UNIVERSITÀ DEGLI STUDI DI PADOVA

Sede Amministrativa: Università degli Studi di Padova

Dipartimento di
Salute della Donna e del Bambino

CORSO DI DOTTORATO DI RICERCA IN: Medicina dello sviluppo e scienze della programmazione sanitaria
CURRICOLO: Scienze della programmazione sanitaria
CICLO XXXI

IMPACT OF PERFLUOROALKYLATED SUBSTANCES (PFAS) EXPOSURE ON MATERNAL AND NEWBORN HEALTH IN VENETO REGION

Coordinatore: Ch.mo Prof. Carlo Giaquinto
Supervisore: Ch.ma Prof.ssa Paola Facchin
Co-Supervisore: Dott.ssa Silvia Manea

Dottorando: Giulia Lorenzoni

Table of contents

Abstract (English)

Background. Perfluoroalkylated substances (PFAS) are persistent organic pollutants that accumulate in the fish, wildlife, and humans. In 2013, it has been discovered an area of the Veneto Region in which ground water, surface water, and drinking water were contaminated by PFAS. Appropriate interventions have been undertaken to contain the water pollution, reducing it effectively. However, it has been estimated that the contamination had started about fifty years before its discovery, leading to the long-term exposure of the population. The long-term exposure to PFAS is worrying because PFAS have been suggested to affect human health. Veneto Region has therefore organized a health surveillance programme of the population living in the polluted area. A specific aspect of such programme concerns the maternal and newborn health, which represents the focus of my PhD research project. The aims of the project were to review animal and human evidence related to this topic and to assess the effects of the exposure to PFAS on maternal and newborn health in the population living in the polluted area of Veneto Region.

Methods. The systematic review included relevant studies in the English language identified through the online database PubMed. Studies were eligible to the review if they assess the effect of PFAS exposure during the reproductive period on the health of the pregnant women and of the infant.

The identification of the outcomes of interest assessed in the study about maternal and newborn health in Veneto Region was based on the systematic review. The outcomes investigated were preeclampsia and gestational diabetes mellitus (GDM) (pregnancy complications), and intrauterine growth restriction, evaluated using a proxy of fetal growth, the Small for Gestational Age (SGA) (birth outcomes). The study was performed using an indirect measure of exposure to PFAS, defined as woman's residence in the contaminated area (including 21 municipalities identified according to a Veneto Region Official Resolution). A control area that included 48 municipalities not exposed to PFAS contamination according to the performance limits of the National Institue of Health was chosen for comparision. The information sources included two administrative datasets, the Veneto Region Birth Registry and the Veneto Region hospital discharge records. For the pregnancy complications (preeclampsia and GDM), a medical chart review of pregnant women hospitalized is ongoing to validate the cases identified from the hospital discharge records.

Results. The systematic review led to the retrieval of 1096 records from PubMed. One hundred and thirty-nine records were judged to be eligible to the study. Overall, evidence retrieved suggests that PFAS exposure might affect the health of the pregnant woman and the development of the fetus.

The epidemiological study showed that newborns of mothers living in the contaminated area were significantly more likely to be SGA compared to newborns of mothers living in the control area (adjusted Odds Ratio 1.26, 95% C.I. 1.14-1.38). Looking at pregnancy complications (preeclampsia

and GDM), preliminary results were available because the review of the medical chart is ongoing. Such preliminary results seem to suggest that the frequency of these pathological conditions is slightly higher in women living in the contaminated area compared to those living in the control ones. However, they must be taken with caution because the validation of preeclampsia and GDM cases is ongoing.

Conclusions. The results of the present research project suggest that PFAS exposure might affect maternal and newborn health. The present topic deserves further research, not only from the epidemiological point of view, but also for what concerns the pathophysiological mechanisms potentially involved in the association between PFAS exposure and adverse health outcomes in pregnant women and newborns.

Abstract (Italiano)

Razionale. Le sostanze perfluoroalchiliche (PFAS) sono inquinanti organici persistenti. Nel 2013, la scoperta di un'area inquinata da PFAS nella Regione Veneto ha portato all'immediata adozione di interventi atti al contenimento della contaminazione. Tuttavia, si stima che la contaminazione sia iniziata circa cinquant'anni prima della sua scoperta, determinando un'esposizione di lungo corso della popolazione. Questa scoperta ha destato grande preoccupazione poichè è stato suggerito che gli PFAS abbiano effetti avversi sulla salute umana. La Regione Veneto ha quindi attivato un piano di sorveglianza sanitaria della popolazione esposta. Un aspetto specifico di questo programma riguarda la salute materno-infantile che ha costituito il focus del mio progetto di Dottorato. Il progetto aveva come obiettivi quello di effettuare una revisione delle evidenze sull'animale e l'uomo riguardo questo tema e di condurre uno studio epidemiologico sulla salute materno-infantile della popolazione esposta nella Regione Veneto.

Metodi. Nella revisione sistematica sono stati inclusi tutti gli studi pertinenti, in lingua inglese, identificati dal motore di ricerca *PubMed*. Gli studi venivano considerati pertinenti se valutavano l'effetto dell'esposizione a PFAS, durante il periodo riproduttivo, sulla crescita intrauterina e le anomalie congenite strutturali e funzionali (esiti sul nato) e sul rischio di sviluppare preeclampsia, diabete gestazionale e disturbi della tiroide (esiti sulla donna in gravidanza).

Sulla base della revisione, sono stati identificati gli esiti di salute materno-infantile analizzati nello studio epidemiologico. Nello specifico, sono stati valutati il rischio di preeclampsia e diabete gestazionale (esiti sulla donna in gravidanza) e quello di nascere piccolo per l'età gestazionale (*SGA: Small for Gestational Age*) come *proxy* di crescita intrauterina. Lo studio ha utilizzato una misura indiretta di esposizione a PFAS rappresentata dalla residenza della donna nell'area contaminata (che include 21 Comuni identificati da una Deliberazione della Giunta Regionale della Regione Veneto). È stata inoltre identificata un'area di controllo impiegata come termine di confronto. Le fonti informative utilizzate sono state il Registro Nascita e le Schede di Dimissione Ospedaliere (SDO) della Regione del Veneto. Per quanto riguarda gli esiti sulla donna in gravidanza (preeclampsia e diabete gestazionale), è in corso un processo di validazione dei casi identificati dalle SDO, mediante la revisione delle cartelle delle donne ricoverate.

Risultati. La revisione sistematica ha identificato 1096 risultati, lo *screening* dei quali ha portato all'inclusione di 139 risultati. Gli studi inclusi sembrano suggerire che l'esposizione a PFAS possa influenzare negativamente la salute della donna in gravidanza e lo sviluppo del nato, sia nel breve che nel lungo termine.

Lo studio epidemiologico mostra che i nati da madri residenti nell'area contaminata hanno una probabilità significativamente maggiore di nascere SGA rispetto ai nati da madri residenti nell'area

di controllo (*Odds Ratio* aggiustato 1.26, 95% I.C. 1.14-1.38). Per quanto riguarda gli esiti sulla donna in gravidanza, vengono presentati i risultati preliminari in quanto la revisione delle cartelle è in corso. Questi risultati sembrano suggerire che la frequenza degli esiti di interesse (preeclampsia e diabete gestazionale) sia maggiore nelle donne nell'area contaminata rispetto a quella nelle donne nell'area di controllo.

Conclusioni. I risultati del presente progetto di ricerca sembrano suggerire che l'esposizione a PFAS possa influire sulla salute della madre e del neonato. Questo argomento merita ulteriori ricerche, non solo dal punto di vista epidemiologico, ma anche riguardo i meccanismi patofisiologici potenzialmente coinvolti nell'associazione tra esposizione a PFAS ed esiti di salute avversi sulla donna in gravidanza e sul nato.

Preface

This thesis is the result of the research project that I have developed during my PhD Programme in Developmental Medicine and Health Planning Sciences (curriculum: Health Planning Sciences), and it concerns the relation between exposure to Perfluoroalkylated substances (PFAS) and mother-child health outcomes.

This research project derives from a public health issue in the Veneto Region. In 2013, after some experimental studies requested by the Ministry of Environment over potentially pollutant substances, the presence of PFAS was discovered in the ground water, surface water, and drinking water in an area of the Veneto Region. This pollution is considered to be due to the release of these substances from a chemical plant located in the polluted area.

The discovery of the contamination triggered the immediate activation of a series of measures aimed to contain the pollution of drinking water, reducing it effectively. However, the water pollution has first occurred some fifty years before its discovery, thus involving a long-term exposure of the population living in the contaminated area. The fact that the population has been exposed for many years, through consumption of contaminated tap water, is a cause of concern. PFAS are persistent environment pollutants, known for their adverse effects on human health, some suspected and some proved by a wide range of studies. Veneto Region has therefore organized a programme aimed at the surveillance of population living in the polluted areas. A specific aspect of this activity concerns mother-child health, the aspect on which my PhD research was focused.

The choice of focusing on the effects of PFAS exposure over mother-child health is due to the fact that studies over this topic have shown that, not only PFAS accumulate in the body through the ingestion of polluted water but also fetus and breastfed newborn are exposed to PFAS through placental and lactational transfer, respectively.

My activities within this research project included the systematic revision of scientific evidence on exposure to PFAS and mother-child health and contributing to the development of a study of the effects of the exposure to PFAS on maternal and newborn health in the population living in the polluted area of the Veneto Region. Furthermore, I had the chance to deepen my knowledge of environmental epidemiology applied to PFAS research during an internship that took place at the WHO European Centre for Environment and Health (ECEH), which is part of the WHO Regional Office for Europe, located in Bonn, Germany.

These activities have resulted in the preparation of three papers, thought as standalone manuscripts, that constitute this thesis, which represents the result of the research project followed during my PhD Programme. The first paper introduces the theme of the relation between PFAS and mother-child's health outcomes through a systematic revision of bibliography related to this topic. The other two

papers report the results of the epidemiological study. Specifically, the second paper presents the preliminary results of the analysis of the epidemiology of pregnancy complications (gestational diabetes and preeclampsia) in pregnant women living in the contaminated area of the Veneto Region. The last paper describes the results of the study of intrauterine growth restrictions (birth outcome) in the newborns of mothers living in the contaminated area of the Veneto Region.

Systematic review of human and animal evidence on the effect of PFAS exposure on maternal and newborn health

1. Introduction

Perfluoroalkylated substances (PFAS) are chemical substances industrially produced. They present characteristics of repulsion to both fats and water, chemical stability, and all-round persistence. Because of these characteristics, they have been widely used both in domestic and industrial use. They can be found in a wide range of widely distributed products, for example, food containers (because of their non-stick characteristics) and fabrics (to make them water or fat repellent). These are just a few examples of a large range of applications.

At the beginning of the 2000s some instances have been reported where water was polluted by these substances. This discovery raised doubts over the safety of these substances, and various studies have been elaborated to assess their real effect over the environment, the animal kingdom, and of course for humans. These studies uncovered that these substances are persistent in the environment, toxic to animals, and they can produce adverse effects on humans (U.S. Environmental Protection Agency 2016b, 2016a). The PFAS most wideley produced and studied are the Perfluorooctanoic acid (PFOA) and the perfluorooctane sulfonate (PFOS), which are long-chain PFAS characterized by eight-carbon backbone (the distinction between short- and long-chain PFAS depends on the number of carbon atoms, with usually 6 carbon atoms used as a cut-off). As a result of such studies, the production and use of PFOA and PFOS have been restricted in recent years (PFOS, in particular, is listed in Stockholm Convention's criteria of persistent organic pollutant (Secretariat 2009)).

Several health effects have been hypothesized to be related to PFAS exposure (U.S. Environmental Protection Agency 2016a, 2016b), including some types of cancer (Benbrahim-Tallaa et al. 2014). An area over which PFAS research concentrated is the one concerning mother-newborn health. This area of research is motivated by the fact that pharmacokinetic studies over animals have demonstrated that PFAS are transferred from mother's blood to placenta during gestation and to mother's milk after birth, thus exposing fetus and newborn (Loccisano et al. 2012). These observations have been confirmed by successive studies regarding body burden of PFAS on humans and, in particular, on the pregnant woman. It has been in fact demonstrated a strong correlation between PFAS concentration in mother's blood, umbilical cord, and placenta (with decreasing concentration) (Glynn et al. 2012; Manzano-Salgado et al. 2015). Recent studies have shown that the strongest predictors of PFAS concentration in a pregnant woman are precedent pregnancy, having breast-fed, and length of the breast-feeding (Berg et al. 2014; Brantsæter et al. 2013; Sagiv et al. 2015). Women that have given birth and breast-fed have a lower concentration of PFAS in their blood compared to women that have

not had children yet (Berg et al. 2014; Brantsæter et al. 2013; Sagiv et al. 2015). A recent study has shown that, because of the exposure in the uterus, and because of breast-feeding, the body burden of PFAS in 6 months old subjects is comparable, if not higher, of the body burden in an adult (Fromme et al. 2010).

It is also interesting to observe how the efficiency of PFAS transfer from mother's blood to the placenta and breast milk can vary according to the characteristics of this substance. In particular, even though PFOA and PFOS are PFAS that contribute the most to the body burden of these substances, partitional analysis of these substances in mother's blood samples and umbilical cord samples suggests that short chain PFAS have a higher transfer rate (Gützkow et al. 2012; S.-K. Kim et al. 2011). These observations testify that not only PFOA and PFOS are a risk for human health, but also other kinds of PFAS that have been taken less into consideration so far, require a careful analysis of their potential effects on health.

Regarding pharmacokinetic of PFAS in the fetus and the newborn, studies are available in limited quantity, nonetheless available data are worrying. Studies over the distribution of PFAS in fetus and animal offspring showed that just like in adults, fetuses and offspring accumulate PFAS mostly in the liver, lungs, and kidneys. In fetuses and offspring, however, we can also observe high concentration of PFAS even in the brain (Borg et al. 2010; Onishchenko et al. 2011), therefore opening the discussion of possible neurodevelopmental effects of this exposure in the brain of the newborn.

Taking into consideration that the exposure to chemical substances in a crucial time, as the one spent in uterus or during the first months of life, can be detrimental because it can affect structural and functional development resulting in adverse health outcomes, the number of studies published over this subject has exponentially increased in less than twenty years.

Some specific aspects (such as the effect of exposure to PFAS over the intrauterine growth) have been deeply studied more than other ones and have been subject to systematic reviews and metanalysis. However, a systematic approach to the evidence published so far over the exposure to PFAS for maternal and newborn health is still missing. For this reason, we have proceeded into a systematic review over this topic.

2. Materials and Methods

2.1 Search strategy

Relevant studies in the English language published before the 5th of July 2018 were identified through the online database PubMed. The search string was made of two parts, the first one referred to the substances of interest (adapted from the search strategy employed in the US Enviromental Protection

Agency (EPA) report (U.S. Environmental Protection Agency 2016b, 2016a)) and the second one referred to the outcomes of interest (Table 1). No limits were applied to publication date.

2.2 Study selection and data extraction

The study aimed to review animal and human evidence of an association between PFAS exposure and maternal/newborn health. The study selection criteria were identified using two PICO (Participants, Intervention/Exposure, Comparator, and Outcomes) approaches (Higgins 2015) (one for animal and the other one for human evidence) (Table 2).

If a study was judged eligible to the review, then the information of interest was extracted. The information extracted for animal studies included the specie, the exposure, the route of exposure, the dose (range), the period of exposure, the outcome/s investigated. The information reported for human studies were the study design, the location in which the study took place, the population of interest, the exposure, the biological matrix (if any) on which the exposure was measured, and the outcome/s investigated. Studies' findings were summarized by reporting only the statistically significant results for the outcomes of interest adjusted for potential confounders (unless otherwise specified) if regression approaches were employed.

3. Results

The study selection procedure is reported in Figure 1 (PRISMA flow-chart). Briefly, 1096 records were retrieved from PubMed. The title/abstract screening led to the exclusion of 791 records. As a result, the full-text of 305 articles underwent the assessment for eligibility. One hundred and thirty-nine studies were judged to be eligible. Eighty-one out of 139 records reported evidence from human studies. The types of chemical substances investigated are reported in Table 3. Studies characteristics and results are summarized in Table 4 and 5 (animal and human evidence, respectively).

3.1 Animal studies

Fifty-eight records reported evidence from animal studies starting from 1984 (Table 4). Animals most frequently involved were the rat and the mouse (32 records). Among the non-mammalians, the zebrafish was the animal most frequently involved (14 records). Three records reported studies involving two species of animal (rat/mouse, rat/rabbit) (Case, York, and Christian 2001; Lau et al. 2003; Thibodeaux et al. 2003). All the studies included a control group not receiving PFAS. The exposure to PFOA and PFOS (either alone or in combination) was the most frequently investigated. The exposure to other types of PFAS has been investigated less frequently and only since the end of 2010, including both short-chain PFAS and long-chain PFAS.

3.2 Human studies

Eighty-one studies were included, corresponding to 38 datasets, published since 2007 (Table 5). In most cases they were birth cohort studies. PFAS exposure was most often directly measured in maternal blood during pregnancy, followed by cord blood. Only in four studies an indirect measure of in-utero exposure was estimated (Nolan et al. 2009, 2010; Savitz, Stein, Elston, et al. 2012; Savitz, Stein, Bartell, et al. 2012). In most cases, the exposure to several PFAS (both long- and short-chain) besides PFOA and PFOS was measured. The outcome most frequently investigated was the intrauterine growth restriction.

3.3 Relationship between PFAS exposure and the outcomes of interest

Animal and human evidence of association for the outcomes of interest is reported in following sections.

3.3.1 Pregnancy complications (Preeclampsia and Gestational Diabetes Mellitus)

Epidemiological studies that have investigated the relationship between PFAS exposure and the risk of developing preeclampsia and gestational diabetes mellitus during pregnancy are scant, if compared to those about intrauterine growth restrictions. It is noteworthy that the exposure to PFOA and PFOS has been suggested to be related to significantly higher gestational weight gain (Ashley-Martin et al. 2016; Jaacks et al. 2016). In addition to that, looking at the lipid panel, blood cholesterol was found to have a significant positive association in pregnant women with PFOA and PFOS (Skuladottir et al. 2015), while triglycerides were found to be inversely associated with PFOA, PFOS, and PFNA (Kishi et al. 2015; Matilla-Santander et al. 2017). Looking specifically at the risk of gestational diabetes mellitus, Zhang et al. have shown that it was significantly positively associated with PFOA in pregnant women (C. Zhang et al. 2015). A recent study based on a Spanish birth cohort, besides confirming such finding, has further shown that impaired glucose tolerance in pregnant women had a positive relationship with PFOA, PFOS, and PFHxS in the blood (Matilla-Santander et al. 2017). As for gestational diabetes mellitus, evidence about the relationship of PFAS with pregnancy-induced hypertension (PIH) and preeclampsia is inconsistent. Savitz et al. published a study showing no significant association between PFAS and PIH (Savitz, Stein, Elston, et al. 2012). The year after, Darrow et al. showed that PIH was significantly positively associated with PFOA and PFOS (Darrow, Stein, and Steenland 2013). Only weak or no association was found out with preeclampsia (Savitz, Stein, Bartell, et al. 2012; Starling et al. 2014; Stein, Savitz, and Dougan 2009).

3.3.2 Intrauterine growth restrictions

Two reviews, conducted using the Navigation Guide methodology, specifically developed for environmental health evidence revision (Woodruff and Sutton 2014), over the effect of PFOA on fetal growth have concluded that there is sufficient evidence of an association between prenatal exposure to PFOA and intrauterine growth restrictions both in animals and humans (Koustas et al. 2014; Johnson et al. 2014). Conversely, a further review published one year later by Bach and colleagues about the epidemiological evidence on the effect of PFOA and PFOS exposure on in-utero human growth concluded that evidence is still inconclusive, even if it seems that growth is affected by high concentrations of PFOA and PFOS (Bach et al. 2015). Not least, a very recent meta-analysis on 24 human studies concluded that there is only modest evidence of an inverse association between PFOA and birthweight (Steenland, Barry, and Savitz 2018).

Undoubtedly, fetal growth is the birth outcome most widely studied in the field of PFAS research. From the public health perspective, it is of great relevance since fetal growth restrictions are a strong predictor of morbidity and mortality.

Non-mammalian studies showed that body length is significantly lower in zebrafish exposed to PFOA and PFOS (Dang, Wang, and Liu 2018; Hagenaars et al. 2011; Jantzen et al. 2016; Shi et al. 2008). In addition to that, it has been shown that larvae volume and pupa weight is significantly lower in fruit fly exposed to PFOA (J. Wang et al. 2010). In rats and mice, it has been shown that both fetal and pups weights are significantly affected mainly by PFOA and PFOS exposure (Case, York, and Christian 2001; Lau et al. 2003; Thibodeaux et al. 2003; Butenhoff et al. 2004; Grasty et al. 2003; Iwai and Hoberman 2014; Lau et al. 2006; C. K. Lee et al. 2015; X. Li et al. 2016; Rogers et al. 2014; Staples, Burgess, and Kerns 1984; Suh et al. 2011; White et al. 2007, 2011; Wolf et al. 2007; Yahia et al. 2010) and, when placental weight was assessed (as a proxy of nutrient transport efficiency), an inverse association with PFAS exposure was found (C. K. Lee et al. 2015; X. Li et al. 2016; Suh et al. 2011).

Epidemiological studies considered a wide variety of proxies of intrauterine growth restriction, including birth weight (continuous or z-score), low birth weight (LBW) (birth weight <2500g), birth length, abdominal circumference, chest circumference, ponderal index (PI), being small for gestational age (SGA) (weight below the 10^{th} percentile for the gestational age), and body mass index (BMI). Such a variety of endpoints makes it difficult to compare the results from different studies. The growth endpoint most widely studied was the birth weight (treated as a continuous variable). Most of the studies that evaluated the birth weight found out a significant inverse association with some PFAS, in particular with PFOA (Andersen et al. 2010; Fei et al. 2007; Lenters et al. 2016; Minatoya et al. 2017; Starling et al. 2017; Wu et al. 2012), PFOS (Bach et al. 2016; M.-H. Chen et

al. 2012, 2017; Darrow, Stein, and Steenland 2013; Lauritzen et al. 2017; Washino et al. 2009), or both (Apelberg et al. 2007; Kwon et al. 2016; M. Li et al. 2017; Maisonet et al. 2012). Only a small number of studies found out a significant inverse association of birth weight with other PFAS, in particular with PFHxS and PFNA (Bach et al. 2016; Kwon et al. 2016; Maekawa et al. 2017; Maisonet et al. 2012; Y. Wang et al. 2016). Four studies found out higher risk of SGA for newborns exposed in-utero to PFOA and PFOS (M.-H. Chen et al. 2012; Govarts et al. 2018; Lauritzen et al. 2017; Y. Wang et al. 2016), even if an earlier study showed an inverse association of SGA with PFOS (Hamm et al. 2010). Only two out of ten studies that have evaluated the effect of PFAS on LBW found out a significant association (Arbuckle et al. 2013; Stein, Savitz, and Dougan 2009). Four studies found out a significant association between PI and PFOS/PFOA (Alkhalawi et al. 2016; Apelberg et al. 2007; Y. J. Lee et al. 2013; Minatoya et al. 2017).

3.3.3 Structural and functional (nervous system and brain problems) birth defects

Non-mammalian studies showed that PFOA and PFOS exposure resulted in higher malformation rate in a dose- and time-dependent manner in zebrafish (J. Chen et al. 2013, 2014; Dang, Wang, and Liu 2018; Du et al. 2009; Hagenaars et al. 2011; Huang et al. 2010; Jantzen et al. 2016; Shi et al. 2008; M. Wang et al. 2011; L. Zhang et al. 2011; Zheng et al. 2011) and Xenopus (M. Kim et al. 2013). In the zebrafish, the malformations involved most often the swim bladder and spine development. PFOA in ovo exposure seemed to result in structural and functional heart defects in chicken (Jiang et al. 2012; Zhao et al. 2017). The impairment of heart function has also been highlighted in the zebrafish (Hagenaars et al. 2011; Huang et al. 2010). Mammalian studies have shown that mouse exposed to 9-30 mg/kg of PFOS between 1-17 gestational days (GDs) presented higher rates of cleft palate (Era et al. 2009). Not least, exposure to PFOA has been suggested to result in impaired ossification in rats (Lau et al. 2006; Staples, Burgess, and Kerns 1984). Epidemiological evidence (in humans) in the field is inconsistent. Three studies did not find significant associations between PFAS exposure and birth defects (Nolan et al. 2010; Savitz, Stein, Bartell, et al. 2012; Stein, Savitz, and Dougan 2009), while Liew at al found out a significantly higher risk of congenital cerebral plasy in boys exposed in-utero to PFOA and PFOS (Liew et al. 2014).

The number of studies specifically about the impact of PFAS exposure on neurodevelopment has grown exponentially in the last ten years since animal studies have shown that PFAS could act as neurotoxicants. PFAS exposure in zebrafish has shown to result in impaired swim rates (Spulber et al. 2014; Ulhaq et al. 2013). Behavioral problems resulting from PFAS exposure have also been highlighted in the chicken; it has been shown that in ovo PFAS exposure might result in impaired imprinting performance (Pinkas et al. 2010). Mammalian studies have suggested that exposure to

PFOA, PFOS, and PFBA could result in pups' delayed eye opening (Das et al. 2008; Lau et al. 2003; Wolf et al. 2007). In addition to that, PFOA and PFOS exposure seemed to affect motor activity and spatial learning in the mouse and the rat (Fuentes et al. 2007; Goulding et al. 2017; Onishchenko et al. 2011). Looking at the epidemiological evidence in this field, two reviews have been published in the last five years (Berghuis et al. 2015; Roth and Wilks 2014). The last update of that of Roth et al. was at the beginning of 2006 and of that of Berghuis et al. was the second semester of 2014. Such reviews claimed that evidence in the field is inconsistent mainly due to a great methodological heterogeneity in studies conduction, making it difficult to compare study results. Head circumference, which could be considered a proxy of brain development, has been found to be in a significant inverse association with PFAS exposure only in a small number of studies (Apelberg et al. 2007; M.-H. Chen et al. 2012; Y. Wang et al. 2016). Only weak and inconsistent associations have been found out with cognitive development in early- and mid-childhood (Stein, Savitz, and Bellinger 2013; Jeddy et al. 2017; Harris et al. 2018; Goudarzi et al. 2016; Forns et al. 2015; Fei and Olsen 2011; Fei et al. 2008). Also, neurobehavioral consequences of PFAS exposure have been studied; however, studies' findings are inconsistent. PFAS exposure seemed to result in a higher risk of hyperactivity and inattention (Høyer et al. 2015; Lien et al. 2016), but no consistent associations have been found out with the risk of suffering of Attention Deficit Hyperactivity Disorder (ADHD) (Liew et al. 2015; Ode et al. 2014).

3.3.4 Thyroid function

A recent review of the relationship between PFAS and thyroid function has suggested that the exposure to such chemicals could result in thyroid disorders (Coperchini et al. 2017). Looking at the effects of PFAS exposure on thyroid function in pregnant women and newborns is even more relevant since thyroid hormones play a key role in the development of the fetus and the child. Animal studies suggest that PFAS act as endocrine disruptors resulting in the impairment of thyroid function (in both mammalian (Lau et al. 2003; Thibodeaux et al. 2003; Yu et al. 2009) and non-mammalian studies (Cassone et al. 2012), PFAS exposure has been put in an inverse relationship with triiodothyronine (T3) and thyroxin (T4) levels).

A review, updated at the end of 2015, about the epidemiological evidence on the effects of PFAS on thyroid function during the prenatal period and childhood showed some kind of association between PFHxS/PFOS and TSH in maternal blood (Ballesteros et al. 2017). After 2015, new studies have been published about such topic. Overall, such studies seemed to confirm the positive association of PFOS, PFHxS, PFHpS and TSH in maternal blood (Berg et al. 2017). However, TSH in maternal and cord blood seemed to be in an inverse relationship with PFNA. Looking at T3 and T4 levels, T3 in maternal and cord blood seemed to be in an inverse relationship with a wide spectrum of PFAS (PFNA,

PFUnDA, PFDA, PFOS, PFTrDA) (Berg et al. 2017, 2015; S. Kim et al. 2011; Yang et al. 2016). The relationship of T4 levels with PFAS exposure has been studied less frequently; even if scant, evidence in the field seemed to suggest that T4 is in an inverse relationship with some PFAS (Y. Wang et al. 2014; Preston et al. 2018; S. Kim et al. 2011; Kato et al. 2016). Despite the fact that most evidence in the field seemed to suggest that PFAS exposure is in a positive relationship with TSH and in an inverse ones with T3 and T4, there are still some exceptions (e.g., it has been shown a direct relationship of T3 and T4 with PFPeA and PFHxS in baby girls (Shah-Kulkarni et al. 2016)). Such inconsistencies in the evidence about PFAS and thyroid hormones do not allow for drawing conclusions about the effect of PFAS on thyroid function during the prenatal period and childhood.

4. Discussion

The present study aimed at reviewing the evidence about the relationship of PFAS exposure with maternal and newborn health. Overall, evidence retrieved suggests that in-utero PFAS exposure might affect the development of the fetus and the newborn. However, despite the efforts in improving the knowledge and the understanding of PFAS effect on maternal and newborn health, especially in the field of fetal growth (testified by the high number of studies in the field identified in this work), the evidence is still inconclusive for most of the outcomes considered in the present review. Even if the overall studies' quality was good (all animal studies included a control group and almost all human studies presented data from large prospective birth cohorts), studies' findings are difficult to be compared and pooled together due to methodological reasons. Such reasons include the heterogeneity in the type of outcomes considered (e.g., eight different proxies of fetal growth were employed in epidemiological studies analyzing the effect of PFAS on intrauterine growth restriction), and the way in which they were analyzed. Another critical aspect that contributes to the methodological heterogeneity is the analysis of the exposure. In human studies, the exposure was measured at different time points (e.g., in different time point of pregnancy) on several biological matrixes (maternal blood, cord blood, breast milk) making it difficult to compare exposure levels and the magnitude of their effect on the endpoints of interest. Although difficult to compare, it is noteworthy that, in recent years, the analysis of the exposure has included different types of PFAS other than PFOA and PFOS (which are still the PFAS most widely studied) (Ulhaq et al. 2013; Chang et al. 2018; Das et al. 2015; Iwai and Hoberman 2014; Jantzen et al. 2016; M. Kim et al. 2013; Rogers et al. 2014). This is relevant in the field of maternal and newborn health research since it has been shown a selective transfer of some PFAS from maternal to cord blood (Gützkow et al. 2012) that should be taken into account when the expsoure of the fetus is studied.

5. Conclusions

According to the present findings, it seems that further efforts should be made to harmonize the new evidence in the field with the existing ones and to strengthen the knowledge about specific endpoints for which evidence are lacking (e.g., birth defects). Such further efforts are essential to developing evidence-based public health programs for the monitoring and the care of pregnant women and their children exposed to PFAS in highly contaminated areas since the PFAS contamination and the subsequent exposure to PFAS of people working or living in contaminated areas represent a severe public health burden. This is even more relevant for pregnant women because their exposure to PFAS implies the exposure of the developing fetus, which is extremely sensitive to any kind of external insult.

6. References

Abbott, Barbara D., Cynthia J. Wolf, Judith E. Schmid, Kaberi P. Das, Robert D. Zehr, Laurence Helfant, Shoji Nakayama, Andrew B. Lindstrom, Mark J. Strynar, and Christopher Lau. 2007. "Perfluorooctanoic Acid Induced Developmental Toxicity in the Mouse Is Dependent on Expression of Peroxisome Proliferator Activated Receptor-Alpha." *Toxicological Sciences: An Official Journal of the Society of Toxicology* 98 (2): 571–81. https://doi.org/10.1093/toxsci/kfm110.

Alkhalawi, Eman, Monika Kasper-Sonnenberg, Michael Wilhelm, Wolfgang Völkel, and Jürgen Wittsiepe. 2016. "Perfluoroalkyl Acids (PFAAs) and Anthropometric Measures in the First Year of Life: Results from the Duisburg Birth Cohort." *Journal of Toxicology and Environmental Health. Part A* 79 (22–23): 1041–49. https://doi.org/10.1080/15287394.2016.1219552.

Andersen, Camilla Schou, Chunyuan Fei, Michael Gamborg, Ellen Aagaard Nohr, Thorkild I. A. Sørensen, and Jørn Olsen. 2010. "Prenatal Exposures to Perfluorinated Chemicals and Anthropometric Measures in Infancy." *American Journal of Epidemiology* 172 (11): 1230–37. https://doi.org/10.1093/aje/kwq289.

Antignac, Jean-Philippe, Bruno Veyrand, Hanane Kadar, Philippe Marchand, Amivi Oleko, Bruno Le Bizec, and Stéphanie Vandentorren. 2013. "Occurrence of Perfluorinated Alkylated Substances in Breast Milk of French Women and Relation with Socio-Demographical and Clinical Parameters: Results of the ELFE Pilot Study." *Chemosphere* 91 (6): 802–8. https://doi.org/10.1016/j.chemosphere.2013.01.088.

Apelberg, Benjamin J., Frank R. Witter, Julie B. Herbstman, Antonia M. Calafat, Rolf U. Halden, Larry L. Needham, and Lynn R. Goldman. 2007. "Cord Serum Concentrations of Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoate (PFOA) in Relation to Weight and Size at Birth." *Environmental Health Perspectives* 115 (11): 1670–76. https://doi.org/10.1289/ehp.10334.

Arbuckle, Tye E., Cariton Kubwabo, Mark Walker, Karelyn Davis, Kaela Lalonde, Ivana Kosarac, Shi Wu Wen, and Douglas L. Arnold. 2013. "Umbilical Cord Blood Levels of Perfluoroalkyl Acids and Polybrominated Flame Retardants." *International Journal of Hygiene and Environmental Health* 216 (2): 184–94. https://doi.org/10.1016/j.ijheh.2012.03.004.

Ashley-Martin, Jillian, Linda Dodds, Tye E. Arbuckle, Anne-Sophie Morisset, Mandy Fisher, Maryse F. Bouchard, Gabriel D. Shapiro, et al. 2016. "Maternal and Neonatal Levels of Perfluoroalkyl Substances in Relation to Gestational Weight Gain." *International Journal of Environmental Research and Public Health* 13 (1). https://doi.org/10.3390/ijerph13010146.

Ashley-Martin, Jillian, Linda Dodds, Tye E. Arbuckle, Maryse F. Bouchard, Mandy Fisher, Anne-Sophie Morriset, Patricia Monnier, et al. 2017. "Maternal Concentrations of Perfluoroalkyl Substances and Fetal Markers of Metabolic Function and Birth Weight." *American Journal of Epidemiology* 185 (3): 185–93. https://doi.org/10.1093/aje/kww213.

Bach, Cathrine Carlsen, Bodil Hammer Bech, Nis Brix, Ellen Aagaard Nohr, Jens Peter Ellekilde Bonde, and Tine Brink Henriksen. 2015. "Perfluoroalkyl and Polyfluoroalkyl Substances and Human Fetal Growth: A Systematic Review." *Critical Reviews in Toxicology* 45 (1): 53–67. https://doi.org/10.3109/10408444.2014.952400.

Bach, Cathrine Carlsen, Bodil Hammer Bech, Ellen Aagaard Nohr, Jørn Olsen, Niels Bjerregård Matthiesen, Eva Cecilie Bonefeld-Jørgensen, Rossana Bossi, and Tine Brink Henriksen. 2016. "Perfluoroalkyl Acids in Maternal Serum and Indices of Fetal Growth: The Aarhus Birth Cohort." *Environmental Health Perspectives* 124 (6): 848–54. https://doi.org/10.1289/ehp.1510046.

Ballesteros, Virginia, Olga Costa, Carmen Iñiguez, Tony Fletcher, Ferran Ballester, and Maria-Jose Lopez-Espinosa. 2017. "Exposure to Perfluoroalkyl Substances and Thyroid Function in Pregnant Women and Children: A Systematic Review of Epidemiologic Studies." *Environment International* 99: 15–28. https://doi.org/10.1016/j.envint.2016.10.015.

Benbrahim-Tallaa, Lamia, Béatrice Lauby-Secretan, Dana Loomis, Kathryn Z. Guyton, Yann Grosse, Fatiha El Ghissassi, Véronique Bouvard, Neela Guha, Heidi Mattock, and Kurt Straif. 2014.

"Carcinogenicity of Perfluorooctanoic Acid, Tetrafluoroethylene, Dichloromethane, 1, 2-Dichloropropane, and 1, 3-Propane Sultone." *The Lancet Oncology* 15 (9): 924–25.

Berg, Vivian, Therese Haugdahl Nøst, Sandra Huber, Charlotta Rylander, Solrunn Hansen, Anna Sofia Veyhe, Ole Martin Fuskevåg, Jon Øyvind Odland, and Torkjel Manning Sandanger. 2014. "Maternal Serum Concentrations of Per- and Polyfluoroalkyl Substances and Their Predictors in Years with Reduced Production and Use." *Environment International* 69 (August): 58–66. https://doi.org/10.1016/j.envint.2014.04.010.

Berg, Vivian, Therese Haugdahl Nøst, Solrunn Hansen, Astrid Elverland, Anna-Sofia Veyhe, Rolf Jorde, Jon Øyvind Odland, and Torkjel Manning Sandanger. 2015. "Assessing the Relationship between Perfluoroalkyl Substances, Thyroid Hormones and Binding Proteins in Pregnant Women; a Longitudinal Mixed Effects Approach." *Environment International* 77 (April): 63–69. https://doi.org/10.1016/j.envint.2015.01.007.

Berg, Vivian, Therese Haugdahl Nøst, Rolf Dagfinn Pettersen, Solrunn Hansen, Anna-Sofia Veyhe, Rolf Jorde, Jon Øyvind Odland, and Torkjel Manning Sandanger. 2017. "Persistent Organic Pollutants and the Association with Maternal and Infant Thyroid Homeostasis: A Multipollutant Assessment." *Environmental Health Perspectives* 125 (1): 127–33. https://doi.org/10.1289/EHP152.

Berghuis, Sietske A., Arend F. Bos, Pieter J. J. Sauer, and Elise Roze. 2015. "Developmental Neurotoxicity of Persistent Organic Pollutants: An Update on Childhood Outcome." *Archives of Toxicology* 89 (5): 687–709. https://doi.org/10.1007/s00204-015-1463-3.

Boberg, Julie, Stine Metzdorff, Rasmus Wortziger, Marta Axelstad, Leon Brokken, Anne Marie Vinggaard, Majken Dalgaard, and Christine Nellemann. 2008. "Impact of Diisobutyl Phthalate and Other PPAR Agonists on Steroidogenesis and Plasma Insulin and Leptin Levels in Fetal Rats." *Toxicology* 250 (2–3): 75–81. https://doi.org/10.1016/j.tox.2008.05.020.

Borg, D., J. Bogdanska, M. Sundström, S. Nobel, H. Håkansson, Å Bergman, J. W. DePierre, K. Halldin, and U. Bergström. 2010. "Tissue Distribution of (35)S-Labelled Perfluorooctane Sulfonate (PFOS) in C57Bl/6 Mice Following Late Gestational Exposure." *Reproductive Toxicology (Elmsford, N.Y.)* 30 (4): 558–65. https://doi.org/10.1016/j.reprotox.2010.07.004.

Brantsæter, A. L., K. W. Whitworth, T. A. Ydersbond, L. S. Haug, M. Haugen, H. K. Knutsen, C. Thomsen, et al. 2013. "Determinants of Plasma Concentrations of Perfluoroalkyl Substances in Pregnant Norwegian Women." *Environment International* 54 (April): 74–84. https://doi.org/10.1016/j.envint.2012.12.014.

Braun, Joseph M., Amy E. Kalkbrenner, Allan C. Just, Kimberly Yolton, Antonia M. Calafat, Andreas Sjödin, Russ Hauser, Glenys M. Webster, Aimin Chen, and Bruce P. Lanphear. 2014. "Gestational Exposure to Endocrine-Disrupting Chemicals and Reciprocal Social, Repetitive, and Stereotypic Behaviors in 4- and 5-Year-Old Children: The HOME Study." *Environmental Health Perspectives* 122 (5): 513–20. https://doi.org/10.1289/ehp.1307261.

Butenhoff, John L., Gerald L. Kennedy, Steven R. Frame, John C. O'Connor, and Raymond G. York. 2004. "The Reproductive Toxicology of Ammonium Perfluorooctanoate (APFO) in the Rat." *Toxicology* 196 (1–2): 95–116. https://doi.org/10.1016/j.tox.2003.11.005.

Butenhoff, John L., David J. Ehresman, Shu-Ching Chang, George A. Parker, and Donald G. Stump. 2009. "Gestational and Lactational Exposure to Potassium Perfluorooctanesulfonate (K+PFOS) in Rats: Developmental Neurotoxicity." *Reproductive Toxicology (Elmsford, N.Y.)* 27 (3–4): 319–30. https://doi.org/10.1016/j.reprotox.2008.12.010.

Callan, A. C., A. Rotander, K. Thompson, J. Heyworth, J. F. Mueller, J. Ø Odland, and A. L. Hinwood. 2016. "Maternal Exposure to Perfluoroalkyl Acids Measured in Whole Blood and Birth Outcomes in Offspring." *The Science of the Total Environment* 569–570 (November): 1107–13. https://doi.org/10.1016/j.scitotenv.2016.06.177.

Cao, Wencheng, Xiao Liu, Xiaofang Liu, Yan Zhou, Xiaotian Zhang, Haoyuan Tian, Jin Wang, et al. 2018. "Perfluoroalkyl Substances in Umbilical Cord Serum and Gestational and Postnatal Growth in a Chinese Birth Cohort." *Environment International* 116 (July): 197–205. https://doi.org/10.1016/j.envint.2018.04.015.

Case, M. T., R. G. York, and M. S. Christian. 2001. “Rat and Rabbit Oral Developmental Toxicology Studies with Two Perfluorinated Compounds.” *International Journal of Toxicology* 20 (2): 101–9.

Cassone, Cristina G., Viengtha Vongphachan, Suzanne Chiu, Kim L. Williams, Robert J. Letcher, Eric Pelletier, Doug Crump, and Sean W. Kennedy. 2012. “In Ovo Effects of Perfluorohexane Sulfonate and Perfluorohexanoate on Pipping Success, Development, MRNA Expression, and Thyroid Hormone Levels in Chicken Embryos.” *Toxicological Sciences: An Official Journal of the Society of Toxicology* 127 (1): 216–24. https://doi.org/10.1093/toxsci/kfs072.

Chan, Emily, Igor Burstyn, Nicola Cherry, Fiona Bamforth, and Jonathan W. Martin. 2011. “Perfluorinated Acids and Hypothyroxinemia in Pregnant Women.” *Environmental Research* 111 (4): 559–64. https://doi.org/10.1016/j.envres.2011.01.011

Chang, Shu-Ching, David J. Ehresman, James A. Bjork, Kendall B. Wallace, George A. Parker, Donald G. Stump, and John L. Butenhoff. 2009. “Gestational and Lactational Exposure to Potassium Perfluorooctanesulfonate (K+PFOS) in Rats: Toxicokinetics, Thyroid Hormone Status, and Related Gene Expression.” *Reproductive Toxicology (Elmsford, N.Y.)* 27 (3–4): 387–99. https://doi.org/10.1016/j.reprotox.2009.01.005.

Chang, Sue, John L. Butenhoff, George A. Parker, Prägati S. Coder, Jeremiah D. Zitzow, Ryan M. Krisko, James A. Bjork, Kendall B. Wallace, and Jennifer G. Seed. 2018. “Reproductive and Developmental Toxicity of Potassium Perfluorohexanesulfonate in CD-1 Mice.” *Reproductive Toxicology (Elmsford, N.Y.)* 78 (June): 150–68. https://doi.org/10.1016/j.reprotox.2018.04.007.

Chen, Jiangfei, Siba R. Das, Jane La Du, Margaret M. Corvi, Chenglian Bai, Yuanhong Chen, Xiaojuan Liu, et al. 2013. “Chronic PFOS Exposures Induce Life Stage-Specific Behavioral Deficits in Adult Zebrafish and Produce Malformation and Behavioral Deficits in F1 Offspring.” *Environmental Toxicology and Chemistry* 32 (1): 201–6. https://doi.org/10.1002/etc.2031.

Chen, Jiangfei, Robert L. Tanguay, Tamara L. Tal, Zengxin Gai, Xue Ma, Chenglian Bai, Susan C. Tilton, et al. 2014. “Early Life Perfluorooctanesulphonic Acid (PFOS) Exposure Impairs Zebrafish Organogenesis.” *Aquatic Toxicology (Amsterdam, Netherlands)* 150 (May): 124–32. https://doi.org/10.1016/j.aquatox.2014.03.005.

Chen, Mei-Huei, Eun-Hee Ha, Ting-Wen Wen, Yi-Ning Su, Guang-Wen Lien, Chia-Yang Chen, Pau-Chung Chen, and Wu-Shiun Hsieh. 2012. “Perfluorinated Compounds in Umbilical Cord Blood and Adverse Birth Outcomes.” *PloS One* 7 (8): e42474. https://doi.org/10.1371/journal.pone.0042474.

Chen, Mei-Huei, Eun-Hee Ha, Hua-Fang Liao, Suh-Fang Jeng, Yi-Ning Su, Ting-Wen Wen, Guang-Wen Lien, Chia-Yang Chen, Wu-Shiun Hsieh, and Pau-Chung Chen. 2013. “Perfluorinated Compound Levels in Cord Blood and Neurodevelopment at 2 Years of Age.” *Epidemiology (Cambridge, Mass.)* 24 (6): 800–808. https://doi.org/10.1097/EDE.0b013e3182a6dd46.

Chen, Mei-Huei, Sharon Ng, Chia-Jung Hsieh, Ching-Chun Lin, Wu-Shiun Hsieh, and Pau-Chung Chen. 2017. “The Impact of Prenatal Perfluoroalkyl Substances Exposure on Neonatal and Child Growth.” *The Science of the Total Environment* 607–608 (December): 669–75. https://doi.org/10.1016/j.scitotenv.2017.06.273.

Coperchini, F., O. Awwad, M. Rotondi, F. Santini, M. Imbriani, and L. Chiovato. 2017. “Thyroid Disruption by Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoate (PFOA).” *Journal of Endocrinological Investigation* 40 (2): 105–21. https://doi.org/10.1007/s40618-016-0572-z.

Dang, Yao, Fei’er Wang, and Chunsheng Liu. 2018. “Real-Time PCR Array to Study the Effects of Chemicals on the Growth Hormone/Insulin-like Growth Factors (GH/IGFs) Axis of Zebrafish Embryos/Larvae.” *Chemosphere* 207 (September): 365–76. https://doi.org/10.1016/j.chemosphere.2018.05.102.

Darrow, Lyndsey A., Cheryl R. Stein, and Kyle Steenland. 2013. “Serum Perfluorooctanoic Acid and Perfluorooctane Sulfonate Concentrations in Relation to Birth Outcomes in the Mid-Ohio Valley, 2005-2010.” *Environmental Health Perspectives* 121 (10): 1207–13. https://doi.org/10.1289/ehp.1206372.

Das, Kaberi P., Brian E. Grey, Mitchell B. Rosen, Carmen R. Wood, Katoria R. Tatum-Gibbs, R. Daniel Zehr, Mark J. Strynar, Andrew B. Lindstrom, and Christopher Lau. 2015. "Developmental Toxicity of Perfluorononanoic Acid in Mice." *Reproductive Toxicology (Elmsford, N.Y.)* 51 (January): 133–44. https://doi.org/10.1016/j.reprotox.2014.12.012.

Das, Kaberi P., Brian E. Grey, Robert D. Zehr, Carmen R. Wood, John L. Butenhoff, Shu-Ching Chang, David J. Ehresman, Yu-Mei Tan, and Christopher Lau. 2008. "Effects of Perfluorobutyrate Exposure during Pregnancy in the Mouse." *Toxicological Sciences: An Official Journal of the Society of Toxicology* 105 (1): 173–81. https://doi.org/10.1093/toxsci/kfn099.

Cock, Marijke de, Michiel R. de Boer, Marja Lamoree, Juliette Legler, and Margot van de Bor. 2014. "Prenatal Exposure to Endocrine Disrupting Chemicals in Relation to Thyroid Hormone Levels in Infants - a Dutch Prospective Cohort Study." *Environmental Health: A Global Access Science Source* 13 (December): 106. https://doi.org/10.1186/1476-069X-13-106.

Cock, Marijke de, Michiel R. De Boer, Marja Lamoree, Juliette Legler, and Margot Van De Bor. 2016. "Prenatal Exposure to Endocrine Disrupting Chemicals and Birth Weight-A Prospective Cohort Study." *Journal of Environmental Science and Health. Part A, Toxic/Hazardous Substances & Environmental Engineering* 51 (2): 178–85. https://doi.org/10.1080/10934529.2015.1087753.

Donauer, Stephanie, Aimin Chen, Yingying Xu, Antonia M. Calafat, Andreas Sjodin, and Kimberly Yolton. 2015. "Prenatal Exposure to Polybrominated Diphenyl Ethers and Polyfluoroalkyl Chemicals and Infant Neurobehavior." *The Journal of Pediatrics* 166 (3): 736–42. https://doi.org/10.1016/j.jpeds.2014.11.021.

Du, Yongbing, Xiongjie Shi, Chunsheng Liu, Ke Yu, and Bingsheng Zhou. 2009. "Chronic Effects of Water-Borne PFOS Exposure on Growth, Survival and Hepatotoxicity in Zebrafish: A Partial Life-Cycle Test." *Chemosphere* 74 (5): 723–29. https://doi.org/10.1016/j.chemosphere.2008.09.075.

Era, Saho, Kouji H. Harada, Megumi Toyoshima, Kayoko Inoue, Mutsuko Minata, Norimitsu Saito, Toshiya Takigawa, Kouhei Shiota, and Akio Koizumi. 2009. "Cleft Palate Caused by Perfluorooctane Sulfonate Is Caused Mainly by Extrinsic Factors." *Toxicology* 256 (1–2): 42–47. https://doi.org/10.1016/j.tox.2008.11.003.

Fei, Chunyuan, Joseph K. McLaughlin, Loren Lipworth, and Jørn Olsen. 2008. "Prenatal Exposure to Perfluorooctanoate (PFOA) and Perfluorooctanesulfonate (PFOS) and Maternally Reported Developmental Milestones in Infancy." *Environmental Health Perspectives* 116 (10): 1391–95. https://doi.org/10.1289/ehp.11277.

Fei, Chunyuan, Joseph K. McLaughlin, Robert E. Tarone, and Jørn Olsen. 2007. "Perfluorinated Chemicals and Fetal Growth: A Study within the Danish National Birth Cohort." *Environmental Health Perspectives* 115 (11): 1677–82. https://doi.org/10.1289/ehp.10506.

Fei, Chunyuan, Joseph K. McLaughlin, Robert E. Tarone, and Jørn Olsen. 2008. "Fetal Growth Indicators and Perfluorinated Chemicals: A Study in the Danish National Birth Cohort." *American Journal of Epidemiology* 168 (1): 66–72. https://doi.org/10.1093/aje/kwn095.

Fei, Chunyuan, and Jørn Olsen. 2011. "Prenatal Exposure to Perfluorinated Chemicals and Behavioral or Coordination Problems at Age 7 Years." *Environmental Health Perspectives* 119 (4): 573–78. https://doi.org/10.1289/ehp.1002026.

Forns, J., N. Iszatt, R. A. White, S. Mandal, A. Sabaredzovic, M. Lamoree, C. Thomsen, L. S. Haug, H. Stigum, and M. Eggesbø. 2015. "Perfluoroalkyl Substances Measured in Breast Milk and Child Neuropsychological Development in a Norwegian Birth Cohort Study." *Environment International* 83 (October): 176–82. https://doi.org/10.1016/j.envint.2015.06.013.

Fromme, Hermann, Christine Mosch, Maria Morovitz, Irene Alba-Alejandre, Sigrun Boehmer, Mandy Kiranoglu, Fabienne Faber, et al. 2010. "Pre- and Postnatal Exposure to Perfluorinated Compounds (PFCs)." *Environmental Science & Technology* 44 (18): 7123–29. https://doi.org/10.1021/es101184f.

Fuentes, Silvia, M. Teresa Colomina, Judit Rodriguez, Paloma Vicens, and José L. Domingo. 2006. "Interactions in Developmental Toxicology: Concurrent Exposure to Perfluorooctane Sulfonate

(PFOS) and Stress in Pregnant Mice." *Toxicology Letters* 164 (1): 81–89. https://doi.org/10.1016/j.toxlet.2005.11.013.

Fuentes, Silvia, M. Teresa Colomina, Paloma Vicens, and José L. Domingo. 2007. "Influence of Maternal Restraint Stress on the Long-Lasting Effects Induced by Prenatal Exposure to Perfluorooctane Sulfonate (PFOS) in Mice." *Toxicology Letters* 171 (3): 162–70. https://doi.org/10.1016/j.toxlet.2007.05.006.

Glynn, Anders, Urs Berger, Anders Bignert, Shahid Ullah, Marie Aune, Sanna Lignell, and Per Ola Darnerud. 2012. "Perfluorinated Alkyl Acids in Blood Serum from Primiparous Women in Sweden: Serial Sampling during Pregnancy and Nursing, and Temporal Trends 1996-2010." *Environmental Science & Technology* 46 (16): 9071–79. https://doi.org/10.1021/es301168c.

Goudarzi, Houman, Sonomi Nakajima, Tamiko Ikeno, Seiko Sasaki, Sachiko Kobayashi, Chihiro Miyashita, Sachiko Ito, Atsuko Araki, Hiroyuki Nakazawa, and Reiko Kishi. 2016. "Prenatal Exposure to Perfluorinated Chemicals and Neurodevelopment in Early Infancy: The Hokkaido Study." *The Science of the Total Environment* 541 (January): 1002–10. https://doi.org/10.1016/j.scitotenv.2015.10.017.

Goulding, David R., Sally S. White, Sandra J. McBride, Suzanne E. Fenton, and G. Jean Harry. 2017. "Gestational Exposure to Perfluorooctanoic Acid (PFOA): Alterations in Motor Related Behaviors." *Neurotoxicology* 58: 110–19. https://doi.org/10.1016/j.neuro.2016.11.008.

Govarts, Eva, Sylvie Remy, Liesbeth Bruckers, Elly Den Hond, Isabelle Sioen, Vera Nelen, Willy Baeyens, et al. 2016. "Combined Effects of Prenatal Exposures to Environmental Chemicals on Birth Weight." *International Journal of Environmental Research and Public Health* 13 (5). https://doi.org/10.3390/ijerph13050495.

Govarts, Eva, Nina Iszatt, Tomas Trnovec, Marijke de Cock, Merete Eggesbø, Lubica Palkovicova Murinova, Margot van de Bor, et al. 2018. "Prenatal Exposure to Endocrine Disrupting Chemicals and Risk of Being Born Small for Gestational Age: Pooled Analysis of Seven European Birth Cohorts." *Environment International* 115 (June): 267–78. https://doi.org/10.1016/j.envint.2018.03.017.

Grasty, Rayetta C., D. C. Wolf, Brian E. Grey, Christopher S. Lau, and John M. Rogers. 2003. "Prenatal Window of Susceptibility to Perfluorooctane Sulfonate-Induced Neonatal Mortality in the Sprague-Dawley Rat." *Birth Defects Research. Part B, Developmental and Reproductive Toxicology* 68 (6): 465–71. https://doi.org/10.1002/bdrb.10046.

Gützkow, Kristine Bjerve, Line Småstuen Haug, Cathrine Thomsen, Azemira Sabaredzovic, Georg Becher, and Gunnar Brunborg. 2012. "Placental Transfer of Perfluorinated Compounds Is Selective--a Norwegian Mother and Child Sub-Cohort Study." *International Journal of Hygiene and Environmental Health* 215 (2): 216–19. https://doi.org/10.1016/j.ijheh.2011.08.011.

Gyllenhammar, Irina, Barbro Diderholm, Jan Gustafsson, Urs Berger, Peter Ridefelt, Jonathan P. Benskin, Sanna Lignell, Erik Lampa, and Anders Glynn. 2018. "Perfluoroalkyl Acid Levels in First-Time Mothers in Relation to Offspring Weight Gain and Growth." *Environment International* 111 (February): 191–99. https://doi.org/10.1016/j.envint.2017.12.002.

Hagenaars, A., L. Vergauwen, W. De Coen, and D. Knapen. 2011. "Structure-Activity Relationship Assessment of Four Perfluorinated Chemicals Using a Prolonged Zebrafish Early Life Stage Test." *Chemosphere* 82 (5): 764–72. https://doi.org/10.1016/j.chemosphere.2010.10.076.

Hagenaars, A., E. Stinckens, L. Vergauwen, L. Bervoets, and D. Knapen. 2014. "PFOS Affects Posterior Swim Bladder Chamber Inflation and Swimming Performance of Zebrafish Larvae." *Aquatic Toxicology (Amsterdam, Netherlands)* 157 (December): 225–35. https://doi.org/10.1016/j.aquatox.2014.10.017.

Hamm, Michele P., Nicola M. Cherry, Emily Chan, Jonathan W. Martin, and Igor Burstyn. 2010. "Maternal Exposure to Perfluorinated Acids and Fetal Growth." *Journal of Exposure Science & Environmental Epidemiology* 20 (7): 589–97. https://doi.org/10.1038/jes.2009.57.

Harris, Maria H., Emily Oken, Sheryl L. Rifas-Shiman, Antonia M. Calafat, Xiaoyun Ye, David C. Bellinger, Thomas F. Webster, Roberta F. White, and Sharon K. Sagiv. 2018. "Prenatal and

Childhood Exposure to Per- and Polyfluoroalkyl Substances (PFASs) and Child Cognition." *Environment International* 115 (June): 358–69. https://doi.org/10.1016/j.envint.2018.03.025.

Higgins, J. P. T. 2015. *Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. 0. The Cochrane Collaboration. 2011*.

Høyer, Birgit Bjerre, Cecilia Høst Ramlau-Hansen, Carsten Obel, Henning Sloth Pedersen, Agnieszka Hernik, Victor Ogniev, Bo A. G. Jönsson, et al. 2015. "Pregnancy Serum Concentrations of Perfluorinated Alkyl Substances and Offspring Behaviour and Motor Development at Age 5-9 Years--a Prospective Study." *Environmental Health: A Global Access Science Source* 14 (January): 2. https://doi.org/10.1186/1476-069X-14-2.

Hu, Qing, Mark J. Strynar, and Jamie C. DeWitt. 2010. "Are Developmentally Exposed C57BL/6 Mice Insensitive to Suppression of TDAR by PFOA?" *Journal of Immunotoxicology* 7 (4): 344–49. https://doi.org/10.3109/1547691X.2010.520045.

Huang, Haihua, Changjiang Huang, Lijun Wang, Xiaowei Ye, Chenglian Bai, Michael T. Simonich, Robert L. Tanguay, and Qiaoxiang Dong. 2010. "Toxicity, Uptake Kinetics and Behavior Assessment in Zebrafish Embryos Following Exposure to Perfluorooctanesulphonicacid (PFOS)." *Aquatic Toxicology (Amsterdam, Netherlands)* 98 (2): 139–47. https://doi.org/10.1016/j.aquatox.2010.02.003.

Iwai, Hiroyuki, and Alan M. Hoberman. 2014. "Oral (Gavage) Combined Developmental and Perinatal/Postnatal Reproduction Toxicity Study of Ammonium Salt of Perfluorinated Hexanoic Acid in Mice." *International Journal of Toxicology* 33 (3): 219–37. https://doi.org/10.1177/1091581814529449.

Jaacks, Lindsay M., Dana Boyd Barr, Rajeshwari Sundaram, Jagteshwar Grewal, Cuilin Zhang, and Germaine M. Buck Louis. 2016. "Pre-Pregnancy Maternal Exposure to Persistent Organic Pollutants and Gestational Weight Gain: A Prospective Cohort Study." *International Journal of Environmental Research and Public Health* 13 (9). https://doi.org/10.3390/ijerph13090905.

Jantzen, Carrie E., Kate A. Annunziato, Sean M. Bugel, and Keith R. Cooper. 2016. "PFOS, PFNA, and PFOA Sub-Lethal Exposure to Embryonic Zebrafish Have Different Toxicity Profiles in Terms of Morphometrics, Behavior and Gene Expression." *Aquatic Toxicology (Amsterdam, Netherlands)* 175 (June): 160–70. https://doi.org/10.1016/j.aquatox.2016.03.026.

Jeddy, Zuha, Terryl J. Hartman, Ethel V. Taylor, Cayla Poteete, and Katarzyna Kordas. 2017. "Prenatal Concentrations of Perfluoroalkyl Substances and Early Communication Development in British Girls." *Early Human Development* 109: 15–20. https://doi.org/10.1016/j.earlhumdev.2017.04.004.

Jiang, Qixiao, Robert M. Lust, Mark J. Strynar, Sonia Dagnino, and Jamie C. DeWitt. 2012. "Perflurooctanoic Acid Induces Developmental Cardiotoxicity in Chicken Embryos and Hatchlings." *Toxicology* 293 (1–3): 97–106. https://doi.org/10.1016/j.tox.2012.01.005.

Johnson, Paula I., Patrice Sutton, Dylan S. Atchley, Erica Koustas, Juleen Lam, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff. 2014. "The Navigation Guide - Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth." *Environmental Health Perspectives* 122 (10): 1028–39. https://doi.org/10.1289/ehp.1307893.

Kato, Shizue, Sachiko Itoh, Motoyuki Yuasa, Toshiaki Baba, Chihiro Miyashita, Seiko Sasaki, Sonomi Nakajima, et al. 2016. "Association of Perfluorinated Chemical Exposure in Utero with Maternal and Infant Thyroid Hormone Levels in the Sapporo Cohort of Hokkaido Study on the Environment and Children's Health." *Environmental Health and Preventive Medicine* 21 (5): 334–44. https://doi.org/10.1007/s12199-016-0534-2.

Kim, Seung-Kyu, Kyu Tae Lee, Chang Seong Kang, Lin Tao, Kurunthachalam Kannan, Kyung-Ryul Kim, Chan-Kook Kim, et al. 2011. "Distribution of Perfluorochemicals between Sera and Milk from the Same Mothers and Implications for Prenatal and Postnatal Exposures." *Environmental Pollution (Barking, Essex: 1987)* 159 (1): 169–74. https://doi.org/10.1016/j.envpol.2010.09.008.

Kim, Sunmi, Kyungho Choi, Kyunghee Ji, Jihyeon Seo, Younglim Kho, Jeongim Park, Sungkyoon Kim, et al. 2011. "Trans-Placental Transfer of Thirteen Perfluorinated Compounds and Relations with Fetal Thyroid Hormones." *Environmental Science & Technology* 45 (17): 7465–72. https://doi.org/10.1021/es202408a.

Kim, Miran, Jungeun Son, Mi Seon Park, Yurim Ji, Soomin Chae, Changduk Jun, Jong-Sup Bae, et al. 2013. "In Vivo Evaluation and Comparison of Developmental Toxicity and Teratogenicity of Perfluoroalkyl Compounds Using Xenopus Embryos." *Chemosphere* 93 (6): 1153–60. https://doi.org/10.1016/j.chemosphere.2013.06.053.

Kishi, Reiko, Tamie Nakajima, Houman Goudarzi, Sachiko Kobayashi, Seiko Sasaki, Emiko Okada, Chihiro Miyashita, et al. 2015. "The Association of Prenatal Exposure to Perfluorinated Chemicals with Maternal Essential and Long-Chain Polyunsaturated Fatty Acids during Pregnancy and the Birth Weight of Their Offspring: The Hokkaido Study." *Environmental Health Perspectives* 123 (10): 1038–45. https://doi.org/10.1289/ehp.1408834.

Kobayashi, Sachiko, Kaoru Azumi, Houman Goudarzi, Atsuko Araki, Chihiro Miyashita, Sumitaka Kobayashi, Sachiko Itoh, et al. 2017. "Effects of Prenatal Perfluoroalkyl Acid Exposure on Cord Blood IGF2/H19 Methylation and Ponderal Index: The Hokkaido Study." *Journal of Exposure Science & Environmental Epidemiology* 27 (3): 251–59. https://doi.org/10.1038/jes.2016.50.

Koustas, Erica, Juleen Lam, Patrice Sutton, Paula I. Johnson, Dylan S. Atchley, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff. 2014. "The Navigation Guide - Evidence-Based Medicine Meets Environmental Health: Systematic Review of Nonhuman Evidence for PFOA Effects on Fetal Growth." *Environmental Health Perspectives* 122 (10): 1015–27. https://doi.org/10.1289/ehp.1307177.

Kwon, Eun Jin, Joon Soo Shin, Byung Mi Kim, Surabhi Shah-Kulkarni, Hyesook Park, Young Lim Kho, Eun Ae Park, Young Ju Kim, and Eun Hee Ha. 2016. "Prenatal Exposure to Perfluorinated Compounds Affects Birth Weight Through GSTM1 Polymorphism." *Journal of Occupational and Environmental Medicine* 58 (6): e198-205. https://doi.org/10.1097/JOM.0000000000000739.

Lau, Christopher, Julie R. Thibodeaux, Roger G. Hanson, Michael G. Narotsky, John M. Rogers, Andrew B. Lindstrom, and Mark J. Strynar. 2006. "Effects of Perfluorooctanoic Acid Exposure during Pregnancy in the Mouse." *Toxicological Sciences: An Official Journal of the Society of Toxicology* 90 (2): 510–18. https://doi.org/10.1093/toxsci/kfj105.

Lau, Christopher, Julie R. Thibodeaux, Roger G. Hanson, John M. Rogers, Brian E. Grey, Mark E. Stanton, John L. Butenhoff, and Lisa A. Stevenson. 2003. "Exposure to Perfluorooctane Sulfonate during Pregnancy in Rat and Mouse. II: Postnatal Evaluation." *Toxicological Sciences: An Official Journal of the Society of Toxicology* 74 (2): 382–92. https://doi.org/10.1093/toxsci/kfg122.

Lauritzen, Hilde B., Tricia L. Larose, Torbjørn Øien, Torkjel M. Sandanger, Jon Ø Odland, Margot van de Bor, and Geir W. Jacobsen. 2017. "Maternal Serum Levels of Perfluoroalkyl Substances and Organochlorines and Indices of Fetal Growth: A Scandinavian Case-Cohort Study." *Pediatric Research* 81 (1–1): 33–42. https://doi.org/10.1038/pr.2016.187.

Lee, Chae Kwan, Sung Goo Kang, Jong Tae Lee, Soo-Woong Lee, Jeong Ho Kim, Dae Hwan Kim, Byung Chul Son, et al. 2015. "Effects of Perfluorooctane Sulfuric Acid on Placental PRL-Family Hormone Production and Fetal Growth Retardation in Mice." *Molecular and Cellular Endocrinology* 401 (February): 165–72. https://doi.org/10.1016/j.mce.2014.10.026.

Lee, Eung-Sun, Sehee Han, and Jeong-Eun Oh. 2016. "Association between Perfluorinated Compound Concentrations in Cord Serum and Birth Weight Using Multiple Regression Models." *Reproductive Toxicology (Elmsford, N.Y.)* 59 (January): 53–59. https://doi.org/10.1016/j.reprotox.2015.10.020.

Lee, Youn Ju, Min-Kyun Kim, Jisuk Bae, and Jae-Ho Yang. 2013. "Concentrations of Perfluoroalkyl Compounds in Maternal and Umbilical Cord Sera and Birth Outcomes in Korea." *Chemosphere* 90 (5): 1603–9. https://doi.org/10.1016/j.chemosphere.2012.08.035.

Lenters, Virissa, Lützen Portengen, Anna Rignell-Hydbom, Bo A. G. Jönsson, Christian H. Lindh, Aldert H. Piersma, Gunnar Toft, et al. 2016. "Prenatal Phthalate, Perfluoroalkyl Acid, and

Organochlorine Exposures and Term Birth Weight in Three Birth Cohorts: Multi-Pollutant Models Based on Elastic Net Regression." *Environmental Health Perspectives* 124 (3): 365–72. https://doi.org/10.1289/ehp.1408933.

Li, Meng, Xiao-Wen Zeng, Zhengmin Min Qian, Michael G. Vaughn, Sébastien Sauvé, Gunther Paul, Shao Lin, et al. 2017. "Isomers of Perfluorooctanesulfonate (PFOS) in Cord Serum and Birth Outcomes in China: Guangzhou Birth Cohort Study." *Environment International* 102: 1–8. https://doi.org/10.1016/j.envint.2017.03.006.

Li, Xiaoheng, Leping Ye, Yufei Ge, Kaiming Yuan, Yufei Zhang, Yong Liang, Jia Wei, et al. 2016. "In Utero Perfluorooctane Sulfonate Exposure Causes Low Body Weights of Fetal Rats: A Mechanism Study." *Placenta* 39 (March): 125–33. https://doi.org/10.1016/j.placenta.2016.01.010.

Lien, Guang-Wen, Ching-Chun Huang, Jia-Shian Shiu, Mei-Huei Chen, Wu-Shiun Hsieh, Yue-Liang Guo, and Pau-Chung Chen. 2016. "Perfluoroalkyl Substances in Cord Blood and Attention Deficit/Hyperactivity Disorder Symptoms in Seven-Year-Old Children." *Chemosphere* 156 (August): 118–27. https://doi.org/10.1016/j.chemosphere.2016.04.102.

Liew, Zeyan, Beate Ritz, Eva Cecilie Bonefeld-Jørgensen, Tine Brink Henriksen, Ellen Aagaard Nohr, Bodil Hammer Bech, Chunyuan Fei, et al. 2014. "Prenatal Exposure to Perfluoroalkyl Substances and the Risk of Congenital Cerebral Palsy in Children." *American Journal of Epidemiology* 180 (6): 574–81. https://doi.org/10.1093/aje/kwu179.

Liew, Zeyan, Beate Ritz, Ondine S. von Ehrenstein, Bodil Hammer Bech, Ellen Aagaard Nohr, Chunyuan Fei, Rossana Bossi, Tine Brink Henriksen, Eva Cecilie Bonefeld-Jørgensen, and Jørn Olsen. 2015. "Attention Deficit/Hyperactivity Disorder and Childhood Autism in Association with Prenatal Exposure to Perfluoroalkyl Substances: A Nested Case-Control Study in the Danish National Birth Cohort." *Environmental Health Perspectives* 123 (4): 367–73. https://doi.org/10.1289/ehp.1408412.

Loccisano, Anne E., Jerry L. Campbell, John L. Butenhoff, Melvin E. Andersen, and Harvey J. Clewell. 2012. "Evaluation of Placental and Lactational Pharmacokinetics of PFOA and PFOS in the Pregnant, Lactating, Fetal and Neonatal Rat Using a Physiologically Based Pharmacokinetic Model." *Reproductive Toxicology (Elmsford, N.Y.)* 33 (4): 468–90. https://doi.org/10.1016/j.reprotox.2011.07.003.

Luebker, Deanna J., Raymond G. York, Kristen J. Hansen, John A. Moore, and John L. Butenhoff. 2005. "Neonatal Mortality from in Utero Exposure to Perfluorooctanesulfonate (PFOS) in Sprague-Dawley Rats: Dose-Response, and Biochemical and Pharamacokinetic Parameters." *Toxicology* 215 (1–2): 149–69. https://doi.org/10.1016/j.tox.2005.07.019.

Maekawa, Ryo, Rie Ito, Yusuke Iwasaki, Koichi Saito, Kazuhiko Akutsu, Satoshi Takatori, Rie Ishii, et al. 2017. "Evidence of Exposure to Chemicals and Heavy Metals during Pregnancy in Japanese Women." *Reproductive Medicine and Biology* 16 (4): 337–48. https://doi.org/10.1002/rmb2.12049.

Maisonet, Mildred, Metrecia L. Terrell, Michael A. McGeehin, Krista Yorita Christensen, Adrianne Holmes, Antonia M. Calafat, and Michele Marcus. 2012. "Maternal Concentrations of Polyfluoroalkyl Compounds during Pregnancy and Fetal and Postnatal Growth in British Girls." *Environmental Health Perspectives* 120 (10): 1432–37. https://doi.org/10.1289/ehp.1003096.

Macon, Madisa B., LaTonya R. Villanueva, Katoria Tatum-Gibbs, Robert D. Zehr, Mark J. Strynar, Jason P. Stanko, Sally S. White, Laurence Helfant, and Suzanne E. Fenton. 2011. "Prenatal Perfluorooctanoic Acid Exposure in CD-1 Mice: Low-Dose Developmental Effects and Internal Dosimetry." *Toxicological Sciences: An Official Journal of the Society of Toxicology* 122 (1): 134–45. https://doi.org/10.1093/toxsci/kfr076.

Manzano-Salgado, Cyntia B., Maribel Casas, Maria-Jose Lopez-Espinosa, Ferran Ballester, Mikel Basterrechea, Joan O. Grimalt, Ana-María Jiménez, et al. 2015. "Transfer of Perfluoroalkyl Substances from Mother to Fetus in a Spanish Birth Cohort." *Environmental Research* 142 (October): 471–78. https://doi.org/10.1016/j.envres.2015.07.020.

Matilla-Santander, Nuria, Damaskini Valvi, Maria-Jose Lopez-Espinosa, Cyntia B. Manzano-Salgado, Ferran Ballester, Jesús Ibarluzea, Loreto Santa-Marina, et al. 2017. "Exposure to Perfluoroalkyl Substances and Metabolic Outcomes in Pregnant Women: Evidence from the Spanish INMA Birth Cohorts." *Environmental Health Perspectives* 125 (11): 117004. https://doi.org/10.1289/EHP1062.

Minatoya, Machiko, Sachiko Itoh, Chihiro Miyashita, Atsuko Araki, Seiko Sasaki, Ryu Miura, Houman Goudarzi, Yusuke Iwasaki, and Reiko Kishi. 2017. "Association of Prenatal Exposure to Perfluoroalkyl Substances with Cord Blood Adipokines and Birth Size: The Hokkaido Study on Environment and Children's Health." *Environmental Research* 156: 175–82. https://doi.org/10.1016/j.envres.2017.03.033.

Monroy, Rocio, Katherine Morrison, Koon Teo, Stephanie Atkinson, Cariton Kubwabo, Brian Stewart, and Warren G. Foster. 2008. "Serum Levels of Perfluoroalkyl Compounds in Human Maternal and Umbilical Cord Blood Samples." *Environmental Research* 108 (1): 56–62. https://doi.org/10.1016/j.envres.2008.06.001.

Nolan, Lynda A., John M. Nolan, Frances S. Shofer, Nancy V. Rodway, and Edward A. Emmett. 2009. "The Relationship between Birth Weight, Gestational Age and Perfluorooctanoic Acid (PFOA)-Contaminated Public Drinking Water." *Reproductive Toxicology (Elmsford, N.Y.)* 27 (3–4): 231–38. https://doi.org/10.1016/j.reprotox.2008.11.001.

———. 2010. "Congenital Anomalies, Labor/Delivery Complications, Maternal Risk Factors and Their Relationship with Perfluorooctanoic Acid (PFOA)-Contaminated Public Drinking Water." *Reproductive Toxicology (Elmsford, N.Y.)* 29 (2): 147–55. https://doi.org/10.1016/j.reprotox.2009.10.012.

Ode, Amanda, Karin Källén, Peik Gustafsson, Lars Rylander, Bo A. G. Jönsson, Per Olofsson, Sten A. Ivarsson, Christian H. Lindh, and Anna Rignell-Hydbom. 2014. "Fetal Exposure to Perfluorinated Compounds and Attention Deficit Hyperactivity Disorder in Childhood." *PloS One* 9 (4): e95891. https://doi.org/10.1371/journal.pone.0095891.

Onishchenko, Natalia, Celia Fischer, Wan Norhamidah Wan Ibrahim, Sara Negri, Stefan Spulber, Danilo Cottica, and Sandra Ceccatelli. 2011. "Prenatal Exposure to PFOS or PFOA Alters Motor Function in Mice in a Sex-Related Manner." *Neurotoxicity Research* 19 (3): 452–61. https://doi.org/10.1007/s12640-010-9200-4.

Oulhote, Youssef, Ulrike Steuerwald, Frodi Debes, Pal Weihe, and Philippe Grandjean. 2016. "Behavioral Difficulties in 7-Year Old Children in Relation to Developmental Exposure to Perfluorinated Alkyl Substances." *Environment International* 97: 237–45. https://doi.org/10.1016/j.envint.2016.09.015.

Peden-Adams, Margie M., Joyce E. Stuckey, Kristen M. Gaworecki, Jennifer Berger-Ritchie, Kathy Bryant, Patrick G. Jodice, Thomas R. Scott, et al. 2009. "Developmental Toxicity in White Leghorn Chickens Following in Ovo Exposure to Perfluorooctane Sulfonate (PFOS)." *Reproductive Toxicology (Elmsford, N.Y.)* 27 (3–4): 307–18. https://doi.org/10.1016/j.reprotox.2008.10.009.

Pinkas, Adi, Theodore A. Slotkin, Yael Brick-Turin, Eddy A. Van der Zee, and Joseph Yanai. 2010. "Neurobehavioral Teratogenicity of Perfluorinated Alkyls in an Avian Model." *Neurotoxicology and Teratology* 32 (2): 182–86. https://doi.org/10.1016/j.ntt.2009.11.004.

Preston, Emma V., Thomas F. Webster, Emily Oken, Birgit Claus Henn, Michael D. McClean, Sheryl L. Rifas-Shiman, Elizabeth N. Pearce, et al. 2018. "Maternal Plasma Per- and Polyfluoroalkyl Substance Concentrations in Early Pregnancy and Maternal and Neonatal Thyroid Function in a Prospective Birth Cohort: Project Viva (USA)." *Environmental Health Perspectives* 126 (2): 027013. https://doi.org/10.1289/EHP2534.

Quaak, Ilona, Marijke de Cock, Michiel de Boer, Marja Lamoree, Pim Leonards, and Margot van de Bor. 2016. "Prenatal Exposure to Perfluoroalkyl Substances and Behavioral Development in Children." *International Journal of Environmental Research and Public Health* 13 (5). https://doi.org/10.3390/ijerph13050511.

Rogers, John M., Robert G. Ellis-Hutchings, Brian E. Grey, Robert M. Zucker, Joel Norwood, Curtis E. Grace, Christopher J. Gordon, and Christopher Lau. 2014. "Elevated Blood Pressure in Offspring of Rats Exposed to Diverse Chemicals during Pregnancy." *Toxicological Sciences: An Official Journal of the Society of Toxicology* 137 (2): 436–46. https://doi.org/10.1093/toxsci/kft248.

Rokoff, Lisa B., Sheryl L. Rifas-Shiman, Brent A. Coull, Andres Cardenas, Antonia M. Calafat, Xiaoyun Ye, Alexandros Gryparis, et al. 2018. "Cumulative Exposure to Environmental Pollutants during Early Pregnancy and Reduced Fetal Growth: The Project Viva Cohort." *Environmental Health: A Global Access Science Source* 17 (1): 19. https://doi.org/10.1186/s12940-018-0363-4.

Roth, N., and M. F. Wilks. 2014. "Neurodevelopmental and Neurobehavioural Effects of Polybrominated and Perfluorinated Chemicals: A Systematic Review of the Epidemiological Literature Using a Quality Assessment Scheme." *Toxicology Letters* 230 (2): 271–81. https://doi.org/10.1016/j.toxlet.2014.02.015.

Sagiv, Sharon K., Sheryl L. Rifas-Shiman, Thomas F. Webster, Ana Maria Mora, Maria H. Harris, Antonia M. Calafat, Xiaoyun Ye, Matthew W. Gillman, and Emily Oken. 2015. "Sociodemographic and Perinatal Predictors of Early Pregnancy Per- and Polyfluoroalkyl Substance (PFAS) Concentrations." *Environmental Science & Technology* 49 (19): 11849–58. https://doi.org/10.1021/acs.est.5b02489.

Savitz, David A., Cheryl R. Stein, Scott M. Bartell, Beth Elston, Jian Gong, Hyeong-Moo Shin, and Gregory A. Wellenius. 2012. "Perfluorooctanoic Acid Exposure and Pregnancy Outcome in a Highly Exposed Community." *Epidemiology (Cambridge, Mass.)* 23 (3): 386–92. https://doi.org/10.1097/EDE.0b013e31824cb93b.

Savitz, David A., Cheryl R. Stein, Beth Elston, Gregory A. Wellenius, Scott M. Bartell, Hyeong-Moo Shin, Veronica M. Vieira, and Tony Fletcher. 2012. "Relationship of Perfluorooctanoic Acid Exposure to Pregnancy Outcome Based on Birth Records in the Mid-Ohio Valley." *Environmental Health Perspectives* 120 (8): 1201–7. https://doi.org/10.1289/ehp.1104752.

Secretariat, Stockholm Convention. 2009. "Governments Unite to Step-up Reduction on Global DDT Reliance and Add Nine New Chemicals under International Treaty." In . Stockholm Convention.

Shah-Kulkarni, Surabhi, Byung-Mi Kim, Yun-Chul Hong, Hae Soon Kim, Eun Jin Kwon, Hyesook Park, Young Ju Kim, and Eun-Hee Ha. 2016. "Prenatal Exposure to Perfluorinated Compounds Affects Thyroid Hormone Levels in Newborn Girls." *Environment International* 94: 607–13. https://doi.org/10.1016/j.envint.2016.06.024.

Shi, Xiongjie, Yongbing Du, Paul K. S. Lam, Rudolf S. S. Wu, and Bingsheng Zhou. 2008. "Developmental Toxicity and Alteration of Gene Expression in Zebrafish Embryos Exposed to PFOS." *Toxicology and Applied Pharmacology* 230 (1): 23–32. https://doi.org/10.1016/j.taap.2008.01.043.

Shi, Yu, Lin Yang, Jingguang Li, Jianqiang Lai, Yuxin Wang, Yunfeng Zhao, and Yongning Wu. 2017. "Occurrence of Perfluoroalkyl Substances in Cord Serum and Association with Growth Indicators in Newborns from Beijing." *Chemosphere* 169 (February): 396–402. https://doi.org/10.1016/j.chemosphere.2016.11.050.

Skuladottir, Margret, Alfons Ramel, Dorte Rytter, Line Småstuen Haug, Azemira Sabaredzovic, Bodil Hammer Bech, Tine Brink Henriksen, Sjurdur F. Olsen, and Thorhallur I. Halldorsson. 2015. "Examining Confounding by Diet in the Association between Perfluoroalkyl Acids and Serum Cholesterol in Pregnancy." *Environmental Research* 143 (Pt A): 33–38. https://doi.org/10.1016/j.envres.2015.09.001.

Sobolewski, Marissa, Katherine Conrad, Joshua L. Allen, Hiromi Weston, Kyle Martin, B. Paige Lawrence, and Deborah A. Cory-Slechta. 2014. "Sex-Specific Enhanced Behavioral Toxicity Induced by Maternal Exposure to a Mixture of Low Dose Endocrine-Disrupting Chemicals." *Neurotoxicology* 45 (December): 121–30. https://doi.org/10.1016/j.neuro.2014.09.008.

Spachmo, Bård, and Augustine Arukwe. 2012. “Endocrine and Developmental Effects in Atlantic Salmon (Salmo Salar) Exposed to Perfluorooctane Sulfonic or Perfluorooctane Carboxylic Acids.” *Aquatic Toxicology (Amsterdam, Netherlands)* 108 (February): 112–24. https://doi.org/10.1016/j.aquatox.2011.07.018.

Spulber, Stefan, Pascal Kilian, Wan Norhamidah Wan Ibrahim, Natalia Onishchenko, Mazhar Ulhaq, Leif Norrgren, Sara Negri, Marcello Di Tuccio, and Sandra Ceccatelli. 2014. “PFOS Induces Behavioral Alterations, Including Spontaneous Hyperactivity That Is Corrected by Dexamfetamine in Zebrafish Larvae.” *PloS One* 9 (4): e94227. https://doi.org/10.1371/journal.pone.0094227.

Staples, R. E., B. A. Burgess, and W. D. Kerns. 1984. “The Embryo-Fetal Toxicity and Teratogenic Potential of Ammonium Perfluorooctanoate (APFO) in the Rat.” *Fundamental and Applied Toxicology: Official Journal of the Society of Toxicology* 4 (3 Pt 1): 429–40.

Starling, Anne P., John L. Adgate, Richard F. Hamman, Katerina Kechris, Antonia M. Calafat, Xiaoyun Ye, and Dana Dabelea. 2017. “Perfluoroalkyl Substances during Pregnancy and Offspring Weight and Adiposity at Birth: Examining Mediation by Maternal Fasting Glucose in the Healthy Start Study.” *Environmental Health Perspectives* 125 (6): 067016. https://doi.org/10.1289/EHP641.

Starling, Anne P., Stephanie M. Engel, David B. Richardson, Donna D. Baird, Line S. Haug, Alison M. Stuebe, Kari Klungsøyr, et al. 2014. “Perfluoroalkyl Substances during Pregnancy and Validated Preeclampsia among Nulliparous Women in the Norwegian Mother and Child Cohort Study.” *American Journal of Epidemiology* 179 (7): 824–33. https://doi.org/10.1093/aje/kwt432.

Steenland, Kyle, Vaughn Barry, and David Savitz. 2018. “Serum Perfluorooctanoic Acid and Birthweight: An Updated Meta-Analysis With Bias Analysis.” *Epidemiology* 29 (6): 765–76.

Stein, Cheryl R., David A. Savitz, and David C. Bellinger. 2013. “Perfluorooctanoate and Neuropsychological Outcomes in Children.” *Epidemiology (Cambridge, Mass.)* 24 (4): 590–99. https://doi.org/10.1097/EDE.0b013e3182944432.

Stein, Cheryl R., David A. Savitz, and Marcelle Dougan. 2009. “Serum Levels of Perfluorooctanoic Acid and Perfluorooctane Sulfonate and Pregnancy Outcome.” *American Journal of Epidemiology* 170 (7): 837–46. https://doi.org/10.1093/aje/kwp212.

Strøm, Marin, Susanne Hansen, Sjúrður Fróði Olsen, Line Småstuen Haug, Panu Rantakokko, Hannu Kiviranta, and Thorhallur Ingi Halldorsson. 2014. “Persistent Organic Pollutants Measured in Maternal Serum and Offspring Neurodevelopmental Outcomes--a Prospective Study with Long-Term Follow-Up.” *Environment International* 68 (July): 41–48. https://doi.org/10.1016/j.envint.2014.03.002.

Suh, Chun Hui, Nam Kyoo Cho, Chae Kwan Lee, Chang Hee Lee, Dae Hwan Kim, Jeong Ho Kim, Byung Chul Son, and Jong Tae Lee. 2011. “Perfluorooctanoic Acid-Induced Inhibition of Placental Prolactin-Family Hormone and Fetal Growth Retardation in Mice.” *Molecular and Cellular Endocrinology* 337 (1–2): 7–15. https://doi.org/10.1016/j.mce.2011.01.009.

Thibodeaux, Julie R., Roger G. Hanson, John M. Rogers, Brian E. Grey, Brenda D. Barbee, Judy H. Richards, John L. Butenhoff, Lisa A. Stevenson, and Christopher Lau. 2003. “Exposure to Perfluorooctane Sulfonate during Pregnancy in Rat and Mouse. I: Maternal and Prenatal Evaluations.” *Toxicological Sciences: An Official Journal of the Society of Toxicology* 74 (2): 369–81. https://doi.org/10.1093/toxsci/kfg121.

Ulhaq, Mazhar, Stefan Orn, Gunnar Carlsson, David A. Morrison, and Leif Norrgren. 2013. “Locomotor Behavior in Zebrafish (Danio Rerio) Larvae Exposed to Perfluoroalkyl Acids.” *Aquatic Toxicology (Amsterdam, Netherlands)* 144–145 (November): 332–40. https://doi.org/10.1016/j.aquatox.2013.10.021.

U.S. Environmental Protection Agency. 2016a. “Health Effects Support Document for Perfluorooctane Sulfonate (PFOS).” In . EPA Document Number: 822-R-16-002.

———. 2016b. “Health Effects Support Document for Perfluorooctanoic Acid (PFOA).” In . EPA Document Number: 822-R-16-003.

Vuong, Ann M., Kimberly Yolton, Glenys M. Webster, Andreas Sjödin, Antonia M. Calafat, Joseph M. Braun, Kim N. Dietrich, Bruce P. Lanphear, and Aimin Chen. 2016. “Prenatal

Polybrominated Diphenyl Ether and Perfluoroalkyl Substance Exposures and Executive Function in School-Age Children." *Environmental Research* 147 (May): 556–64. https://doi.org/10.1016/j.envres.2016.01.008.

Wang, Jianshe, Yan Li, Yang Liu, Hongxia Zhang, and Jiayin Dai. 2010. "Disturbance of Perfluorooctanoic Acid on Development and Behavior in Drosophila Larvae." *Environmental Toxicology and Chemistry* 29 (9): 2117–22. https://doi.org/10.1002/etc.237.

Wang, Mingyong, Jiangfei Chen, Kuanfei Lin, Yuanhong Chen, Wei Hu, Robert L. Tanguay, Changjiang Huang, and Qiaoxiang Dong. 2011. "Chronic Zebrafish PFOS Exposure Alters Sex Ratio and Maternal Related Effects in F1 Offspring." *Environmental Toxicology and Chemistry* 30 (9): 2073–80. https://doi.org/10.1002/etc.594.

Wang, Yan, Anne P. Starling, Line S. Haug, Merete Eggesbo, Georg Becher, Cathrine Thomsen, Gregory Travlos, et al. 2013. "Association between Perfluoroalkyl Substances and Thyroid Stimulating Hormone among Pregnant Women: A Cross-Sectional Study." *Environmental Health: A Global Access Science Source* 12 (1): 76. https://doi.org/10.1186/1476-069X-12-76.

Wang, Yan, Walter J. Rogan, Pau-Chung Chen, Guang-Wen Lien, Hsiao-Yen Chen, Ying-Chih Tseng, Matthew P. Longnecker, and Shu-Li Wang. 2014. "Association between Maternal Serum Perfluoroalkyl Substances during Pregnancy and Maternal and Cord Thyroid Hormones: Taiwan Maternal and Infant Cohort Study." *Environmental Health Perspectives* 122 (5): 529–34. https://doi.org/10.1289/ehp.1306925.

Wang, Yan, Margaret Adgent, Pen-Hua Su, Hsiao-Yen Chen, Pau-Chung Chen, Chao A. Hsiung, and Shu-Li Wang. 2016. "Prenatal Exposure to Perfluorocarboxylic Acids (PFCAs) and Fetal and Postnatal Growth in the Taiwan Maternal and Infant Cohort Study." *Environmental Health Perspectives* 124 (11): 1794–1800. https://doi.org/10.1289/ehp.1509998.

Wang, Yu, Wei Liu, Qian Zhang, Huimin Zhao, and Xie Quan. 2015. "Effects of Developmental Perfluorooctane Sulfonate Exposure on Spatial Learning and Memory Ability of Rats and Mechanism Associated with Synaptic Plasticity." *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 76 (February): 70–76. https://doi.org/10.1016/j.fct.2014.12.008

Washino, Noriaki, Yasuaki Saijo, Seiko Sasaki, Shizue Kato, Susumu Ban, Kanae Konishi, Rie Ito, et al. 2009. "Correlations between Prenatal Exposure to Perfluorinated Chemicals and Reduced Fetal Growth." *Environmental Health Perspectives* 117 (4): 660–67. https://doi.org/10.1289/ehp.11681.

Webster, Glenys M., Scott A. Venners, Andre Mattman, and Jonathan W. Martin. 2014. "Associations between Perfluoroalkyl Acids (PFASs) and Maternal Thyroid Hormones in Early Pregnancy: A Population-Based Cohort Study." *Environmental Research* 133 (August): 338–47. https://doi.org/10.1016/j.envres.2014.06.012.

White, Sally S., Antonia M. Calafat, Zsuzsanna Kuklenyik, LaTonya Villanueva, Robert D. Zehr, Laurence Helfant, Mark J. Strynar, et al. 2007. "Gestational PFOA Exposure of Mice Is Associated with Altered Mammary Gland Development in Dams and Female Offspring." *Toxicological Sciences: An Official Journal of the Society of Toxicology* 96 (1): 133–44. https://doi.org/10.1093/toxsci/kfl177.

White, Sally S., Kayoko Kato, Lily T. Jia, Brian J. Basden, Antonia M. Calafat, Erin P. Hines, Jason P. Stanko, Cynthia J. Wolf, Barbara D. Abbott, and Suzanne E. Fenton. 2009. "Effects of Perfluorooctanoic Acid on Mouse Mammary Gland Development and Differentiation Resulting from Cross-Foster and Restricted Gestational Exposures." *Reproductive Toxicology (Elmsford, N.Y.)* 27 (3–4): 289–98. https://doi.org/10.1016/j.reprotox.2008.11.054

White, Sally S., Jason P. Stanko, Kayoko Kato, Antonia M. Calafat, Erin P. Hines, and Suzanne E. Fenton. 2011. "Gestational and Chronic Low-Dose PFOA Exposures and Mammary Gland Growth and Differentiation in Three Generations of CD-1 Mice." *Environmental Health Perspectives* 119 (8): 1070–76. https://doi.org/10.1289/ehp.1002741.

Whitworth, Kristina W., Line S. Haug, Donna D. Baird, Georg Becher, Jane A. Hoppin, Rolv Skjaerven, Cathrine Thomsen, et al. 2012. "Perfluorinated Compounds in Relation to Birth Weight in the Norwegian Mother and Child Cohort Study." *American Journal of Epidemiology* 175 (12): 1209–16. https://doi.org/10.1093/aje/kwr459.

Wolf, Cynthia J., Suzanne E. Fenton, Judith E. Schmid, Antonia M. Calafat, Zsuzsanna Kuklenyik, Xavier A. Bryant, Julie Thibodeaux, et al. 2007. "Developmental Toxicity of Perfluorooctanoic Acid in the CD-1 Mouse after Cross-Foster and Restricted Gestational Exposures." *Toxicological Sciences: An Official Journal of the Society of Toxicology* 95 (2): 462–73. https://doi.org/10.1093/toxsci/kfl159.

Woodruff, Tracey J., and Patrice Sutton. 2014. "The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes." *Environmental Health Perspectives* 122 (10): 1007.

Wu, Kusheng, Xijin Xu, Lin Peng, Junxiao Liu, Yongyong Guo, and Xia Huo. 2012. "Association between Maternal Exposure to Perfluorooctanoic Acid (PFOA) from Electronic Waste Recycling and Neonatal Health Outcomes." *Environment International* 48 (November): 1–8. https://doi.org/10.1016/j.envint.2012.06.018.

Yahia, Doha, Mahmoud Abd El-Nasser, Manal Abedel-Latif, Chiaki Tsukuba, Midori Yoshida, Itaru Sato, and Shuji Tsuda. 2010. "Effects of Perfluorooctanoic Acid (PFOA) Exposure to Pregnant Mice on Reproduction." *The Journal of Toxicological Sciences* 35 (4): 527–33.

Yanai, Joseph, Sharon Dotan, Roman Goz, Adi Pinkas, Frederic J. Seidler, Theodore A. Slotkin, and Frederic Zimmerman. 2008. "Exposure of Developing Chicks to Perfluorooctanoic Acid Induces Defects in Prehatch and Early Posthatch Development." *Journal of Toxicology and Environmental Health. Part A* 71 (2): 131–33. https://doi.org/10.1080/15287390701613280.

Yang, Lin, Jingguang Li, Jianqiang Lai, Hemi Luan, Zongwei Cai, Yibaina Wang, Yunfeng Zhao, and Yongning Wu. 2016. "Placental Transfer of Perfluoroalkyl Substances and Associations with Thyroid Hormones: Beijing Prenatal Exposure Study." *Scientific Reports* 6 (February): 21699. https://doi.org/10.1038/srep21699.

Yu, Wen-Guang, Wei Liu, Yi-He Jin, Xiao-Hui Liu, Fa-Qi Wang, Li Liu, and Shoji F. Nakayama. 2009. "Prenatal and Postnatal Impact of Perfluorooctane Sulfonate (PFOS) on Rat Development: A Cross-Foster Study on Chemical Burden and Thyroid Hormone System." *Environmental Science & Technology* 43 (21): 8416–22. https://doi.org/10.1021/es901602d.

Zhang, Cuilin, Rajeshwari Sundaram, José Maisog, Antonia M. Calafat, Dana Boyd Barr, and Germaine M. Buck Louis. 2015. "A Prospective Study of Prepregnancy Serum Concentrations of Perfluorochemicals and the Risk of Gestational Diabetes." *Fertility and Sterility* 103 (1): 184–89. https://doi.org/10.1016/j.fertnstert.2014.10.001.

Zhang, Ling, Yuan-yuan Li, Tian Chen, Wei Xia, Yin Zhou, Yan-jian Wan, Zi-quan Lv, Geng-qi Li, and Shun-qing Xu. 2011. "Abnormal Development of Motor Neurons in Perfluorooctane Sulphonate Exposed Zebrafish Embryos." *Ecotoxicology (London, England)* 20 (4): 643–52. https://doi.org/10.1007/s10646-011-0604-6.

Zhao, Meng, Qixiao Jiang, Wencheng Wang, Min Geng, Meng Wang, Yantao Han, and Chunbo Wang. 2017. "The Roles of Reactive Oxygen Species and Nitric Oxide in Perfluorooctanoic Acid-Induced Developmental Cardiotoxicity and l-Carnitine Mediated Protection." *International Journal of Molecular Sciences* 18 (6). https://doi.org/10.3390/ijms18061229.

Zheng, Xin-Mei, Hong-Ling Liu, Wei Shi, Si Wei, John P. Giesy, and Hong-Xia Yu. 2011. "Effects of Perfluorinated Compounds on Development of Zebrafish Embryos." *Environmental Science and Pollution Research International* 19 (7): 2498–2505. https://doi.org/10.1007/s11356-012-0977-y.

Table 1. PubMed search string (last update made on the 5th of July 2018)

N	Search string	Records
1	(perfluorooctanoate OR “perfluorooctanoic acid” OR “perfluoroctanoic acid” OR pfoa OR “perfluorinated chemicals” OR “perfluorinated compounds” OR “perfluorinated contaminants” OR “perfluorinated surfactants” OR perfluoroalkyl acids OR “perfluorinated alkylated substances” OR “perfluoroalkylated substances” OR pfba OR “perfluorobutanoic acid” OR perfluorochemicals OR “telomer alcohol” OR “telomer alcohols” OR “fluorotelomer alcohols” OR “polyfluoroalkyl compounds” OR “perfluorooctane sulfonate” OR pfos OR “perfluorooctanesulfonic acid” OR “perfluorooctane sulfonic acid” OR “perfluorooctane sulphonate” OR “perfluorooctane sulfonate” OR “perfluorooctanyl sulfonate” OR perfluorononanoate OR pfhxa OR “perfluorohexanoic acid” OR “fluorinated surfactants”)	4837
2	(Reproduction[Mesh] OR Reproduction[Title/Abstract] OR "Growth and Development"[Mesh] OR "Development and Growth"[Title/Abstract] OR Development[Title/Abstract] OR Developmental[Title/Abstract] OR Growth [Title/Abstract] OR “Pregnancy Complications”[Mesh] OR “Pregnancy Complication”[Title/Abstract] OR “Pregnancy Complications”[Title/Abstract] OR "Developmental Biology"[Mesh] OR "Developmental Biology"[Title/Abstract])	4665226
3	**1 AND 2**	**1096**

Table 2. PICO (Participants, Intervention/Exposure, Comparator, and Outcomes) approach for animal and human evidence

Animals	
Participants	Animals (both mammalian and non-mammalian) exposed to PFAS during the reproductive phase
Exposure	Any type of PFAS at any dosage by any route of administration
Comparator	Animals not exposed to PFAS and/or exposed to different doses of PFAS
Outcomes	Intrauterine growth restrictions, structural and functional (nervous system and brain problems) birth defects, preeclampsia, gestational diabetes, thyroid disorders
Humans	
Participants	Pregnant women and children
Exposure	Direct measure of exposure in maternal blood, cord blood, breast milk or estimated (indirect) measure of exposure in maternal blood, cord blood, breast milk
Comparator	Continuous or categorized levels of PFAS
Outcomes	Intrauterine growth restrictions, structural and functional (nervous system and brain problems) birth defects, preeclampsia, gestational diabetes, thyroid disorders
Study design	Retrospective study, prospective study, cross-sectional study, case-control study

Table 3. Chemical substances investigated in the studies included in the review

Acronym	Full meaning
PFBA	Perfluorobutyric acid
PFBS	Perfluorobutane sulfonate
PFPeA	Perfluoropentanoic acid
PFHxA	Perfluorohexanoic acid
PFHxS	Perfluorohexane sulfonate
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonate
PFDeA (or PFDA)	Perfluorodecanoic acid
PFDoA (or PFDoDA)	Perfluorododecanoic acid
PFHpA	Perfluoroheptanoic acid
PFHpS	Perfluoroheptane sulfonate
PFHxDA	Perfluorohexadecanoic acid
PFNA	Perfluorononanoic acid
PFOSA	Perfluorooctane sulfonamide
PFTeDA	Perfluorotetradecanoic acid
PFUnA (or PFUnDA)	Perfluoroundecanoic acid
PFTrDA	Perfluorotridecanoic acid

Table 4. Animal evidence included in the review. Significant adverse effects are in bold

Author, Year	Species	Outcome/s	Exposure	Route	Dose (range)	Period of exposure	Results
(Abbott et al. 2007)	Mouse	PW, Eye opening	PFOA	Gavage	0.1-20 mg/kg	1-17 GDs	**Eye opening: significantly delayed (dose-dependent trend)**
(Boberg et al. 2008)	Rat	FW	PFOA	Gavage	20 mg/kg	7-21 GDs	No significant association
(Butenhoff et al. 2009)	Rat	GL, MW, Thyroid function (pups), Learning/Memory, Behavior	PFOS	Gavage	0.1-1 mg/kg	0 GD-20 PND	No significant association
(Butenhoff et al. 2004)	Rat	PW, Malformations	PFOA	Gavage	1-30 mg/kg	6 weeks of age-at least 70d before cohabitation	**PW: significantly lower at 30 mg/kg**
(Case, York, and Christian 2001)	Rat Rabbit	MWG, FW	PFOS	Gavage	0.1-3.75 mg/kg	Rat: 6-17 GDs Rabbit: 6-20 GDs	**Rabbit** **• MWG: significantly lower** **• FW: significantly lower at >= 2.5 mg/kg**
(Cassone et al. 2012)	Chicken	Tarsus length, Embryo mass, T4	PFHxS PFHxA	Injection	PFHxS: 8.9-38000 ng/g PFHxA: 9.7-9700 ng/g	Single dose prior of incubation	**• Tarsus length: significantly lower at 38000 ng/g PFHxS** **• Embryo mass: significantly lower at 38000 ng/g PFHxS** **• T4: significantly lower at >=890 ng/g PFHxS**
(S. Chang et al. 2018)	Mouse	GL, PW, Thyroid function	PFHxS	Gavage	0.3-3 mg/kg	Before mating, gestation, lactation	No significant association
(S.-C. Chang et al. 2009)	Rat	Thyroid function (dams and pups)	PFOS	Gavage	0.1-1 mg/kg	0 GD-20 PND	No significant association
(J. Chen et al. 2013)	Zebrafish	Malformations, Behavior	PFOS	Immersion	0.5μM	1-21 dpf 21-120 dpf 1-120 dpf	**• Malformations: significantly higher rate (uninflated swim bladder and curved spine)** **• Behavior: significantly higher swim rate**
(J. Chen et al. 2014)	Zebrafish	Malformations	PFOS	Immersion	16 μM	0-48 hpf 48-96 hpf	**Malformations: uninflated swim bladder, less developed gut, and curved spin in 48-96 hpf exposed group**

(Dang, Wang, and Liu 2018)	Zebrafish	Body length, Malformations, Heart rate	PFOS	Immersion	1-10 µM	2-96 hpf	**• Body length: significantly lower in exposed groups** **• Malformations: significantly higher rate at 10 µM**
(Das et al. 2008)	Mouse	MW, FW, Malformations, Eye opening	PFBA	Gavage	35-350 mg/kg	1-17/35 GDs	**Eye opening: significantly delayed in exposed groups**
(Das et al. 2015)	Mouse	MWG, FW, Eye opening	PFOA PFOS PFNA	Gavage	1-10 mg/kg	1-17 GDs	**Eye opening: significantly delayed at >=3 mg/kg**
(Du et al. 2009)	Zebrafish	Malformations, Thyroid function	PFOS	Immersion	10-250 µgL-1	70 days (zebrafish fry)	**Malformations: significantly higher rate at 50 and 250 µgL-1 (most frequent: curved spine)**
(Era et al. 2009)	Mouse	Cleft palate	PFOS	Gavage	9-30 mg/kg	1-17 GDs	**Cleft palate: significant higher rate in exposed groups**
(Fuentes et al. 2006)	Mouse	MW, FW, Thyroid function (dams)	PFOS	Gavage	1.5-6 mg/kg	6-18 GDs	No significant association
(Fuentes et al. 2007)	Mouse	Motor activity, Spatial learning at 3 month of age	PFOS	Gavage	6 mg/kg	12-18 GDs	**• Motor activity: significantly lower when considering PFOS*restrain** **• Spatial learning: significantly delayed learning when considering PFOS*restrain**
(Goulding et al. 2017)	Mouse	Motor activity at 18,19,20 PNDs	PFOA	Gavage	0.1-1 mg/kg	1-17 GDs	**Significantly higher activity at PND28 at 1 mg/kg and subsequent decrease**
(Grasty et al. 2003)	Rat	MWG, PW	PFOS	Gavage	4 GDs: 25 mg/kg 2 GDs: 25-50 mg/kg	4 GDs 2 GD (19-20 GDs)	**• MWG: significantly lower** **• PW: significantly lower (in 4GDs exposure, before 14 GDs)**
(Hagenaars et al. 2014)	Zebrafish	Body length, Swim activity	PFOS	Immersion	0.5-5 mgL-1	1-144 hpf	**Body length: significantly reduced** **Swim activity: significantly reduced**

(Hagenaars et al. 2011)	Zebrafish	Body length, Malformations, Heart rate	PFOA PFOS PFBS PFBA	Immersion	10-500 mgL-1 1-100 mgL-1 50-3000 mgL-1 50-3000 mgL-1	8-120 hpf	**• Body length: significantly lower at PFOS >=1 mgL-1 and PFOA >=100 mgL-1** **• Malformations (head): PFOA and PFOS** **• Malformations (tail): all PFAS** **• Heart rate: significantly altered at the highest concentrations of PFOS, PFOA, PFBS**
(Hu, Strynar, and DeWitt 2010)	Mouse	MWG, PW	PFOA	Drinking water	0.5-1 mg/kg	6-17 GDs	No significant association
(Huang et al. 2010)	Zebrafish	Malformations, Heart rate, Swim activity	PFOS	Immersion	0.01-16.0 µM	6-120 hpf	**• Malformations: higher rate in exposed in a dose-dependent manner** **• Heart rate: significantly lower** **• Swim activity: significantly higher speed and swim rate in exposed groups**
(Iwai and Hoberman 2014)	Mouse	PW	PFHxA	Gavage	100-500 mg/kg	6-18 GDs	**PW: significantly lower at 350-500 mg/kg**
(Jantzen et al. 2016)	Zebrafish	Body length, Interoocular distance (proxy of cranofacial development), Swim activity	PFOS PFOA PFNA	Immersion	0.02-2 µM	3-120 hpf	**• Body length: significantly lower at >=2 µM of PFOA, PFOS, PFNA** **• Interoocular distance: significantly higher for PFOA (2 µM) and PFOS (all concentrations)** **• Swim activity: significantly lower speed (PFOS, PFNA), increased in distance travelled (PFOS, PFOA, PFNA)**
(Jiang et al. 2012)	Chicken	Yolk-free weight, Heart structure and morphology	PFOA	Egg injection	0.5-2 mg/kg	Single dose at incubation day 0	**PFOA exposure associated with heart morphology and function alterations**
(M. Kim et al. 2013)	Xenopus	Growth, Malformations	PFOA PFNA PFDA PFuDA	Immersion	130 µM 40 µM (PFuDA)	10 days	**• Growth: significantly lower in exposed groups** **• Malformations: exposed groups developed several malformations in a dose-dependent manner**

(Lau et al. 2003)	Rat Mouse	PW, Eye opening, Thyroid function (pups)	PFOS	Gavage	Rat: 1-10 mg/kg Mouse: 1-20 mg/kg	Rat: 2-21 GDs Mouse: 1-17 GDs	**Rats** **• PW: significantly lower at >= 2mg/kg** **• Eye opening: significantly delayed at >= 2mg/kg** **• Thyroid: T4 significantly lower** **Mice** **• Eye opening: significantly delayed in exposed groups**
(Lau et al. 2006)	Mouse	MWG, PW, Ossification	PFOA	Gavage	1-40 mg/kg	1-17 GDs	**• PW: significantly lower in 20 mg/kg groups** **• Ossification: significantly lower in 10-20 mg/kg groups**
(C. K. Lee et al. 2015)	Mouse	MWG, Placental weight, FW, Placental efficiency (FW/placental weight)	PFOS	Gavage	0.5-8 mg/kg	11-16 GDs	**• MWG: significantly lower at >=2 mg/kg** **• Placental weight: significantly lower in exposed groups** **• FW: significantly lower in exposed groups** **• Placental efficiency: significantly lower in exposed groups**
(X. Li et al. 2016)	Rat	Placental weight, FW	PFOS	Gavage	5-20 mg/kg	12-18 GDs	**• Placental weight: significantly lower in 20mg/kg group** **• FW: significantly lower in 20mg/kg group**
(Luebker et al. 2005)	Rat	PW; Eye opening	PFOS	Gavage	0.1-3.2 mg/kg	Prior to mating-Gestation-Lactation	**Eye opening: significantly delayed at 0.4 mg/kg**
(Macon et al. 2011)	Mouse	PW	PFOA	Gavage	0.3-3 mg/kg 0.01-1 mg/kg	1-17 GDs 10-17 GDs	No significant association
(Onishchenko et al. 2011)	Mouse	MWG, PW, Locomotor activity, Circadian activity, Emotion-related behavior, Muscle strength	PFOA PFOS	Food	0.3 mg/kg	1 GD-through pregnancy	**• Locomotor activity: significant inverse association with PFOS in males** **• Circadian activity: significantly higher in males exposed to PFOA** **• Emotion-related behavior: activity significantly reduced in males exposed to PFOS**
(Peden-Adams et al. 2009)	Chicken	Malformations	PFOS	Injection	1-5 mg/kg	Single dose at incubation day 0	**Right wing significantly shorted in exposed groups**

(Pinkas et al. 2010)	Chicken	Imprinting performance	PFOA PFOS	Eggs injection	5-10 mg/kg	Single dose at incubation day 0	**Lower scores in imprinting performance in exposed animals**
(Rogers et al. 2014)	Rat	MWG, PW, BP (pups)	PFOS PFNA	Gavage	PFOS: 18.75 mg/kg PFNA: 5 mg/kg	PFOS: 2-6 GDs PFNA: 1-20 GDs	**• MWG: significantly lower in exposed groups** **• PW: significantly lower exposed to PFOS (only females) and PFNA** **BP: significantly higher in PFOS and PFNA exposed animals**
(X. Shi et al. 2008)	Zebrafish	Body length, Malformations	PFOS	Immersion	0.1-5 mg/L	4 hpf-until observation	**• Body length: significantly lower at >=03 mg/L** **• Malformations: significantly higher rate in a dose-dependent manner**
(Sobolewski et al. 2014)	Mouse	PW, Locomotor behavior, Novel object exploration, Fixed interval reinforcement schedule	PFOA	Gavage	0.1 mg/kg	7 GD-until weaning	**• Locomotor activity: significantly higher in exposed** **• Object exploration: significantly lower in exposed**
(Spachmo and Arukwe 2012)	Atlantic salmon	W (larvae), BL, Bone development	PFOA PFOS	Immersion	100 Mg/L	52 days (from egg stage)	No significant association
(Spulber et al. 2014)	Zebrafish	Swim activity	PFOS	Food	0.1-1 mg/L	2 hpf-6 dpf	**Hyperactivity at 1 mg/L**
(Staples, Burgess, and Kerns 1984)	Rat	MWG, FW, Malformations	PFOA	Gavage Inhalation	Gavage: 100 mg/kg Inhalation: 0.1-25 mg/m3	6-15 GDs	**Inhalation** **• MWG: significantly lower at 25mg/m3** **• FW: significantly lower at 25mg/m3** **• Malformations (ossification): higher incidence at 25mg/m3** **Gavage** **• MWG: significantly lower in exposed**
(Suh et al. 2011)	Mouse	MW, Placental weight, FW	PFOA	Gavage	2-25 mg/kg	11-16 GDs	**• MW: significantly lower at >=13 GDs** **• Placental weight: significantly lower at >=2 mg/kg** **• FW: significantly lower at >=10 mg/kg**
(Thibodeaux et al. 2003)	Rat Mouse	MWG, FW, T3 (dam), T4 (dam), TSH (dam)	PFOS	Gavage	Rat: 1-10 mg/kg Mouse: 0.1-2 mg/ml vehicle	Rat: 2-20 GDs Mouse: 1-17 GDs	**Rat** **• MWG: significantly lower at >=2mg/kg**

							• T3: significantly lower in exposed **• T4: significantly lower in exposed** **• FW: significantly lower at 10mg/kg** **• Malformations: significantly higher incidence of skeletal abnormalities at 10 mg/kg**
(Ulhaq et al. 2013)	Zebrafish	Locomotor activity	PFOA PFOS PFNA PFBA PFDA PFBS TFAA	Immersion	3-1000 mg/L 0.03-10 mg/L 0.03-10 mg/L 10-3000 mg/L 0.1-30 mg/L 10-3000 mg/L 10-3000 mg/L	144 hpf	**Changes in behavioural patterns in exposed to PFNA, PFBS, PFOS, TFAA**
(J. Wang et al. 2010)	Fruit fly	Larvae volume, Pupae weight, Larvae activity	PFOA	Food	100-500 µM	Egg laying	**• Larvae volume: significantly lower at 500 µM** **• Pupae weight: significantly lower at 500 µM** **• Larvae activity: significantly lower contractions at 500 µM**
(M. Wang et al. 2011)	Zebrafish	Body length Malformations	PFOS	Immersion	5-250 µg/L	8 hpf-150 dpf	**Body length: significantly lower at 250 µg/L** **Malformations: significantly higher incidence in F1 larvae from parental exposure at 250 µg/L**
(Yu Wang et al. 2015)	Rat	Spatial learning, Memory	PFOS	Water	5-15 mg/kg	Gestation and lactation	**Spatial learning: escape latency significantly higher in exposed**
(White et al. 2007)	Mouse	MWG, PW	PFOA	Gavage	5 mg/kg	1-17 GDs 8-17 GDs 12-17 GDs	**PW: lower in exposed following an exposure-duration fashion**
(White et al. 2009)	Mouse	MWG, PW	PFOA	Gavage	5 mg/kg	8-17 GDs	**MWG: significantly higher in exposed**
(White et al. 2011)	Mouse	MWG, PW	PFOA	Gavage	1-5 mg/kg	1-17 GDs	**PW: significantly lower at 5 mg/kg**
(Wolf et al. 2007)	Mouse	MWG, PW, Eye opening	PFOA	Gavage	3-5 mg/kg	1-17 GDs	**• PW: significantly lower at 5 mg/kg** **• Eye opening: significantly delayed in exposed**

(Yahia et al. 2010)	Mouse	MWG, FW, PW	PFOA	Gavage	1-10 mg/kg	0-17 GDs 0-18 GDs	**• MWG: significantly lower at 10 mg/kg** **• FW: significantly lower at 5-10 mg/kg** **• PW: significantly lower at 5-10 mg/kg**
(Yanai et al. 2008)	Chicken	Malformations	PFOA	Injection	5-40 mg/kg	Single dose at incubation day 0	**Significant higher rate of splayed leg and atypical pigmentation at >=20 mg/kg**
(Yu et al. 2009)	Rat	T3 (pups), T4 (pups)	PFOS	Food	3.2 mg/kg feed	Gestation, Lactation	**T4: significantly lower at PND 21 and 35**
(L. Zhang et al. 2011)	Zebrafish	Malformations	PFOS	Immersion	1 mg/L	6-192 hpf	**Significantly higher rate in a time-dependent manner**
(Zhao et al. 2017)	Chicken	Cardiotoxicity	PFOA	Injection	2 mg/kg	Single dose at incubation day 0	**Heart rate: significantly higher** **ROS and NOS: significantly higher at ED19**
(Zheng et al. 2011)	Zebrafish	Malformations	PFOA PFOS PFNA	Immersion	150-270 mg/L 6.25-200 mg/L 6.25-200 mg/L	4-96 hpf	**Malformations: higher rate incidence at >=72 hpf**

GL (gestational length); MW (maternal weight); MWG (maternal weight gain); PW (pups' weight); FW (fetal weight); GD (gestational day); PND (postnatal day); ED (embryonic day), HPF (hours post fertilization); BP (blood pressure); ROS (reactive oxygen species); NO (nitric oxide)

Table 5. Human evidence included in the review. Significant adverse effects are in bold.

Author, Year	Outcome/s	Exposure	Matrix	Study design	Setting	Population	Results
(Alkhalawi et al. 2016)	BW, BL, PI	PFOA PFOS PFHxS	Maternal blood	Cohort study (DBCS)	Duisburg (Germany)	156 mother–child pairs	**PI: significant inverse association with PFOA and PFOS**
(Andersen et al. 2010)	BW, BL	PFOA PFOS	Maternal blood	Cohort study (DNBC)	Denmark	1144 mother–child pairs	**BW: significant inverse association with PFOA**
(Antignac et al. 2013)	BW	PFOA PFOS PFHxS	Breast milk	Retrospective study (ELFE)	France	48 breast milk samples	No significant association
(Apelberg et al. 2007)	GA, BW, BL, HC, PI	PFOA PFOS	Cord blood	Cross-sectional	Baltimore, Maryland (USA)	293 mother-child pairs	**• BW: significant inverse association with PFOA and PFOS adjusted for GA** **• HC: significant inverse association with PFOA and PFOS** **• PI: significant inverse association with PFOA and PFOS**
(Arbuckle et al. 2013)	LBW (<2500g)	PFOA PFOS PFNA PFHxS	Cord blood	Cohort study	Ottawa (Canada)	100 mother-child pairs	**Weak association with PFOA**
(Ashley-Martin et al. 2016)	GWG	PFOA PFOS PFHxS	Maternal blood Cord blood	Cohort study (MIREC)	Canada	1723 woman (maternal blood) 1301 woman (cord blood)	**Significant positive association with PFOA and PFOS**
(Ashley-Martin et al. 2017)	BW	PFOA PFOS PFHxS	Maternal blood	Cohort study (MIREC)	Canada	1705 mother-child pairs	**Weak inverse association of PFOA with BW z-score**
(Bach et al. 2016)	BW (continuous and z-score), BL, HC	PFOA PFOS PFHxS PFHpS PFNA PFDA PFUnA	Maternal blood	Cohort study (Aarhus)	Aarhus (Denmark)	1507 mother-child pairs	**BW: weak inverse association with PFHxS, PFHpS, PFOS**

(Berg et al. 2015)	TSH, T3, T4, TH-BPs (mother)	PFOA PFOS PFHxS PFHpS PFNA PFDA PFUnDA	Maternal blood	Cohort study (MISA)	Northern Norway	391 pregnant women	**• TSH: significant positive association with PFOS** **• T3: significant inverse association with PFDA** **• FT3: significant inverse association with PFUnDA** **only for highest quartiles**
(Berg et al. 2017)	T3 (mother), T4 (mother), TSH (mother and child)	PFOA PFOS PFHxS PFHpS PFDA PFUnDA	Maternal blood	Cohort study (MISA)	Norway	391 mother-child pairs	**T3: significant inverse association with PFDA, PFUnDA** **TSH: significant direct association with PFOS, PFHxS, PFHpS**
(Braun et al. 2014)	Social Responsiveness Scale (SRS)	PFOA PFOS PFNA PFHxS	Maternal blood and Maternal urine	Cohort study (HOME)	Cincinnati, Ohio (US)	222 mother-child pairs	No significant association
(Callan et al. 2016)	BW, BL, HC	PFOA PFOS PFHxS PFHpA PFNA PFDA PFUnDA	Maternal blood	Cross-sectional (AMETS)	Western Australia	98 mother-child pairs	**Proportion of optimal BW: significant positive association with PFUnDA, significant inverse association with PFHxS**
(Cao et al. 2018)	BW, BL, HC	PFOA PFOS PFNA PFDA PFUdA PFDoA PFTrDA PFTeDA PFHxDA PFHxS	Cord blood	Cohort study	Zhoukou (China)	337 mother-child pairs	**• BW: significant inverse association with PFDoA** **• BL: significant inverse association with PFOA and PFHxS**
(Chan et al. 2011)	T4 (mother)	PFOA PFOS PFHxS	Maternal blood	Case-control study	Edmonton, Alberta (Canada)	Pregnant women (96 cases-175 controls)	No significant association

(M.-H. Chen et al. 2012)	GA, BW, BL, HC, PI, PB, LBW (<2500G), SGA (<10th percentile)	PFOA PFOS PFNA PFuDA	Cord blood	Cohort study (TBPS)	Taiwan	428 mother-child pairs	**• GA: significant inverse association with PFOS** **• BW: significant inverse association with PFOS** **• HC: significant inverse association with PFOS** **• SGA: significant higher odds (PFOS)**
(M.-H. Chen et al. 2013)	Comprehensive Developmental inventory for infants and Toddlers at 2 years of age	PFOA PFOS	Cord blood	Cohort study (TBPS)	Taiwan	239 mother-child pairs	**Significant inverse association with PFOS (whole test and gross motor subscale)**
(M.-H. Chen et al. 2017)	BW, BL, BMI	PFOA PFOS	Cord blood	Cohort study (TBPS)	Taiwan	429 mother-child pairs	**• BW: significant inverse association with PFOS** **• BL: significant inverse association with PFOS** **• BMI: significant inverse association with PFOS (only at crude analysis)**
(Darrow, Stein, and Steenland 2013)	PB, LBW (<2500g), BW, PIH	PFOA PFOS	Maternal blood	Population-based study (C8 Health Project)	Ohio and West Virginia (USA)	1630 birth 1330 women	**• BW: modest inverse association with PFOS** **• PIH: significant positive association with PFOA and PFOS**
(de Cock et al. 2014)	T4 (child)	PFOA PFOS	Cord blood Breast milk	Cohort study (LINC)	Netherlands	83 mother-child pairs	**• Females: significant positive association with PFOA at the highest quartile** **• Males: significant inverse association with PFOS at first and second quartiles (crude analysis)**
(de Cock et al. 2016)	BW	PFOA PFOS	Cord blood	Cohort study	Zwolle (The Netherlands)	91 mother-child pairs	No significant association
(Donauer et al. 2015)	Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) at 5 week of age	PFOA PFOS	Maternal blood	Cohort study (HOME)	Cincinnati (Ohio)	349 mother-child pairs	**Hypotonia: significant higher risk for PFOA**
(Fei et al. 2007)	GA, BW, LBW (<2500g), SGA (<10th percentile), PB	PFOA PFOS	Maternal blood	Cohort study (DNBC)	Denmark	1400 mother-child pairs	**BW: significant inverse association with PFOA**
(Fei, McLaughlin, Lipworth, et al. 2008)	Developmental milestones at 6 and 18 months of age	PFOA PFOS	Maternal blood	Cohort study (DNBC)	Denmark	1400 mother-child pairs	No significant association

(Fei, McLaughlin, Tarone, et al. 2008)	PW, BL, HC, AC, PI	PFOA PFOS	Maternal blood	Cohort study (DNBC)	Denmark	1400 mother-child pairs	**• BL: significant inverse association with PFOA** **• AC: significant inverse association with PFOA**
(Fei and Olsen 2011)	Strengths and Difficulties Questionnaire (SDQ) Developmental Cordination Disorder Questionnaire (DCDQ) at 7 years of age	PFOA PFOS	Maternal blood	Cohort study (DNBC)	Denmark	787 mother-child pairs	No significant association
(Forns et al. 2015)	Ages and Stages Questionnaire (ASQ-II) at 6 and 24 month of age Infant/Toddler Symptoms Checklist (ITSC) at 12 and 24 month of age	PFOA PFOS	Breast milk	Cohort study (HUMIS)	Norway	843 mother-child pairs	No significant association
(Goudarzi et al. 2016)	Bayley Scales of Infant Development (BSID II) Mental Developmental Index (MDI) Psychomotor Developmental Index (PDI) at 6 and 18 month of age	PFOA PFOS	Maternal blood	Cohort study (Hokkaido)	Hokkaido (Japan)	173 mother-child pairs (6-month) 133 mother-child pairs (18-month)	**Significant inverse association with MDI scores at 6-month of age in females**
(Govarts et al. 2018)	SGA (<10th percentile)	PFOA PFOS	Cord blood (measured or estimated)	FLEHS I FLEHS II HUMIS INMA cord INMA mat LINC PCB PELAGIE pooled analysis of birth cohorts (OBELIX birth cohorts)	Belgium Belgium Norway Spain Spain The Netherlands Slovakia France	1105 242 440 1287 860 84 1034 394 OBELIX birth cohorts: 5446 mother-child pairs (subset of 693 for PFAS)	**Significant higher odds of SGA for PFOA and PFOS in smokers**
(Govarts et al. 2016)	BW	PFOA PFOS	Cord blood	Cohort study (FLEHS II)	Flanders (Belgium)	248 mother-child pairs	No significant association

(Gyllenhammar et al. 2018)	GL, BW, BL, HC	PFOA PFOS PFHxS PFNA PFBS PFUnDA	Maternal blood	Cohort study (POPUP)	Sweden	381 mother-child pairs	No significant association
(Hamm et al. 2010)	GA, BW, SGA (<10th percentile), PB	PFOA PFOS PFHxS	Maternal blood	Cohort study	Edmonton, Alberta (Canada)	52 mother-child pairs	SGA: protective role of PFOS
(Harris et al. 2018)	Peabody Picture Vocabulary Test (PPVT-III) Wide Range Assessment of Visual Motor Abilities (WRAVMA) Kaufman Brief Intelligence Test (KBIT-2) Visual Memory Index of the Wide Range Assessment of Memory and Learning (WRAML2) in early (3 years) and mid (7 years) childhood	PFOA PFOS PFHxS	Maternal blood	Cohort study (Project Viva)	Massachusetts (USA)	986 (early childhood) 865 (mid-childhood)	**Weak inverse association of visual-motor scores with PFOA and PFOS in mid-childhood**
(Høyer et al. 2015)	Developmental Coordination Disorder Questionnaire 2007 (DCDQ) and Strength and Difficulties Questionnaire (SDQ) at 5-9 years of age	PFOA PFOS	Maternal blood	Cohort study (INUENDO)	Greenland, Poland, Ukraine	1016 mother-child pairs	**Significant higher risk of hyperactivity for PFOA**
(Jaacks et al. 2016)	GWG	PFOA PFOS PFOSA PFNA PFDeA	Maternal blood	Cohort study (LIFE)	Michigan and Texas (USA)	218 pregnant women	**Significant positive association of PFOS with GWG AUC in normal weight women**

		Et-PFOSA-AcOH Me-PFOSA-					
(Jeddy et al. 2017)	Communication development at 15 and 38 months of age	PFOA PFOS PFHxS PFNA	Maternal blood	Cohort study (ALSPAC)	Avon (Great Britain)	432 mother-child pairs (females)	Inconsistent associations
(Kato et al. 2016)	T4, TSH (mother and child)	PFOA PFOS	Maternal blood	Cohort study (Hokkaido)	Hokkaido (Japan)	392 mother-child pairs	**Mother** **• TSH: significant inverse association with PFOS** **• T4: significant inverse association with PFOS** **Child** **• TSH: significant positive association with PFOS**
(S. Kim et al. 2011)	T3, T4, TSH (cord blood), BW	PFOA PFOS PFHxS PFHpS PFNA PFDA PFUnDA PFTrDA	Maternal blood Cord blood	Cross-sectional	Seoul, Cheongju, Gumi (South Korea)	35 mother-child pairs (including 4 pairs of twins)	**• T3: significant inverse association with maternal PFOS and PFTrDA** **• T4: significant inverse association with maternal PFTrDA** **• TSH: significant positive association with maternal PFOA**
(Kishi et al. 2015)	Maternal FAs and TG, BW	PFOA PFOS	Maternal blood	Cohort study (Hokkaido)	Hokkaido (Japan)	306 mother-child pairs	**• FAs: significant inverse association with PFOS** **• TG: significant inverse association with PFOS** **• BW: significant inverse association with PFOS in females**
(Kobayashi et al. 2017)	DNA methylation (IGF2, H19, LINE1) and its association with BW, HC, PI	PFOA PFOS	Maternal blood	Cohort study (Hokkaido)	Hokkaido (Japan)	177 mother-child pairs	**IGF2 methylation: significant inverse association with PFOA** **explaining ~ 21% of the association between PFOA and PI (even if not significant)**

(Kwon et al. 2016)	BW	PFOA PFOS PFHxS PFNA PFDA PFUnDA PFDoDA PFTrDA	Cord blood	Cohort study (EBGRC)	Seoul (Korea)	268 mother-child pairs	**BW: significant inverse association with PFOA, PFOS, PFNA, PFDA, PFUnDA**
(Lauritzen et al. 2017)	GA, BW, BL, HC, SGA (<10th percentile)	PFOA PFOS	Maternal blood	Cohort study (NICHD)	Norway and Sweden	424 mother-child pairs	**Sweden cohort** **• BW: significant inverse association with PFOS** **• BL: significant inverse association with PFOA and PFOS** **• SGA: significant higher odds (PFOA)**
(E.-S. Lee, Han, and Oh 2016)	BW	PFOA PFOS PFHxS PFNA PFDA PFUnA PFDoA	Cord blood	Cross-sectional	Seoul (South Korea)	85 mother-child pairs	No significant association
(Y. J. Lee et al. 2013)	BW, BL, HC, PI	PFOA PFOS PFHxS	Cord blood	Cross-sectional	Gyeongbuk county (South Korea)	59 mother-child pairs	**• BW: significant inverse association with PFHxS** **• BL: significant inverse association with PFHxS** **• PI: significant inverse association with PFOS**
(Lenters et al. 2016)	BW	PFOA PFOS PFHxS PFHpA PFNA PFDA PFUnDA PFDoDA	Maternal blood	Cohort study (INUENDO)	Greenland, Poland, Ukraine	1250 mother-child pairs	**Significant inverse association with PFOA**

(M. Li et al. 2017)	GA, BW, PB, LBW (<2500g)	PFOA PFOS PFHxS PFNA PFDA PFUnDA PFHpA PFBA PFDoDA isomers of PFOA and PFOS	Cord blood	Cohort study (GBCS)	Guangzhou (China)	321 mother-child pairs	**BW: significant inverse association with PFOA, PFOS, and their isomers**
(Lien et al. 2016)	ADHD at 7 years of age	PFOA PFOS PFNA PFuDA	Cord blood	Cohort study (TBPS and TEC)	Taiwan	282 mother-child pairs	**Significant inverse association of inattention with PFNA**
(Liew et al. 2014)	Congenital cerebral plasy	PFOA PFOS PFHxS PFNA PFHpS PFDA	Maternal blood	Case-control study based on DNBC cohort	Denmark	156 cases-550 controls	**Significant positive association with PFOA and PFOS in boys**
(Liew et al. 2015)	ADHD and Autism	PFOA PFOS PFHxS PFHpS PFNA PFDA	Maternal blood	Case-control study based on DNBC cohort	Denmark	220 ADHD 220 Autism 550 Controls	No significant (or consistent) association
(Maekawa et al. 2017)	BW, PW	PFOA PFOS PFHxS PFNA	Maternal blood Cord blood	Cross-sectional	Yamaguchi (Japan)	145 pregnant women	**• BW: significant inverse association with PFNA** **• PW: significant inverse association with PFNA** **analyses not adjusted by potential confounders**
(Maisonet et al. 2012)	GA, BW, BL, PI	PFOA PFOS PFHxS	Maternal blood	Cohort study (ALSPAC)	Avon (Great Britain)	447 mother-child pairs (females)	**• BW: significant inverse association with PFOA, PFOS, PFHxS** **• BL: significant inverse association with PFOS and PFHxS**

(Manzano-Salgado et al. 2017)	GA, BW, BL, HC, SGA (<10th percentile), LBW (<2500g) (+ modifying effect of GFR)	PFOA PFOS PFHxS PFNA	Maternal blood	Cohort study (INMA)	Spanish	1202 mother-child pairs	No significant association
(Matilla-Santander et al. 2017)	IGT, GDM, Cholesterol, TG, CRP	PFOA PFOS PFHxS PFNA	Maternal blood	Cohort study (INMA)	Spain	1240 pregnant women	**• IGT: significant positive association with PFOA, PFOS, PFHxS** **• GDM: significant positive association with PFOA, PFOS, PFHxS** **• TG: significant inverse association with PFOS and PFNA**
(Minatoya et al. 2017)	BW, PI, leptin and adiponectin in cord blood	PFOA PFOS	Maternal blood	Cohort study (Hokkaido)	Hokkaido (Japan)	168 mother-child pairs	**• BW: significant inverse association with PFOA** **• PI: significant inverse association with PFOS** **• Adiponectin: significant positive association with PFOS**
(Monroy et al. 2008)	BW	PFOA PFOS PFDeA PFHxS PFHpA PFNA	Maternal blood Cord blood	Cohort study (Family Study)	Canada	101 pregnant women 105 cord blood samples	No significant association
(Nolan et al. 2009)	BW, PB, LBW (<2500g)	Maternal residing as proxy of expsoure to PFOA	NA	Cross-sectional	Ohio (USA)	1555 newborns	No significant association
(Nolan et al. 2010)	Congenital anomalies, labor/delivery complications	Maternal residing as proxy of expsoure to PFOA	NA	Cross-sectional	Ohio (USA)	1548 newborns	**Labor/delivery compl.: significant positive association with contaminated water service**
(Ode et al. 2014)	ADHD	PFOA PFOS PFNA	Cord blood	Case-control study	Malmo, Sweden	206 cases-206 controls	No significant association
(Oulhote et al. 2016)	Strengths and Difficulties Questionnaire (SDQ) at 7 years of age	PFOA PFOS PFHxS PFNA PFDA	Maternal blood	Cohort study	Faroe Islands	539 mother-child pairs	No significant association

(Preston et al. 2018)	TSH (mother) T4 (mother and child) T3 (mother) T3U (mother)	PFOA PFOS PFHxS PFNA	Maternal blood	Cohort study (Project Viva)	Massachusetts (USA)	732 mother-child pairs	**Mother** **FT4I: significant inverse association with PFOA** **Child** **T4: significant inverse association with PFHxS in males**
(Quaak et al. 2016)	Behavioral development at 18 months of age	PFOA PFOS PFHxS PFNA PFDA PFHpS PFUnDA	Cord blood	Cohort study (LINC)	Netherlands	59 mother-child pairs	**Significant inverse association of PFOA with externalizing behavior in males**
(Rokoff et al. 2018)	BW/GA z-score	PFOA PFOS PFHxS PFNA	Maternal blood	Cohort study (Project Viva)	Massachusetts (USA)	1597 mother-child pairs	Significant inverse association with PFNA
(Savitz, Stein, Elston, et al. 2012)	PIH, PB, LBW (<2500g), SGA (<10th percentile)	Retrospective estimation of PFOA	Maternal blood	Retrospective study	Ohio and West Virginia (USA)	8253 births	No significant association
(Savitz, Stein, Bartell, et al. 2012)	Preeclampsia, PB, LBW (<2500g), birth defects	Retrospective estimation of PFOA	Maternal blood	Retrospective study based on C8 Health Project	Ohio and West Virginia (USA)	11737 pregnancies	No significant association (only weak for preeclampsia)
(Shah-Kulkarni et al. 2016)	T3, T4, TSH (cord blood)	PFOA PFOS PFNA PFDoDA PFTrDA PFTeDA PFPeA PFUnDA PFHxS	Cord blood	Cohort study (EBGRC)	Seoul (Korea)	279 mother-child pairs	**• T3: significant positive association with PFDA (overall); significant inverse association with PFPeA (males); significant positive association with PFHxS (females)** **• T4: significant positive association with PFPeA (overall and females)** **• TSH: significant inverse association with PFNA in girls**
(Y. Shi et al. 2017)	GA, BW, BL, PI	PFOA PFOS PFHxS PFNA PFDA PFUna	Cord blood	Cross-sectional	Beijing (China)	170 newborns	No significant association

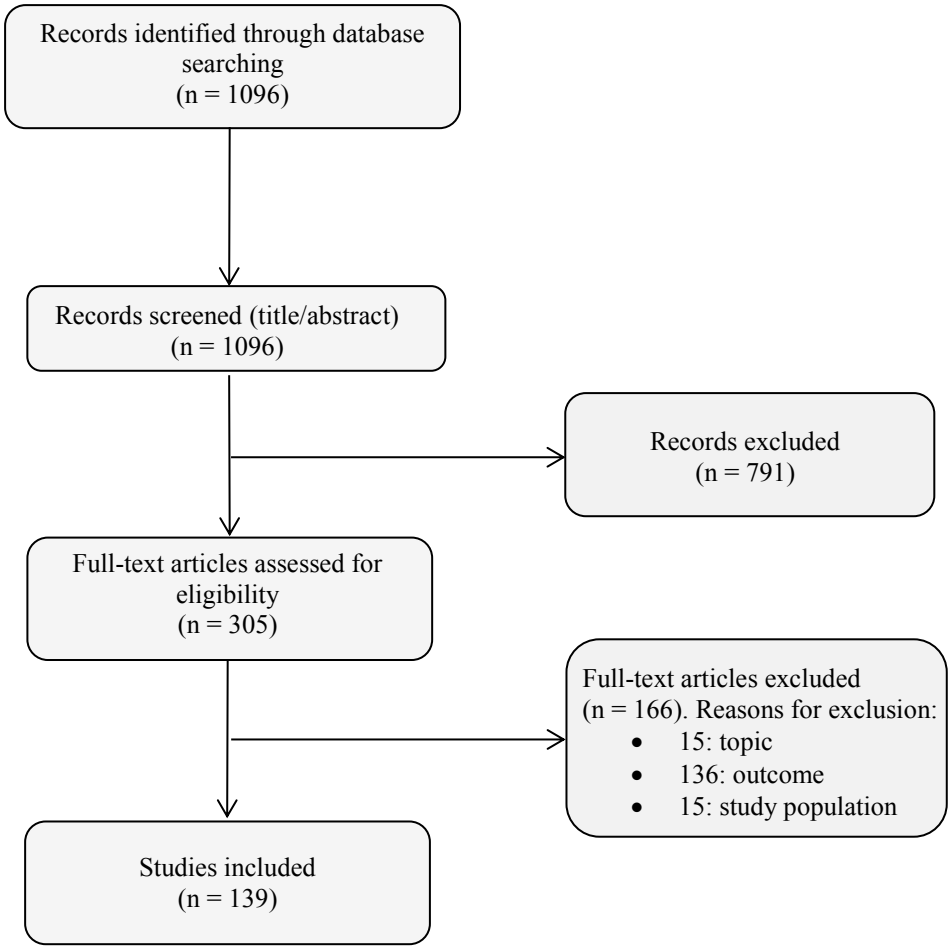
(Skuladottir et al. 2015)	Cholesterol (+ modifying effect of diet)	PFOA PFOS	Maternal blood	Cohort study	Aarhus (Denmark)	854 pregnant women	**• Cholesterol: significant positive association with PFOA and PFOS** **• Diet: predictor of PFOA and PFOS but not modifying the association with cholesterol**
(Starling et al. 2017)	BW, body adiposity (+ modifying effect of maternal gluose and lipids)	PFOA PFOS PFNA PFDeA PFHxS	Maternal blood	Cohort study (Healthy Start)	Colorado (USA)	628 mother-child pairs	**• BW: significant inverse association with PFOA and PFNA** **• Maternal glucose: significant inverse association with PFOA, PFNA, PFDeA** **~10% of the effect of PFAS on neonatal adiposity mediated by glucose**
(Starling et al. 2014)	Preeclampsia	PFOA PFOS PFNA PFUnDA PFHxS PFHpS	Maternal blood	Cohort study (MoBa)	Norway	976 pregnant women	No significant association
(Stein, Savitz, and Dougan 2009)	Preeclampsia, PB, LBW (<2500g), birth defects	PFOA PFOS	Maternal blood	Retrospective study (C8 Health Project)	Ohio and West Virginia (USA)	1845 pregnant women (PFOA) 5262 pregnant women (PFOS)	**• LBW: weak association with PFOS** **• Preeclampsia: weak association with PFOS and PFOA** **• Birth defects: weak association with PFOA**
(Stein, Savitz, and Bellinger 2013)	Wechsler Abbreviated Scale of Intelligence NEPSY-II Connors' Continuous Performance Test-II at 6-12 years of age	PFOA	Estimated in utero PFOA	Retrospective study (C8 Health Project)	Ohio and West Virginia (USA)	320 children	No suggestive association
(Strøm et al. 2014)	ADHD, Depression, Scholastic achievement until 20 years of age	PFOA PFOS	Maternal blood	Cohort study	Aarhus (Denmark)	876 mother-child pairs	No significant association
(Vuong et al. 2016)	Behavior Rating Inventory of Executive Function (BRIEF)	PFOA PFOS PFHxS PFNA PFDeA	maternal blood	Cohort study (HOME)	Cincinnati, Ohio (U.S.A)	256 mother-child pairs	**PFOS significantly associated with lower BRIEF score**

(Yan Wang et al. 2016)	BW, BL, HC, SGA (<10th percentile)	PFOA PFNA PFDeA PFUnDA PFDoDA	Maternal blood	Cohort study (TMICS)	Taiwan	223 mother-child pairs	**• BW: significant inverse association with PFNA, PFDeA, PFUnDA, PFDoDA** **• HC: significant inverse association with PFDoDA** **• SGA: significant inverse association with PFUnDA, PFDeA** **in females**
(Yan Wang et al. 2014)	T3, T4, TSH (mother and blood cord)	PFOA PFOS PFHxS PFNA PFDeA PFUnDA PFDoDA PFHpA PFHxA	Maternal blood	Cohort study (TMICS)	Taiwan	285 mother-child pairs	**Mother** **• FT4/TT4: significant inverse association with PFNA, PFUnDA, PFDoDA** **• T3: significant positive association with PFDeA** **• TSH: significant positive association with PFHxS** **Child** **• TT4: significant inverse association with PFNA, PFUnDA, PFDoDA** **• TT3: significant inverse association with PFNA, PFDeA, PFUnDA, PFDoDA**
(Yan Wang et al. 2013)	TSH (mother)	PFOA PFOS PFHpA PFNA PFDA PFDoDA PFTrDA PFTeDA PFBA PFHxS PFOSA	Maternal blood	Cross-sectional based on MoBA cohort	Norway	903 pregnant women	**Weak significant positive association with PFOS**
(Washino et al. 2009)	BW, BL, HC, CC	PFOA PFOS	Maternal blood	Cohort study (Hokkaido)	Hokkaido (Japan)	428 mother-child pairs	**BW: significant inverse association with PFOS**
(Webster et al. 2014)	T4, TSH	PFOA PFOS PFNA PFHxS	Maternal blood	Cohort study (CHirP)	Vancouver (Canada)	152 pregnant women	**TSH: significant positive association with PFOA, PFOS, PFNA in high TPOAb women**
(Whitworth et al. 2012)	BW z-score, PB, SGA (<10th percentile), LGA (>90 percentile)	PFOA PFOS	Maternal blood	Cohort study (MoBa)	Norway	950 mother-child pairs	No significant association

(Wu et al. 2012)	GA, BW, BL, PI	PFOA	Maternal blood	Case-control study	Guangdong (China)	108 cases (exposed)-59 controls (unexposed)	**• GA: significant inverse association with PFOA** **• BW: significant inverse association with PFOA** **• BL: significant inverse association with PFOA**
(Yang et al. 2016)	T3, T4, TSH (mother)	PFOA PFOS PFHxS PFNA PFDA PFUnA PFDoA	Maternal blood Cord blood	Cross-sectional	Beijing (China)	157 mother-child pairs	**Maternal blood** **• TSH: significant inverse association with PFNA, PFDA, PFUnA, PFDoA, PFOS** **• FT3/T3: significant inverse association with PFDoA** **Cord blood** **T3/FT3: significant inverse association with all PFAS**
(C. Zhang et al. 2015)	GDM	PFOA PFOS PFNA PFOSA PFDeA	Maternal blood	Cohort study (LIFE)	Michigan and Texas (USA)	272 pregnant women	**Significant positive association with PFOA**

BW (birth weight); LBW (low birth weight); BL (birth length); HC (head circumference); AC (abdominal circumference); CC (chest circumference); PI (ponderal index); SGA (small for gestational age); LGA (large for gestational age); BMI (body mass index); PW (placental weight); GA (gestational age); PB (preterm birth); GWG (gestational weight gain); FAs (fatty acids); TG (triglyceride); FGR (fetal growth restrictions); IGT (impaired glucose tolerance); GDM (gestational diabetes mellitus); CRP (C-reactive protein); GFR (glomerular filtration rate); attention deficit hyperactivity disorder (ADHD)

Figure 1. Flow-chart of the study selection procedure



Pregnancy complications in women living in an area contaminated by PFAS in Veneto Region: preliminary results

1. Introduction

Perfluoroalkylated substances (PFAS) have been extensively produced for a long time (since the mid of the 20th century), but only at the beginning of the 21st century it has been discovered that they are persistent organic pollutants and that they bioaccumulate in the fish, wildlife, and humans (U.S. Environmental Protection Agency 2016a, 2016b). Given such characteristics, they are ubiquitous. This is testified by the fact that low concentrations of PFAS were detected in the blood of more than 98% of the U.S. general population. In the National Health and Nutrition Examination Survey (NHANES) 2003-2004, the median concentrations of blood perfluorooctane sulfonate (PFOS) and Perfluorooctanoic acid (PFOA), which were the most widely produced PFAS, were 21.1 μg/L and 4 μg/L, respectively (Calafat et al. 2007).

Besides the fact that the general population has been found to be exposed to background levels of PFAS, in recent years have been identified highly-exposed communities living in several areas around the world massively contaminated by PFAS. The median PFOA concentration in the residents of the mid-Ohio valley, an area contaminated by PFAS dramatically, was found to be 28.2 μg/L in 2005-2006 (Steenland et al. 2009), seven times higher than that of the general population with low background exposure to PFAS (Calafat et al. 2007).

The population living in geographical areas contaminated by PFAS is exposed to these chemicals mainly through the ingestion of contaminated drinking water and food (U.S. Environmental Protection Agency 2016a, 2016b). The analysis of PFAS distribution in the human body has shown that they distribute through the binding with serum albumin (Pérez et al. 2013) and several studies have been done to understand if PFAS exposure affects the function of PFAS' target organs, focusing particularly on the liver (especially for what concern lipid metabolism) and the kidneys function. PFAS exposure has been found to be associated with higher concentrations of total and LDL cholesterol (Eriksen et al. 2013; Fu et al. 2014), while there is limited evidence of an association between PFAS exposure and type 2 diabetes (Lind and Lind 2018). Not least, PFAS exposure seems to be associated with higher uric acid (a marker of reduced kidney function) (Gleason, Post, and Fagliano 2015; Shankar, Xiao, and Ducatman 2011; Steenland et al. 2010), which is, in turn, a risk factor for hypertension (Feig 2014). Such studies were conducted mainly on workers, highly exposed communities, and the general population, while only a few studies in this field were done in pregnant women, with inconsistent findings. This research topic deserves further attention since liver and kidneys dysfunction is involved in the pathophysiology of pregnancy-induced hypertension,

preeclampsia, and of gestational diabetes mellitus (GDM), which affect the health of the woman and the fetus dramatically.

The present work is aimed at presenting the preliminary results of a study aimed at assessing the epidemiology of GDM and preeclampsia in pregnant women living in an area contaminated by PFAS in Veneto Region, Italy.

2. Materials and Methods

Retrospective study on pregnant women suffering from preeclampsia or GDM who gave birth to a live birth or a stillbirth (2009-2015), living in the area of Veneto Region contaminated by PFAS.

For the present work, a case of GDM was defined as a hospital admission with a diagnosis of GDM in the nine months before the delivery or at time of the delivery. A case of preeclampsia was defined as a hospital admission with a diagnosis of preeclampsia in the nine months before the delivery or at time of the delivery.

In the present work, we present the preliminary data (frequencies of preeclampsia and GDM derived from the hospital discharge records) because a medical chart review of pregnant women hospitalized is ongoing to validate the cases of preeclampsia and GDM identified from the hospital discharge records. The choice of revising the medical charts is motivated by the fact that the use of multi-source approaches is considered the most reliable method for the identification of the cases of interest, especially if these approaches include medical charts (Lipscombe et al. 2018). The accuracy of hospitalization data has been shown to depend on the severity of the disease (the most severe forms of diabetes and preeclampsia and those associated with complications are more likely to be reported) and on the presence of concomitant chronic diseases not related to pregnancy (diabetes mellitus and chronic hypertension) (Roberts et al. 2008). Using only hospital discharge records would provide biased estimates, overestimating the most severe forms of the pathological conditions of interest and underestimating the less severe and chronic ones (Roberts et al. 2008; Abell, Zoungas, and Teede 2017).

2.1 Exposure

An indirect measure of exposure to PFAS, defined as a pregnant woman's residence in the contaminated area, was used. The area extends for about 200 km^2 mainly in the province of Vicenza and, to a lesser extent, in those of Verona and Padova. The contamination was discovered in 2013 and it involved drinking water, surface water, and ground water. It was caused by the wastewater and the water from the waste-water treatment of a chemical plant located in the contaminated area (WHO 2017). Immediately after the discovery of the contamination, appropriate interventions were made to contain the drinking water contamination through the application of carbon filters (in the summer of

2013 (WHO 2017)). The analysis of drinking water showed that such intervention resulted in the drop of drinking water concentrations of both PFOA (from 1,475 ng/L to 386 ng/L) and PFOS (from 117 ng/L to 36 ng/L) within three months from filters' application (WHO 2017). However, it has been estimated that the contamination had lasted about 50 years (starting from the 60s), leading to long-term exposure of the population living in the contaminated area (Dell'Acqua and Mazzola 2017).

The residence was identified from the Veneto Region Birth Registry, a compulsory, web-based, data collection system of all births (including stillbirth) in Veneto Region (reporting woman residence). The contaminated area was identified according to an official resolution of the Veneto Region (Deliberazione della Giunta Regionale n. 2133 del 23 dicembre 2016, n.d.) and it includes 21 municipalities located in the southwest of the Veneto Region. According to the Veneto Region resolution, the contaminated area includes all that municipalities that presented higher concentrations of PFAS in the drinking water than those established by the performance limits of the National Institute of Health ("Istituto Superiore Di Sanità. Prot. 16/01/2014-0001584," n.d.). Municipalities exceeding at least one of the following limits were included in the contaminated area: PFOS: ≤ 0.03 µg/L; PFOA: ≤ 0.5 µg/L; the sum of other PFAS: ≤ 0.5 µg/L. The sum of other PFAS included: perfluorobutyric acid (PFBA), perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDeA), perfluorododecanoic acid (PFDoA), perfluoroundecanoic acid (PFUnA), perfluorohexane sulfonate (PFHxS), perfluorobutane sulfonate (PFBS).

The choice of using the residence as a proxy of PFAS exposure is motivated by the fact that living nearby a chemical plant is the strongest predictor of blood levels of PFAS and that the consumption of contaminated tap water correlates with PFAS concentration in blood (Ingelido et al. 2018).

A control area was chosen for comparison (Figure 1). The area includes 48 contiguous municipalities, far away from the contaminated area, and not exposed to PFAS contamination according to the performance limits of the National Institute of Health.

2.2 Study population

Pregnant women living in the contaminated and control area (between 2009 and 2015) were identified from the Veneto Region Birth Registry. A record linkage procedure was performed between the Veneto Region Birth Registry and the Veneto Region hospital discharge records to identify all women with a hospital admission for preeclampsia or GDM in the nine months before the delivery or at time of delivery.

The hospital discharge record represents a compulsory data collection system of all hospital admissions in Italian hospitals facilities. Each hospital discharge record reports data about the subject

hospitalized (e.g., age, gender, residence), the hospitalization characteristics (e.g., type, duration, outcome), the reason of the hospitalization (diagnosis), and the type of interventions done during the hospitalizations. The diagnoses and the interventions are coded using the International Classification of Diseases – 9th revision – Clinical Modification (ICD-9-CM). Hospitalizations for preeclampsia and GDM have been identified using the ICD-9-CM diagnosis' codes 642 and 648.8 (including all fourth e fifth digits specifications), respectively. The codes of interest can be reported both in the main and secondary diagnosis field.

2.3 Statistical analysis

Descriptive statistics was computed as percentage (absolute numbers) for categorical variables and Pearson chi-squared was performed. An alpha of 0.05 was used as the cut-off for significance. Analyses were performed using SAS software (version 9.4).

3. Results

During the study period, 45,853 pregnant women have been identified from the Veneto Region Birth Registry in the contaminated and control area (7,999 in the contaminated ones). Maternal characteristics are reported in Table 1. Pregnant women in the contaminated area have been found to be more likely to be younger (p-value <0.001) and to come from a foreign country (especially North Africa, p-value <0.001) compared to those living in the control area. For what concern the obstetrical history, women in the control area were more likely to be first-time mothers compared to those in the contaminated area (p-value <0.001) and they were found to be slightly more likely to have twins (p-value 0.011).

The frequency of both preeclampsia and GDM derived from hospital discharge records has been found to be slightly higher in pregnant women living in the contaminated area compared to those living in the control ones (4.58% vs. 3.25% and 5.5% vs. 3.13%, for preeclampsia and GDM, respectively) (Table 2).

4. Discussion

This study is based on preliminary data and requires more work. For this reason, present results must be taken with caution since a medical chart review is ongoing to validate the cases of preeclampsia and GDM identified from the hospital discharge records. On the other side, it is worth pointing out that hospital discharge records are generally considered a reliable source for the identification of the most severe forms of preeclampsia (Roberts et al. 2008) and GDM (Devlin, Desai, and Walaszek 2009).

Literature on the relationship between PFAS exposure and preeclampsia does not provide consistent results, as shown in the first chapter of the present work. Savitz et al. and Stein et al. have found out evidence of a weak association of PFOA with self-reported preeclampsia (Savitz, Stein, Bartell, et al. 2012; Stein, Savitz, and Dougan 2009). Conversely, Starling et al. did not find any significant association between PFAS exposure and preeclampsia in Norwegian women (Starling et al. 2014). Other studies focused on pregnancy-induced hypertension instead of preeclampsia, showing a significant positive association with PFOA (Savitz, Stein, Elston, et al. 2012) and also PFOS (Darrow, Stein, and Steenland 2013). The fact that no consistent and strong associations were found between preeclampsia and PFAS exposure could be related to the heterogeneous approaches that were used to define the preeclampsia cases. Some studies have evaluated only pregnancy-induced hypertension (Savitz, Stein, Elston, et al. 2012; Darrow, Stein, and Steenland 2013), while the other studies have focused specifically on preeclampsia (Savitz, Stein, Bartell, et al. 2012; Stein, Savitz, and Dougan 2009; Starling et al. 2014), which represents the most severe form of pregnancy-induced hypertension by involving the impairment of kidney function. Furthermore, Savitz et al. and Stein et al. (Savitz, Stein, Bartell, et al. 2012; Stein, Savitz, and Dougan 2009) considered self-reported preeclampsia (which is known to have a low positive predictive value (Stuart et al. 2013)) and only Starling et al. employed a validated definition of preeclampsia (Starling et al. 2014).

As for preeclampsia, evidence about the relationship between PFAS exposure and GDM is still inconsistent. Two studies have found out a positive association between PFAS exposure and GDM (Zhang et al. 2015; Matilla-Santander et al. 2017). Conversely, two other recent studies on Chinese and Canadian pregnant women did not find a significant association between PFAS exposure and GDM (Wang et al. 2018; Shapiro et al. 2016). Again, different definitions of GDM cases were employed. Zhang et al. based their study on GDM self-reported by the women themselves (Zhang et al. 2015), while the other studies derived GDM cases from medical records (Matilla-Santander et al. 2017; Wang et al. 2018; Shapiro et al. 2016).

It is noteworthy that no previous studies have analysed the association between PFAS exposure and these outcomes in such a large sample of pregnant women. On the other hand, the definition used to identify PFAS exposure represents a study limitation since an indirect measure of exposure has been employed (woman residence), potentially leading to some misclassification. However, it has been demonstrated that living in a geographical area served by contaminated water supply is the strongest predictor of PFAS blood concentration (Steenland et al. 2009), so that maternal residence could be considered a good proxy of PFAS exposure.

5. Conclusions

We will be waiting for further results from the validation process of GDM and preeclampsia cases through the review of the medical records (which is ongoing) in order to confirm or disconfirm the ones presented in this work.

6. References

Abell, S. K., S. Zoungas, and H. J. Teede. 2017. "Caution in Clinical Interpretation of Population Level Administrative Data." *BJOG: An International Journal of Obstetrics & Gynaecology* 124 (5): 814–814.

Calafat, Antonia M., Lee-Yang Wong, Zsuzsanna Kuklenyik, John A. Reidy, and Larry L. Needham. 2007. "Polyfluoroalkyl Chemicals in the US Population: Data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and Comparisons with NHANES 1999–2000." *Environmental Health Perspectives* 115 (11): 1596.

Darrow, Lyndsey A., Cheryl R. Stein, and Kyle Steenland. 2013. "Serum Perfluorooctanoic Acid and Perfluorooctane Sulfonate Concentrations in Relation to Birth Outcomes in the Mid-Ohio Valley, 2005-2010." *Environmental Health Perspectives* 121 (10): 1207–13. https://doi.org/10.1289/ehp.1206372.

Deliberazione della Giunta Regionale n. 2133 del 23 dicembre 2016. n.d. "Approvazione Del 'Piano Di Sorveglianza Sanitaria Sulla Popolazione Esposta Alle Sostanze Perfluoroalchiliche' e Del 'Piano Di Campionamento per Il Monitoraggio Degli Alimenti in Relazione Alla Contaminazione Da Sostanze Perfluoroalchiliche (PFAS) in Alcuni Ambiti Della Regione Del Veneto.'"

Dell'Acqua, Nicola, and Massimo Mazzola. 2017. "Contaminanti Emergenti, Una Sfida Continua per Il Sistema Delle Agenzie Ambientali."

Devlin, Heather M., Jay Desai, and Anne Walaszek. 2009. "Reviewing Performance of Birth Certificate and Hospital Discharge Data to Identify Births Complicated by Maternal Diabetes." *Maternal and Child Health Journal* 13 (5): 660.

Eriksen, Kirsten T., Ole Raaschou-Nielsen, Joseph K. McLaughlin, Loren Lipworth, Anne Tjønneland, Kim Overvad, and Mette Sørensen. 2013. "Association between Plasma PFOA and PFOS Levels and Total Cholesterol in a Middle-Aged Danish Population." *PloS One* 8 (2): e56969.

Feig, Daniel I. 2014. "Serum Uric Acid and the Risk of Hypertension and Chronic Kidney Disease." *Current Opinion in Rheumatology* 26 (2): 176–85.

Fu, Yaning, Tieyu Wang, Quanliang Fu, Pei Wang, and Yonglong Lu. 2014. "Associations between Serum Concentrations of Perfluoroalkyl Acids and Serum Lipid Levels in a Chinese Population." *Ecotoxicology and Environmental Safety* 106: 246–52.

Gleason, Jessie A., Gloria B. Post, and Jerald A. Fagliano. 2015. "Associations of Perfluorinated Chemical Serum Concentrations and Biomarkers of Liver Function and Uric Acid in the US Population (NHANES), 2007–2010." *Environmental Research* 136: 8–14.

Ingelido, Anna Maria, Annalisa Abballe, Simonetta Gemma, Elena Dellatte, Nicola Iacovella, Giovanna De Angelis, Franco Zampaglioni, et al. 2018. "Biomonitoring of Perfluorinated

Compounds in Adults Exposed to Contaminated Drinking Water in the Veneto Region, Italy." *Environment International* 110: 149–59. https://doi.org/10.1016/j.envint.2017.10.026.

"Istituto Superiore Di Sanità. Prot. 16/01/2014-0001584." n.d.

Lind, P. Monica, and Lars Lind. 2018. "Endocrine-Disrupting Chemicals and Risk of Diabetes: An Evidence-Based Review." *Diabetologia*, May. https://doi.org/10.1007/s00125-018-4621-3.

Lipscombe, Lorraine L., Jeremiah Hwee, Lauren Webster, Baiju R. Shah, Gillian L. Booth, and Karen Tu. 2018. "Identifying Diabetes Cases from Administrative Data: A Population-Based Validation Study." *BMC Health Services Research* 18 (1): 316.

Matilla-Santander, Nuria, Damaskini Valvi, Maria-Jose Lopez-Espinosa, Cyntia B. Manzano-Salgado, Ferran Ballester, Jesús Ibarluzea, Loreto Santa-Marina, et al. 2017. "Exposure to Perfluoroalkyl Substances and Metabolic Outcomes in Pregnant Women: Evidence from the Spanish INMA Birth Cohorts." *Environmental Health Perspectives* 125 (11): 117004. https://doi.org/10.1289/EHP1062.

Pérez, Francisca, Martí Nadal, Alícia Navarro-Ortega, Francesc Fàbrega, José L. Domingo, Damià Barceló, and Marinella Farré. 2013. "Accumulation of Perfluoroalkyl Substances in Human Tissues." *Environment International* 59: 354–362.

Roberts, Christine L., Jane C. Bell, Jane B. Ford, Ruth M. Hadfield, Charles S. Algert, and Jonathan M. Morris. 2008. "The Accuracy of Reporting of the Hypertensive Disorders of Pregnancy in Population Health Data." *Hypertension in Pregnancy* 27 (3): 285–97.

Savitz, David A., Cheryl R. Stein, Scott M. Bartell, Beth Elston, Jian Gong, Hyeong-Moo Shin, and Gregory A. Wellenius. 2012. "Perfluorooctanoic Acid Exposure and Pregnancy Outcome in a Highly Exposed Community." *Epidemiology (Cambridge, Mass.)* 23 (3): 386–92. https://doi.org/10.1097/EDE.0b013e31824cb93b.

Savitz, David A., Cheryl R. Stein, Beth Elston, Gregory A. Wellenius, Scott M. Bartell, Hyeong-Moo Shin, Veronica M. Vieira, and Tony Fletcher. 2012. "Relationship of Perfluorooctanoic Acid Exposure to Pregnancy Outcome Based on Birth Records in the Mid-Ohio Valley." *Environmental Health Perspectives* 120 (8): 1201–7. https://doi.org/10.1289/ehp.1104752.

Shankar, Anoop, Jie Xiao, and Alan Ducatman. 2011. "Perfluoroalkyl Chemicals and Elevated Serum Uric Acid in US Adults." *Clinical Epidemiology* 3: 251–58. https://doi.org/10.2147/CLEP.S21677.

Shapiro, Gabriel D., Linda Dodds, Tye E. Arbuckle, Jillian Ashley-Martin, Adrienne S. Ettinger, Mandy Fisher, Shayne Taback, Maryse F. Bouchard, Patricia Monnier, and Renée Dallaire. 2016. "Exposure to Organophosphorus and Organochlorine Pesticides, Perfluoroalkyl Substances,

and Polychlorinated Biphenyls in Pregnancy and the Association with Impaired Glucose Tolerance and Gestational Diabetes Mellitus: The MIREC Study." *Environmental Research* 147: 71–81.

Starling, Anne P., Stephanie M. Engel, David B. Richardson, Donna D. Baird, Line S. Haug, Alison M. Stuebe, Kari Klungsøyr, et al. 2014. "Perfluoroalkyl Substances during Pregnancy and Validated Preeclampsia among Nulliparous Women in the Norwegian Mother and Child Cohort Study." *American Journal of Epidemiology* 179 (7): 824–33. https://doi.org/10.1093/aje/kwt432.

Steenland, Kyle, Chuangfang Jin, Jessica MacNeil, Cathy Lally, Alan Ducatman, Veronica Vieira, and Tony Fletcher. 2009. "Predictors of PFOA Levels in a Community Surrounding a Chemical Plant." *Environmental Health Perspectives* 117 (7): 1083.

Steenland, Kyle, Sarah Tinker, Anoop Shankar, and Alan Ducatman. 2010. "Association of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) with Uric Acid among Adults with Elevated Community Exposure to PFOA." *Environmental Health Perspectives* 118 (2): 229.

Stein, Cheryl R., David A. Savitz, and Marcelle Dougan. 2009. "Serum Levels of Perfluorooctanoic Acid and Perfluorooctane Sulfonate and Pregnancy Outcome." *American Journal of Epidemiology* 170 (7): 837–46. https://doi.org/10.1093/aje/kwp212.

Stuart, Jennifer J., C. Noel Bairey Merz, Sarah L. Berga, Virginia M. Miller, Pamela Ouyang, Chrisandra L. Shufelt, Meir Steiner, Nanette K. Wenger, and Janet W. Rich-Edwards. 2013. "Maternal Recall of Hypertensive Disorders in Pregnancy: A Systematic Review." *Journal of Women's Health* 22 (1): 37–47.

U.S. Environmental Protection Agency. 2016a. "Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)." In . EPA Document Number: 822-R-16-002.

———. 2016b. "Health Effects Support Document for Perfluorooctanoic Acid (PFOA)." In . EPA Document Number: 822-R-16-003.

Wang, Hexing, Jiaqi Yang, Hongyi Du, Linji Xu, Shuping Liu, Jianping Yi, Xu Qian, Yue Chen, Qingwu Jiang, and Gengsheng He. 2018. "Perfluoroalkyl Substances, Glucose Homeostasis, and Gestational Diabetes Mellitus in Chinese Pregnant Women: A Repeat Measurement-Based Prospective Study." *Environment International* 114 (May): 12–20. https://doi.org/10.1016/j.envint.2018.01.027.

WHO. 2017. "Keeping Our Water Clean: The Case of Water Contamination In the Veneto Region, Italy." http://www.euro.who.int/__data/assets/pdf_file/0019/341074/pfas-report-20170606-h1330-print-isbn.pdf?ua=1.

Zhang, Cuilin, Rajeshwari Sundaram, José Maisog, Antonia M. Calafat, Dana Boyd Barr, and Germaine M. Buck Louis. 2015. "A Prospective Study of Prepregnancy Serum Concentrations of

Perfluorochemicals and the Risk of Gestational Diabetes." *Fertility and Sterility* 103 (1): 184–89. https://doi.org/10.1016/j.fertnstert.2014.10.001.

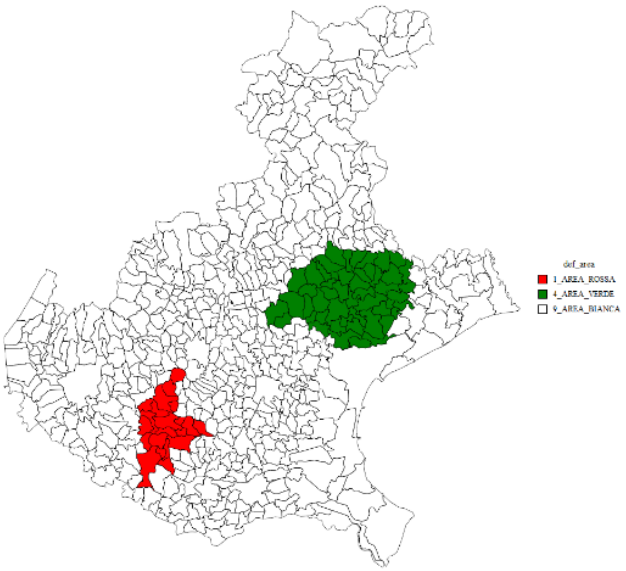
Table 1. Maternal characteristics stratified according to maternal residence in the contaminated and control area. Data are percentages (absolute numbers)

	Contaminated area (n=7,999)	Control area (n=37,854)	P-value
Maternal age			
<24	11.83 (946)	8.78 (3,325)	<0.001
25-34	58.17 (4653)	55.89 (21,157)	
>35	30 (2,400)	35.33 (13,372)	
Nationality			
Italian	67.22 (5,377)	70.92 (26,845)	<0.001
European	0.6 (48)	1.23 (465)	
Eastern European	10.23 (818)	13.46 (5,097)	
North African	12.24 (979)	4.47 (1,693)	
African	2.74 (219)	3.23 (1,221)	
Middle Eastern	0.05 (4)	0.12 (46)	
Chinese	0.8 (64)	2.28 (863)	
South-East Asia	0.08 (6)	0.26 (98)	
Other Asian	5.04 (403)	1.72 (652)	
American	1.01 (81)	2.22 (839)	
Oceanian	0 (0)	0.09 (35)	
Pregnancy			
Singleton	98.67 (7,893)	98.28 (37,203)	0.011
Twin	1.33 (106)	1.72 (651)	
Parity			
Primipara	46.27 (3,701)	49.48 (18,732)	<0.001
Multipara	53.73 (4,298)	50.52 (19,122)	

Table 2. Frequency of preeclampsia and gestational diabetes mellitus in the contaminated and in the control area. Data are percentages (absolute numbers).

	Contaminated area (n=7,999)	Control area (n=37,854)
Preeclampsia		
Yes	4.58 (366)	3.25 (1,232)
No	95.42 (7,633)	96.75 (36,622)
Gestational Diabetes Mellitus		
Yes	5.5 (440)	3.13 (1,183)
No	94.5 (7,559)	96.87 (36,671)

Figure 1. Contaminated area (red) and control area (green). *Red: Albaredo D'Adige, Alonte, Arcole, Asigliano Veneto, Bevilacqua, Bonavigo, Boschi Sant'Anna, Brendola, Cologna Veneta, Legnago, Lonigo, Minerbe, Montagnana, Noventa Vicentina, Poiana Maggiore, Pressana, Roveredo di Gua', Sarego, Terrazzo, Veronella, Zimella*. *Green: Arcade, Breda di Piave, Carbonera, Casale sul Sile, Casier, Castelfranco Veneto, Chiarano, Cimadolmo, Fontanelle, Giavera del Montello, Gorgo al Monticano, Istrana, Mansue', Mareno di Piave, Maserada sul Piave, Mogliano Veneto, Monastier di Treviso, Montebelluna, Morgano, Nervesa della Battaglia, Oderzo, Ormelle, Paese, Ponte di Piave, Ponzano Veneto, Povegliano, Preganziol, Quinto di Treviso, Resana, Roncade, Salgareda, San Biagio di Callalta, San Polo di Piave, Santa Lucia di Piave, Silea, Spresiano, Susegana, Trevignano, Treviso, Vazzola, Vedelago, Villorba, Volpago del Montello, Zenson di Piave, Zero Branco, Fossalta di Piave, Marcon, Meolo, Noventa di Piave, Quarto D'altino*



Birth outcomes in newborns of mothers living in an area contaminated by PFAS in Veneto Region

1. Introduction

Perfluoroalkylated substances (PFAS) are persistent organic pollutants that accumulate in the human body. PFAS enter the human body through ingestion (via contaminated drinking water and food, which are the main routes of exposure for the general population) and inhalation (which is the main route of exposure for workers). Such chemicals are distributed to the organs by binding serum albumin and accumulate mainly in the liver, the lungs, and the kidneys (Lau et al. 2007). In pregnant women, PFAS cross the placenta and accumulate in the fetus (F. Chen et al. 2017). PFAS also transfer from maternal blood to breast milk in lactating women, thus affecting breastfed infants (Cariou et al. 2015). The transplacental and lactational route are the main sources of exposures to PFAS of the fetus and the breastfed child (Cariou et al. 2015).

The evidence of transplacental and lactational transfer of PFAS arouses concern about the potential developmental effects of PFAS exposure. Several studies on both animals and humans have been published about the relationship between in-utero exposure to PFAS (especially to Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) - the PFAS most widely produced and studied) and adverse birth outcomes, focusing mainly on fetal growth. In laboratory animals, it has been shown that exposure to PFAS, and especially to PFOA, is associated with lower fetal and pups' weight (Koustas et al. 2014). However, animals are exposed to higher doses of PFAS compared to humans. In a systematic review of the human evidence, Johnson and colleagues have concluded that there is sufficient evidence to support the existence of an association between PFOA exposure and the reduction of fetal growth (Johnson et al. 2014). Subsequently, a review by Bach et al. considered the relationship between PFOA/PFOS exposure and fetal growth, concluding that the evidence suggests the existence of the relationship but that the findings are still inconsistent (Bach et al. 2015). Several studies on human fetal growth have been published after the publication of these reviews. Most of them confirm the hypothesis that PFAS exposure is significantly (inversely) associated to fetal growth (Bach et al. 2016; Cao et al. 2018; M.-H. Chen et al. 2017; Li et al. 2017; Minatoya et al. 2017; Rokoff et al. 2018; Starling et al. 2017; Wang et al. 2016), although a few studies report no association (de Cock et al. 2016; Govarts et al. 2016; Gyllenhammar et al. 2018; Manzano-Salgado et al. 2017).

Almost all these studies used birth weight (or other continuous endpoints such as birth length or head circumference) as the main index of fetal growth, even if its interpretation is not straightforward. Conversely, the small for gestational age (SGA), a measure based on birth weight and gestational age at birth, has been used only in a small number of studies (Lauritzen et al. 2017; Wang et al. 2016;

Govarts et al. 2018; M.-H. Chen et al. 2012; Manzano-Salgado et al. 2017; Whitworth et al. 2012; Hamm et al. 2010). However, SGA is a well-known proxy of intrauterine growth restrictions and a strong predictor of both short- and long-term morbidity (e.g., neurodevelopmental sequelae, high risk of suffering from metabolic and cardiovascular diseases in adulthood (Varvarigou 2010)) and mortality (Wennerström, Simonsen, and Melbye 2015).

The present retrospective study aimed at assessing the relationship between PFAS exposure and the risk of SGA among newborns of mothers living in an area contaminated by PFAS in Veneto Region (Italy).

2. Materials and Methods

The study was conducted in an area within the Veneto Region, northeast Italy, where PFAS contamination of groundwater, surface water, and drinking water was detected in 2013. The area, of about 200 km^2, crosses the province of Vicenza and, to a lesser extent, those of Verona and Padova. The source of the pollution was identified in a chemical plant located in the contaminated area. The main contaminant pathways were found to be the wastewater of the chemical plant and the water of the wastewater treatment (WHO 2017). At the time of the discovery of the contamination, concentrations of PFOA and PFOS in drinking water were found to be very high (1,475 ng/L and 117 ng/L, respectively) (WHO 2017).

The detection of the water pollution was quickly followed by remedial interventions aimed at containing drinking water contamination, using carbon filters (installed in the summer of 2013) (WHO 2017). This resulted in a marked drop of PFOA and PFOS concentrations in drinking water, observed within three months from the application of carbon filters (WHO 2017). However, it was established that the PFAS contamination had begun back in the 1960s (Dell'Acqua and Mazzola 2017), which implies a long-term exposure to PFAS of the population living in the contaminated area.

2.1 Exposure

Maternal residence in the contaminated area reported in the birth certificate was used as a proxy of exposure to PFAS, since it has been demonstrated that living in a contaminated area and drinking tap water are strictly associated with serum PFAS (Ingelido et al. 2018). The contaminated area was defined as specified in a Veneto Region official resolution (Deliberazione della Giunta Regionale n. 2133 del 23 dicembre 2016, n.d.) and included 21 municipalities, located in the South-West of Veneto Region, with higher concentrations of PFAS in the drinking water than the performance limits established by the Italian National Institute of Health ("Istituto Superiore Di Sanità. Prot. 16/01/2014-0001584," n.d.). Municipalities exceeding at least one of the following values were included in the contaminated area, PFOS: 0.03 µg/L; PFOA: 0.5 µg/L; sum of other PFAS: 0.5 µg/L

(perfluorobutyric acid (PFBA), perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDeA), perfluorododecanoic acid (PFDoA), perfluoroundecanoic acid (PFUnA), perfluorohexane sulfonate (PFHxS), perfluorobutane sulfonate (PFBS)). A control area was chosen for comparison. The area includes 48 contiguous municipalities, far away from the contaminated area, and not exposed to PFAS contamination according to the performance limits of the National Institute of Health.

2.2 Study population

The study included all singletons live births reported in the Veneto Region Birth Registry between the 1st of January 2003 and the 31st of December 2017 from mothers living in the contaminated and the control area (according to maternal municipality of residence reported in the birth certificate). The Veneto Region Birth Registry represents a mandatory electronic data collection system of all births (included stillbirths) occurring in the Region. Information about each birth is recorded by the attending midwife and by the pediatrician in charge of the care of the newborn. Such information includes parental, pregnancy, delivery, and newborn (or stillbirth) characteristics. For the study, the information considered were: maternal socio-demographic characteristics (age, nationality, marital status, educational level, and working status), smoking habit, and obstetric history (parity, preeclampsia, adverse outcomes in previous pregnancies -stillbirth and abortion-).

2.3 Outcome

SGA was defined as birth weight <3rd percentile for the gestational age according to sex-specific Italian growth charts (Bertino et al. 2010). Data about gestational age, newborn gender, and birth weight for each singleton live birth were derived from the Veneto Region Birth Registry.

2.4 Statistical analysis

Descriptive statistic was reported as percentage (absolute number), and the Pearson chi square test was performed.

Odds Ratio (OR) and 95% Confidence Intervals (C.I.) of the occurrence of SGA births in the contaminated and control area were calculated in a univariate analysis first and through stepwise logistic regression, including all the aforementioned maternal characteristics. Analyses were also conducted breaking down data into two periods, before and after the filters were applied, i.e., 2003-2014 and 2015-2017. The 2014 was included in the period before filters' installation because filters were installed in the summer of 2013 and the drop of PFAS in the drinking water took about 3 months. This means that pregnant women who gave birth in the first half of 2014 were exposed to PFAS

though the consumption of contaminated drinking water during at least the first trimester of the pregnancy.

An alpha of 0.05 was used as the cut-off for significance. Analyses were performed using SAS software (version 9.4).

3. Results

There were 99,247 singletons live births in the contaminated and control area during the study period (17,021 in the contaminated area). Maternal and newborn characteristics stratified according to the area in which the mother lived are reported in Table 2. Mothers in the contaminated area were more likely to be younger (p-value <0.001), to come from a foreign country (especially from north Africa) (p-value <0.001), and to be married (p-value <0.001). They were also of lower socio-economic level (mothers in the control area were significantly more likely to have a high educational level and to have a job compared to mothers in the contaminated area). Regarding obstetric history, women in the contaminated area were less likely to be primiparies and, in case they had previous conceptions, they were less likely to have suffered from adverse outcomes (stillbirths and abortions).

The prevalence of SGA was 3.41% (95% C.I. 3.15-3.70) in the contaminated area and 2.65% (95% C.I. 2.54-2.76) in the control ones. Table 3 shows the crude and adjusted association of residential exposure to PFAS (living in the contaminated area vs. control area) with SGA. Crude OR for SGA was 1.33 (95% C.I. 1.26-1.40) before the application of filters. The association remained significant even if lower in magnitude after the application of filters (1.15 95% C.I. 1.02-1.29). The multivariate analysis confirmed that living in the contaminated area significantly increased the odds of SGA (OR 1.26 (95% C.I. 1.14-1.38)), also when the other explanatory variables preserved by stepwise regression were taken into account. The analyses stratified according to the period before and after filters showed that living in the contaminated area was significantly associated with SGA before filters' application (OR 1.28 95% C.I. 1.15-1.42, 2003-2014), but the association was no more significant after that (1.14 95% C.I. 0.91-1.45, 2015-2017).

4. Discussion

These findings show that newborns of mothers living in the contaminated area are significantly more likely to be SGA compared to those of mothers living in the control area, with or without consideration of available covariates associated to the outcome. The odds of being SGA in the contaminated area decrease after deployment of filters reducing exposure. Such finding supports the hypothesis of a causal relationship between PFAS exposure and intrauterine growth restrictions, although the pathophysiological mechanism underlying a causal association between PFAS exposure and intrauterine growth restriction is not yet fully clear. PFAS seem to act as endocrine disruptors

leading to an impairment of thyroid hormones homeostasis (Ballesteros et al. 2017), which play a key role in fetal development. However, even if the studies on the effects of PFAS exposure on thyroid hormones have been carried out in both animal and humans, the evidence is still inconclusive. It has been suggested that intrauterine growth restrictions could depend on histopathological alterations of the placenta leading to lower placental transfer efficiency (Lee et al. 2015), but evidence in the field is available only for animals. Not least, it has been hypothesized that developmental toxicity depends on PFAS disturbance of the Peroxisome proliferator-activated receptors (PPARs) (Abbott 2009), which are nuclear receptors involved in the regulation of complex mechanisms related to development and metabolism. Also in that case, no definitive evidence is available. Clearly, that of the mechanism by which PFAS disrupt fetal growth is a research area that deserves further attention.

Looking at the epidemiological evidence in the field, some other studies that investigated the relationship between PFAS exposure and the risk of SGA produced positive results, although not fully univocally. A significantly elevated OR for SGA in newborns of tobacco smoking mothers exposed to PFOA and PFOS in a pooled analysis of eight birth cohorts was previously documented (Govarts et al. 2018). Significantly higher odds for SGA in exposed to PFOS were also found in the Taiwan Birth Panel Study (TBPS) (M.-H. Chen et al. 2012). Another study conducted in Taiwan (Wang et al. 2016) found out a significant positive association with some long-chain PFAS (PFDeA and PFUnDA), but only in female newborns. Not least, the analysis of the association between SGA and PFAS in a prospective multicentre study conducted in Norway and Sweden showed a statistically significant OR of 5.25 (95% C.I. 1.68–16.4) for SGA in newborns exposed to PFOA in the Swedish cohort (Lauritzen et al. 2017). Conversely, some studies found no associations between PFAS exposure and SGA (Manzano-Salgado et al. 2017; Whitworth et al. 2012), and in one study PFOS was found to be protective for the risk of SGA (Hamm et al. 2010).

A strength of the present study is its large number of observations (99,247 singleton live births), compared with all other studies published so far, presenting data on much smaller samples (no more than 5,500 mother-child pairs). This is remarkable since only a small portion of the newborn population is affected by SGA (by definition, less than 10%) and this might affect the accuracy in estimating the association between PFAS and this growth endpoint, especially if the study sample is small. Also, it is worth pointing out that this research work uses a more restrictive definition of SGA than in previous studies (weight $<3^{rd}$ percentile for gestational age instead of $<10^{th}$ percentile for gestational age), which should favour specificity over sensitivity, thereby diminishing the chances that our findings are false positives. On the other hand, an indirect measure of PFAS exposure was used (relying on the assumption that mothers living in the contaminated area were exposed to PFAS through contaminated drinking water consumption). This approximation is bound to produce some

misclassification, non-differtial in nature, in estimating the expsoure to PFAS (i.e., if a misclassification in PFAS expsoure occurs, it has been resulted in an underestimation of the magnitude of the association between PFAS expsoure and the outcome of interest). In addition to that, it has been shown that tap water consumption is correlated with serum levels of PFAS (Ingelido et al. 2018). Considering such a framework, the use of maternal residence in a geographical area served by a contaminated water supply could be considered a good proxy of PFAS exposure.

5. Conclusions

The findings of this study, the largest of its kind to date, suggest that PFAS plays a role in affecting fetal growth and they support the hypothesis of a causal association between PFAS exposure and SGA. However, the present topic deserves further research for what concerns the pathophysiological mechanisms potentially involved in the association between PFAS exposure and intrauterine growth.

6. References

Abbott, Barbara D. 2009. "Review of the Expression of Peroxisome Proliferator-Activated Receptors Alpha (PPAR Alpha), Beta (PPAR Beta), and Gamma (PPAR Gamma) in Rodent and Human Development." *Reproductive Toxicology (Elmsford, N.Y.)* 27 (3–4): 246–57. https://doi.org/10.1016/j.reprotox.2008.10.001.

Bach, Cathrine Carlsen, Bodil Hammer Bech, Nis Brix, Ellen Aagaard Nohr, Jens Peter Ellekilde Bonde, and Tine Brink Henriksen. 2015. "Perfluoroalkyl and Polyfluoroalkyl Substances and Human Fetal Growth: A Systematic Review." *Critical Reviews in Toxicology* 45 (1): 53–67. https://doi.org/10.3109/10408444.2014.952400.

Bach, Cathrine Carlsen, Bodil Hammer Bech, Ellen Aagaard Nohr, Jørn Olsen, Niels Bjerregård Matthiesen, Eva Cecilie Bonefeld-Jørgensen, Rossana Bossi, and Tine Brink Henriksen. 2016. "Perfluoroalkyl Acids in Maternal Serum and Indices of Fetal Growth: The Aarhus Birth Cohort." *Environmental Health Perspectives* 124 (6): 848–54. https://doi.org/10.1289/ehp.1510046.

Ballesteros, Virginia, Olga Costa, Carmen Iñiguez, Tony Fletcher, Ferran Ballester, and Maria-Jose Lopez-Espinosa. 2017. "Exposure to Perfluoroalkyl Substances and Thyroid Function in Pregnant Women and Children: A Systematic Review of Epidemiologic Studies." *Environment International* 99: 15–28. https://doi.org/10.1016/j.envint.2016.10.015.

Bertino, Enrico, Elena Spada, Luciana Occhi, Alessandra Coscia, Francesca Giuliani, Luigi Gagliardi, Giulio Gilli, Gianni Bona, Claudio Fabris, and Mario De Curtis. 2010. "Neonatal Anthropometric Charts: The Italian Neonatal Study Compared with Other European Studies." *Journal of Pediatric Gastroenterology and Nutrition* 51 (3): 353–61.

Cao, Wencheng, Xiao Liu, Xiaofang Liu, Yan Zhou, Xiaotian Zhang, Haoyuan Tian, Jin Wang, et al. 2018. "Perfluoroalkyl Substances in Umbilical Cord Serum and Gestational and Postnatal Growth in a Chinese Birth Cohort." *Environment International* 116 (July): 197–205. https://doi.org/10.1016/j.envint.2018.04.015.

Cariou, Ronan, Bruno Veyrand, Ami Yamada, Alain Berrebi, Daniel Zalko, Sophie Durand, Charles Pollono, et al. 2015. "Perfluoroalkyl Acid (PFAA) Levels and Profiles in Breast Milk, Maternal and Cord Serum of French Women and Their Newborns." *Environment International* 84 (November): 71–81. https://doi.org/10.1016/j.envint.2015.07.014.

Chen, Fangfang, Shanshan Yin, Barry C. Kelly, and Weiping Liu. 2017. "Chlorinated Polyfluoroalkyl Ether Sulfonic Acids in Matched Maternal, Cord, and Placenta Samples: A Study of Transplacental Transfer." *Environmental Science & Technology* 51 (11): 6387–94. https://doi.org/10.1021/acs.est.6b06049.

Chen, Mei-Huei, Eun-Hee Ha, Ting-Wen Wen, Yi-Ning Su, Guang-Wen Lien, Chia-Yang Chen, Pau-Chung Chen, and Wu-Shiun Hsieh. 2012. "Perfluorinated Compounds in Umbilical Cord Blood and Adverse Birth Outcomes." *PloS One* 7 (8): e42474. https://doi.org/10.1371/journal.pone.0042474.

Chen, Mei-Huei, Sharon Ng, Chia-Jung Hsieh, Ching-Chun Lin, Wu-Shiun Hsieh, and Pau-Chung Chen. 2017. "The Impact of Prenatal Perfluoroalkyl Substances Exposure on Neonatal and Child Growth." *The Science of the Total Environment* 607–608 (December): 669–75. https://doi.org/10.1016/j.scitotenv.2017.06.273.

Cock, Marijke de, Michiel R. De Boer, Marja Lamoree, Juliette Legler, and Margot Van De Bor. 2016. "Prenatal Exposure to Endocrine Disrupting Chemicals and Birth Weight-A Prospective Cohort Study." *Journal of Environmental Science and Health. Part A, Toxic/Hazardous Substances & Environmental Engineering* 51 (2): 178–85. https://doi.org/10.1080/10934529.2015.1087753.

Deliberazione della Giunta Regionale n. 2133 del 23 dicembre 2016. n.d. "Approvazione Del 'Piano Di Sorveglianza Sanitaria Sulla Popolazione Esposta Alle Sostanze Perfluoroalchiliche' e Del 'Piano Di Campionamento per Il Monitoraggio Degli Alimenti in Relazione Alla Contaminazione Da Sostanze Perfluoroalchiliche (PFAS) in Alcuni Ambiti Della Regione Del Veneto.'"

Dell'Acqua, Nicola, and Massimo Mazzola. 2017. "Contaminanti Emergenti, Una Sfida Continua per Il Sistema Delle Agenzie Ambientali."

Govarts, Eva, Nina Iszatt, Tomas Trnovec, Marijke de Cock, Merete Eggesbø, Lubica Palkovicova Murinova, Margot van de Bor, et al. 2018. "Prenatal Exposure to Endocrine Disrupting Chemicals and Risk of Being Born Small for Gestational Age: Pooled Analysis of Seven European Birth Cohorts." *Environment International* 115 (June): 267–78. https://doi.org/10.1016/j.envint.2018.03.017.

Govarts, Eva, Sylvie Remy, Liesbeth Bruckers, Elly Den Hond, Isabelle Sioen, Vera Nelen, Willy Baeyens, et al. 2016. "Combined Effects of Prenatal Exposures to Environmental Chemicals on Birth Weight." *International Journal of Environmental Research and Public Health* 13 (5). https://doi.org/10.3390/ijerph13050495.

Gyllenhammar, Irina, Barbro Diderholm, Jan Gustafsson, Urs Berger, Peter Ridefelt, Jonathan P. Benskin, Sanna Lignell, Erik Lampa, and Anders Glynn. 2018. "Perfluoroalkyl Acid Levels in First-Time Mothers in Relation to Offspring Weight Gain and Growth." *Environment International* 111 (February): 191–99. https://doi.org/10.1016/j.envint.2017.12.002.

Hamm, Michele P., Nicola M. Cherry, Emily Chan, Jonathan W. Martin, and Igor Burstyn. 2010. "Maternal Exposure to Perfluorinated Acids and Fetal Growth." *Journal of Exposure Science & Environmental Epidemiology* 20 (7): 589–97. https://doi.org/10.1038/jes.2009.57.

Ingelido, Anna Maria, Annalisa Abballe, Simonetta Gemma, Elena Dellatte, Nicola Iacovella, Giovanna De Angelis, Franco Zampaglioni, et al. 2018. "Biomonitoring of Perfluorinated Compounds in Adults Exposed to Contaminated Drinking Water in the Veneto Region, Italy." *Environment International* 110: 149–59. https://doi.org/10.1016/j.envint.2017.10.026.

"Istituto Superiore Di Sanità. Prot. 16/01/2014-0001584." n.d.

Johnson, Paula I., Patrice Sutton, Dylan S. Atchley, Erica Koustas, Juleen Lam, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff. 2014. "The Navigation Guide - Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth." *Environmental Health Perspectives* 122 (10): 1028–39. https://doi.org/10.1289/ehp.1307893.

Koustas, Erica, Juleen Lam, Patrice Sutton, Paula I. Johnson, Dylan S. Atchley, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff. 2014. "The Navigation Guide - Evidence-Based Medicine Meets Environmental Health: Systematic Review of Nonhuman Evidence for PFOA Effects on Fetal Growth." *Environmental Health Perspectives* 122 (10): 1015–27. https://doi.org/10.1289/ehp.1307177.

Lau, Christopher, Katherine Anitole, Colette Hodes, David Lai, Andrea Pfahles-Hutchens, and Jennifer Seed. 2007. "Perfluoroalkyl Acids: A Review of Monitoring and Toxicological Findings." *Toxicological Sciences: An Official Journal of the Society of Toxicology* 99 (2): 366–94. https://doi.org/10.1093/toxsci/kfm128.

Lauritzen, Hilde B., Tricia L. Larose, Torbjørn Øien, Torkjel M. Sandanger, Jon Ø Odland, Margot van de Bor, and Geir W. Jacobsen. 2017. "Maternal Serum Levels of Perfluoroalkyl Substances and Organochlorines and Indices of Fetal Growth: A Scandinavian Case-Cohort Study." *Pediatric Research* 81 (1–1): 33–42. https://doi.org/10.1038/pr.2016.187.

Lee, Chae Kwan, Sung Goo Kang, Jong Tae Lee, Soo-Woong Lee, Jeong Ho Kim, Dae Hwan Kim, Byung Chul Son, et al. 2015. "Effects of Perfluorooctane Sulfuric Acid on Placental PRL-Family Hormone Production and Fetal Growth Retardation in Mice." *Molecular and Cellular Endocrinology* 401 (February): 165–72. https://doi.org/10.1016/j.mce.2014.10.026.

Li, Meng, Xiao-Wen Zeng, Zhengmin Min Qian, Michael G. Vaughn, Sébastien Sauvé, Gunther Paul, Shao Lin, et al. 2017. "Isomers of Perfluorooctanesulfonate (PFOS) in Cord Serum and Birth Outcomes in China: Guangzhou Birth Cohort Study." *Environment International* 102: 1–8. https://doi.org/10.1016/j.envint.2017.03.006.

Manzano-Salgado, Cyntia B., Maribel Casas, Maria-Jose Lopez-Espinosa, Ferran Ballester, Carmen Iñiguez, David Martinez, Olga Costa, et al. 2017. "Prenatal Exposure to Perfluoroalkyl

Substances and Birth Outcomes in a Spanish Birth Cohort." *Environment International* 108: 278–84. https://doi.org/10.1016/j.envint.2017.09.006.

Minatoya, Machiko, Sachiko Itoh, Chihiro Miyashita, Atsuko Araki, Seiko Sasaki, Ryu Miura, Houman Goudarzi, Yusuke Iwasaki, and Reiko Kishi. 2017. "Association of Prenatal Exposure to Perfluoroalkyl Substances with Cord Blood Adipokines and Birth Size: The Hokkaido Study on Environment and Children's Health." *Environmental Research* 156: 175–82. https://doi.org/10.1016/j.envres.2017.03.033.

Rokoff, Lisa B., Sheryl L. Rifas-Shiman, Brent A. Coull, Andres Cardenas, Antonia M. Calafat, Xiaoyun Ye, Alexandros Gryparis, et al. 2018. "Cumulative Exposure to Environmental Pollutants during Early Pregnancy and Reduced Fetal Growth: The Project Viva Cohort." *Environmental Health: A Global Access Science Source* 17 (1): 19. https://doi.org/10.1186/s12940-018-0363-4.

Starling, Anne P., John L. Adgate, Richard F. Hamman, Katerina Kechris, Antonia M. Calafat, Xiaoyun Ye, and Dana Dabelea. 2017. "Perfluoroalkyl Substances during Pregnancy and Offspring Weight and Adiposity at Birth: Examining Mediation by Maternal Fasting Glucose in the Healthy Start Study." *Environmental Health Perspectives* 125 (6): 067016. https://doi.org/10.1289/EHP641.

Varvarigou, Anastasia A. 2010. "Intrauterine Growth Restriction as a Potential Risk Factor for Disease Onset in Adulthood." *Journal of Pediatric Endocrinology and Metabolism* 23 (3): 215–24.

Wang, Yan, Margaret Adgent, Pen-Hua Su, Hsiao-Yen Chen, Pau-Chung Chen, Chao A. Hsiung, and Shu-Li Wang. 2016. "Prenatal Exposure to Perfluorocarboxylic Acids (PFCAs) and Fetal and Postnatal Growth in the Taiwan Maternal and Infant Cohort Study." *Environmental Health Perspectives* 124 (11): 1794–1800. https://doi.org/10.1289/ehp.1509998.

Wennerström, E. Christina M., Jacob Simonsen, and Mads Melbye. 2015. "Long-Term Survival of Individuals Born Small and Large for Gestational Age." *PloS One* 10 (9): e0138594.

Whitworth, Kristina W., Line S. Haug, Donna D. Baird, Georg Becher, Jane A. Hoppin, Rolv Skjaerven, Cathrine Thomsen, et al. 2012. "Perfluorinated Compounds in Relation to Birth Weight in the Norwegian Mother and Child Cohort Study." *American Journal of Epidemiology* 175 (12): 1209–16. https://doi.org/10.1093/aje/kwr459.

WHO. 2017. "Keeping Our Water Clean: The Case of Water Contamination In the Veneto Region, Italy." http://www.euro.who.int/__data/assets/pdf_file/0019/341074/pfas-report-20170606-h1330-print-isbn.pdf?ua=1.

Table 1. List of municipalities included in the contaminated and in the control area

Area	Municipalities
Contaminated area	Albaredo D'Adige, Alonte, Arcole, Asigliano Veneto, Bevilacqua, Bonavigo, Boschi Sant'Anna, Brendola, Cologna Veneta, Legnago, Lonigo, Minerbe, Montagnana, Noventa Vicentina, Poiana Maggiore, Pressana, Roveredo di Gua', Sarego, Terrazzo, Veronella, Zimella
Control area	Arcade, Breda di Piave, Carbonera, Casale sul Sile, Casier, Castelfranco Veneto, Chiarano, Cimadolmo, Fontanelle, Giavera del Montello, Gorgo al Monticano, Istrana, Mansue', Mareno di Piave, Maserada sul Piave, Mogliano Veneto, Monastier di Treviso, Montebelluna, Morgano, Nervesa della Battaglia, Oderzo, Ormelle, Paese, Ponte di Piave, Ponzano Veneto, Povegliano, Preganziol, Quinto di Treviso, Resana, Roncade, Salgareda, San Biagio di Callalta, San Polo di Piave, Santa Lucia di Piave, Silea, Spresiano, Susegana, Trevignano, Treviso, Vazzola, Vedelago, Villorba, Volpago del Montello, Zenson di Piave, Zero Branco, Fossalta di Piave, Marcon, Meolo, Noventa di Piave, Quarto D'altino

Table 2. Maternal and newborn characteristics stratified according to maternal residence in the contaminated and control area. Data are percentages (absolute numbers)

	Contaminated area (n= 17,021)	Control area (n=82,226)	P-value
SGA			
Yes	3.41 (578)	2.65 (2,168)	<0.001
No	99.48 (16,359)	99.44 (79,616)	
Maternal age			
<17	0.24 (41)	0.19 (157)	<0.001
18-24	12.28 (2,091)	8.95 (7,360)	
25-29	24.89 (4,238)	22.07 (18,148)	
30-34	34.81 (5,926)	36.20 (29,767)	
35-39	22.33 (3,802)	26.08 (21,448)	
>40	5.42 (923)	6.49 (5,343)	
Nationality			
Italian	69.79 (11,879)	72.73 (59,724)	<0.001
European	0.63 (108)	1.24 (1,019)	
Eastern European	9.80 (1,669)	12.50 (10,271)	
North African	10.84 (1,845)	4.23 (3,474)	
African	2.50 (427)	3.07 (2,527)	
Middle Eastern	0.05 (9)	0.10 (87)	
Chinese	0.72 (123)	2.27 (1,868)	
South-East Asia	0.07 (13)	0.23 (192)	
Other Asian	4.62 (788)	1.47 (1,213)	
American	0.93 (159)	2.02 (1,659)	
Oceanian	0	0.09 (78)	
Educational level			
High	18.52 (3,145)	22.83 (18,501)	<0.001
Medium	45.95 (7,801)	48.83 (39,577)	
Low	35.51 (6,029)	28.33 (22,959)	
Working status			
Housewife	29.67 (5,041)	23.28 (19,118)	<0.001
Unemployed	9.70 (1,648)	7.26 (5,963)	
Employed	60.62 (10,297)	69.45 (57,038)	
Marital status			
Other	2.61 (444)	2.70 (2,213)	<0.001
Married	79.74 (13,544)	76.15 (62,418)	
Unmarried	17.64 (2,997)	21.14 (17,328)	
Parity			
Primipara	47.32 (7,986)	49.01 (39,312)	<0.001
Multipara	52.67 (8,890)	50.98 (40,894)	
Smoking habit			
Yes	5.70 (958)	4.72 (3,753)	<0.001
No	94.29 (15,833)	95.27 (75,742)	
Adverse outcomes in previous pregnancies			
Yes	23.51 (3,745)	25.95 (19,401)	<0.001

No	76.48 (12,179)	74.04 (55,359)	
Preeclampsia			
Yes	2.58 (422)	2.23 (1,755)	0.013
No	97.41 (15,894)	97.76 (76,923)	

Table 3. Crude and adjusted OR (95% Confidence Intervals (C.I.)) for SGA (contaminated vs. control area)

	Crude OR (95% C.I.)	P-value	Adjusted* OR (95% C.I.)	P-value
2003-2014	1.33 (1.26-1.40)	<0.001	1.28 (1.15-1.42)	<0.001
2015-2017	1.15 (1.02-1.29)	0.013	1.14 (0.91-1.45)	0.24
Overall	1.29 (1.24-1.36)	<0.001	1.26 (1.14-1.38)	<0.001

*Maternal age, nationality, educational level, marital status, smoking habit, parity, preeclampsia, adverse outcomes in previous pregnancies -stillbirths and/or abortion-, newborn gender