phosphatidylcholine (56). Treatment of the JAR cell line with PFOS increased the mRNA expression of fatty acid binding proteins (FABPs) and enhanced fatty acid uptake (57). These *in vitro* studies are supported by epidemiological data. Specifically, in women enrolled in the Columbia World Trade Center birth cohort, the concentration of PFOA, PFOS, PFHxS, PFNA, and PFDS were positively associated with cholesterol, total lipids, and triglycerides in cord blood (58). In that study, PFOA and PFHxS in particular demonstrated a strong linear relationship with cord blood lipids (58). It should be noted, however, that cord blood measurements are not representative of placental-specific changes but are rather a cumulative mixture of lipids produced by the mother, placenta, and fetus. Nevertheless, these studies in placenta and cord blood are consistent with the breadth of evidence demonstrating that PFAS dysregulate lipid homeostasis and increase overall lipid accumulation in liver (Reviewed in 59).

Placental lipid dysregulation may itself drive metabolic disease during and after pregnancy. Multiple studies have shown that placentas from obese women have higher lipid content, lower mitochondrial fatty acid oxidation activity, and altered gene or protein expression of fatty acid transporters and enzymes, many of which are known PPAR targets (37, 60, 61). For instance, placental mRNA expression of fatty acid transporters 1 and 3, adipose

triglyceride lipase, adipose differentiation-related protein, as well as PPARγ itself were positively associated with pre-pregnancy BMI (60). In terms of fetal development, dysregulation of placental fatty acid turnover would modify the amount and types of lipids that accumulate in the fetal compartment, influencing adipose deposition and adipocyte programming (62). However, this evidence must be considered alongside the previously described thyroid dysfunction well characterized of PFAS exposure, which would itself contribute to metabolic dysfunction (Reviewed in 35).

Studies described above also highlight sexually dimorphic effects of PFAS exposure. These can, at least in part, be explained through PPAR signaling, which is well documented to dislpay sexually dimorphic responses (Reviewed in 63, 64). PPARα expression is responsive to pituitary and gonadal hormones (65), and the involvement of PPARα specifically in obesity is modified by the presence of estrogen (66). Moreover, transcriptomic analyses of human and baboon placenta have demonstrated sex-dependent differences the expression of in PPAR target genes (67, 68).

Taken together, interaction between environmental exposure to PFAS and placental PPAR signaling may in part be driving the development or exacerbation of metabolic disease during pregnancy and for children after birth. PFAS are associated with maternal obesity, childhood obesity, and gestational diabetes. Mechanistically, this may be supported by the experimental evidence that those same chemicals alter PPAR-dependent lipid metabolism and transport in trophoblasts and, as a result, contribute to metabolic dysfunction during and after pregnancy.

Placental insufficiency

Fetal weight

Birth weight is used as a general indicator of health at birth, and pregnancy disorders such as preeclampsia often precede low birth weight (69). Previous studies have demonstrated that low birth weight is significantly associated with occurrence of metabolic diseases, cardiovascular disease, respiratory disease, and abnormal neurodevelopment in adulthood (69).

Birth weight and fetal growth restriction have been tied to maternal PFAS exposure across multiple studies in humans (Reviewed in 33, 36). In the Maternal Infant Research on Environmental Chemicals (MIREC) study, a trans-Canada birth cohort study, maternal PFOA concentration was associated with decreased birth weight (70). Specifically in that study, Bayesian hierarchical modeling was used to demonstrate that a 1-unit increase in $\log_{10}$ PFOA level was associated with a 0.10 unit decrease in birth weight z score (70). Similarly, a modest negative association was found between maternal PFOS and birth weight in full-term infants in a population-based study in a Mid-Ohio Valley Community exposed to high levels of PFAS through groundwater contamination (71, 72). Specifically, fetal weight was decreased by a median value of 29 g per log unit increase of PFOS, but no significant relationship was observed with PFOA (71). Moreover in that study, in samples which blood sample collection preceded conception, fetal weight decreased 49 g per log unit increase of PFOS (71). These data indicate that the fetal development during the earliest stages of

pregnancy may be more susceptible to the effects of PFOS than later in pregnancy. In a hospital-based prospective cohort study in Japan, maternal serum PFOS was also negatively correlated with birth weight, but only in female infants (73). In that study, per $\log_{10}$ unit increase of PFOS, there was a median decrease in fetal weight of 148.8 g across all samples and 297.0 g in females (73). These data highlight that *in utero* exposure to PFAS hinder fetal growth, which is consistent with studies conducted *in vivo*. In pregnant rodents, PFOS and PFOA cause neonatal deaths, developmental delay and growth deficits, and PFOA, but not PFOS, had no effect in Ppara$^{-/-}$ mice (13, 14, 74). This suggests that PPARα is a critical signaling pathway mediating PFOA toxicity in mice, whereas PFOS may be acting through alternative or compensatory mechanisms. Prenatal exposure to GenX, a novel PFAS contaminant in drinking water, was also associated with lower fetal growth and placental abnormalities in rodents (75, 76).

The mechanisms driving the negative association between *in utero* exposure to PFAS and weight at birth in humans are not yet known. Based on *in vivo* studies, it is possible, that PFAS are interfering with placental function through PPAR signaling. There is evidence that PPAR signaling ensures controlled development of fetal metabolic tissue during gestation (77), and genetic studies in mice have established the essential role of PPARy in placental development (78). In addition, placental PPAR expression itself has been associated with fetal weight in humans (79). Since the placenta is itself critical for nutrient and waste exchange, placental insufficiency, as in the case of preeclampsia (detailed below), can be detrimental to fetal growth. Examining the association between environmental chemicals and diseases of placental insufficiency may therefore elucidate the mechanisms driving fetal growth inhibition resulting from PPAR agonist exposure.

Preeclampsia

Preeclampsia is defined as clinical hypertension and proteinuria that results specifically from pregnancy (80). It affects 2-8% of pregnancies and is a worldwide leading cause of maternal morbidity during pregnancy (81). Importantly, neonates from preeclamptic pregnancies are commonly lower weight than those from healthy pregnancies (82, 83). Preeclampsia is also associated with increased risk of neonatal thrombocytopenia, bronchopulmonary dysplasia, and stillbirth (Reviewed in 84). Individuals born from preeclamptic pregnancies are also higher risk for developing hypertension, obesity, and diabetes later in life (Reviewed in 84). Although a precise cause of preeclampsia is not known, dysregulated PPARα and γ signaling have been implicated, among others such as TGFβ, oxidative phosphorylation, and proteasome activity (85, 86).

Across multiple studies, PFAS are positively associated with hypertensive disorders (both preeclamptic and non-preeclamptic) during pregnancy (71, 87, 88). Maternal serum PFOA and PFOS were positively associated with pregnancy-induced hypertension in women from a Mid-Ohio Valley community (71). Similar results were observed in a cohort of Swedish women; the risk of preeclampsia increased with increasing maternal serum concentrations of PFOS and PFNA (87). Cord serum concentrations of PFBS, PFHxS, and PFUA were associated with increased risk of preeclampsia and overall hypertensive disorders in pregnant mothers from Shanghai, China (88). PFAS may therefore contribute to

hypertensive disorders during pregnancy, and this is supported by studies on the effects of these chemicals on trophoblast invasion *in vitro* as described below.

Trophoblast invasion into the maternal endometrium is a critical step in establishing adequate blood flow, and therefore nutrient supply, to the developing fetus (1). Shallow trophoblast invasion is a hallmark of preeclampsia and may be a central etiologic factor of the disease (1). PPAR itself is a central regulator of trophoblast invasion and differentiation from cytotrophoblasts to invasive extravillous trophoblasts (Reviewed in 78). Specifically, it has been demonstrated across multiple studies that PPARγ agonists inhibit trophoblast invasion in trophoblast cell lines, placental explant cultures, and in rodent models (89-91).

Exposures to PFAS demonstrate similar effects on trophoblast invasion *in vitro* as PPAR agonists. In JEG-3 spheroids, PFOA decreased attachment to RL95-2 endometrial cells, a consequence of poor trophoblast invasion *in vitro*, and the expression of pro-invasion genes (20). Interestingly, PFOA treatment did not alter PPARα, β/δ, or γ gamma expression in either cell type, but addition of a PPARα antagonist reversed all the observed effects of PFOA (20). This indicates that PFOA does not directly impact the expression of PPARs in JEG-3 cells but that PPARα is somehow involved in its effects. PFOS, PFOA, and GenX differentially decrease trophoblast migration and invasion in the extravillous trophoblast cell line HTR-8/SVneo as demonstrated using a modified scratch assay (92). Treatment with those PFAS also decreased the expression and secretion of inflammatory proteins involved in trophoblast migration, such as CCL7 and CXCL8 (92). In HTR-8/SVneo cells, PFOS also decreased expression of matrix metalloproteinases, which digest extracellular matrix proteins to promote invasion (92). This is consistent with the previously observed immunosuppressive effects observed with PFAS exposure across multiple models (Reviewed in 12). It is hypothesized that environmental PPAR agonists may inhibit trophoblasts *in vivo* as they do *in vitro*, thus explaining their involvement in preeclampsia.

Taken together, PFAS exposure has been negatively associated with fetal growth and appears to be detrimental to placental function, at least in part through PPAR. Fetal growth restriction could be a result from placental insufficiency, as seen in preeclampsia. PFAS have themselves been associated with the incidence of preeclampsia and, in support of this, have been shown to decrease trophoblast invasion *in vitro*.

Summary

Proper placental function is vital for fetal growth and development, and its dysfunction is intimately tied to poor health outcomes early and later in life. In support of fetal and maternal health during pregnancy, it is worthwhile to consider the interaction between environmental chemicals and the placenta, their effects, and the mechanisms therein.

In utero exposure to the prevalent environmental contaminants PFAS are associated with negative health outcomes at birth and later in life (48). Moreover, while PFAS likely interact with multiple molecular targets in the placenta, there is strong evidence to suggest that PPARs are involved in their toxicity (8, 13-23). In the placenta, PPARs are known to regulate

trophoblast differentiation and function (Reviewed in 26), and the effects of PFAS *in utero* may therefore be explained through their interaction with placental PPAR signaling.

Specifically discussed here were the clinical associations between PFAS and the incidence of gestational diabetes, childhood obesity, preeclampsia, and fetal growth restriction. Moreover, those observations were discussed alongside studies demonstrating how those same chemicals interfere with placental function indicative of their interaction with PPAR. Their association with metabolic disease could be driven, in part by dysregulating placental lipid homeostasis. Significant trends were observed between PFAS and fetal growth along with preeclampsia. In support of this, *in vitro* studies with those contaminants demonstrated a PPAR-mediated decrease in trophoblast invasion.

Many challenges exist in examining the precise interactions between environmental chemicals that act as PPAR agonists, placental function, pregnancy complications, and child health. *First*, it should be noted that the class of chemicals defined as PFAS comprises an array of chemical analogs. Each of these chemical analogs has its own chemical properties and toxicological profile driven, in part, by their differential interactions with each PPAR isoform. Moreover, although toxicological data exists for the most prevalent compounds, namely PFOS and PFOA, the majority of these compounds have not been examined for their effects on placenta. *Second*, while these studies have been presented in the context of PPAR, PPAR is not the only molecular target of PFAS. For instance, PFAS are known to directly inhibit mitochondrial beta oxidation, alter plasma membrane potential, and increase intracellular calcium (9-11). *Third*, placental PPAR signaling is inherently diverse in a human population and is subject to both genetic and environmental factors, such as single nucleotide polymorphisms and maternal nutrition, respectively (93, 94). Lastly, investigating the interactions of PFAS with placenta in a laboratory setting incurs its own challenges beyond the scope of this review. The human placenta is unique among mammals, and both *in vitro* and *in vivo* models of placenta fall short at perfectly recapitulating it (95, 96).

Although both clinical and experimental data have inherent weaknesses, they are complimentary to one another. Therefore, in order to uncover and understand the risks posed by exposure to environmental contaminants to public health, a multi-disciplinary approach is required. This review was to summarize studies that highlight PFAS and their interaction with the placenta as it pertains to fetal development. By integrating observations made at the clinical and molecular level, it can be hypothesized that interaction of environmental contaminants with placental PPAR contributes to diseases of pregnancy and developmental toxicity.

In conclusion, the literature summarized here provides evidence for the effects of PFAS in the placenta as well as a potential target for therapeutic and preventative intervention. For instance, as placental PPAR expression is influenced by genetic polymorphisms (93, 94), it is also be possible that PPAR genotypes may serve as biomarkers of individual susceptibility to the effects of environmental contaminants. Those individuals with specific variants of PPAR may be more sensitive to the effects of PFAS as well as other environmental PPAR agonists, such as polychlorinated biphenyls and phthalates. Moreover, in building upon the evidence presented here, future research could target placental PPAR and lipid metabolism

for therapeutic or preventative intervention of diseases of pregnancy. Supplementation with Ω-3 polyunsaturated fatty acids, which themselves interact with PPARs, has prevented some of the hepatotoxic effects of PFOA in particular (97). While the precise interaction between PFOA and Ω-3 polyunsaturated fatty acids has not been elucidated, Ω-3 polyunsaturated fatty acids could be a safe and accessible countermeasure to PFAS exposure and are already commonly incorporated in prenatal vitamin regimens. By understanding the molecular mechanisms driving the *in utero* toxicity of environmental chemicals such as PFAS, research can aim to improve maternal and fetal health during pregnancy and to minimize later-in-life health effects.

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