Published in final edited form as:
Reprod Toxicol. 2014 August ; 0: 15–20. doi:10.1016/j.reprotox.2014.04.006.

Perfluorooctanoate Exposure and Major Birth Defects

Cheryl R. Stein[a], **David A. Savitz**[b], **Beth Elston**[b], **Phoebe G. Thorpe**[c], and **Suzanne M. Gilboa**[c]

Cheryl R. Stein: cheryl.stein@mssm.edu; David A. Savitz: david_savitz@brown.edu; Beth Elston: beth_elston@brown.edu; Phoebe G. Thorpe: pht1@cdc.gov; Suzanne M. Gilboa: suz0@cdc.gov

[a]Department of Preventive Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1057, New York, NY 10029-6574

[b]Department of Epidemiology, Brown University School of Public Health, Providence, RI

[c]National Center on Birth Defects and Developmental Disabilities, US Centers for Disease Control and Prevention, Atlanta, GA

Abstract

Perfluorooctanoate (PFOA) is detectable in umbilical cord blood and amniotic fluid. Some toxicological findings suggest that perfluoroalkyl substances may be teratogenic.

Using data from the C8 Health Project, a 2005 – 2006 survey in a Mid-Ohio Valley community exposed to PFOA through contaminated drinking water, we examined the association between estimated prenatal PFOA concentration and maternally reported birth defects (n=325) among 10,262 live singleton or multiple births from 1990 – 2006. Logistic regression models accounted for siblings using generalized estimating equations.

There was generally no association between estimated PFOA concentration and birth defects, with the possible exception of brain defects, where the odds ratio adjusted for year of conception was 2.6 (95% confidence interval 1.3 – 5.1) for an increase in estimated PFOA exposure from the 25th to 75th percentile. This estimate, however, was based on 13 cases and may represent a chance finding. Further investigation of this potential association may be warranted.

Keywords

congenital abnormalities; epidemiology; fluorocarbons; perfluorooctanoic acid

CORRESPONDING AUTHOR: Cheryl R. Stein, Ph.D., Assistant Professor, Department of Preventive Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1057, New York, NY 10029-6574, Phone: 212-824-7083, Fax: 212-996-0407, cheryl.stein@mssm.edu.

The authors declare no conflicts of interest.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

1. Introduction

Perfluorooctanoate (PFOA) is a perfluoroalkyl substance (PFAS) that has been widely used in the manufacture of consumer products since the 1950s [1]. PFAS are used as surfactants, surface treatment chemicals, and processing aids for many products, including oil, stain, grease, and water repellent coatings on carpet, textiles, leather, and paper [1–3]. Human exposure to PFOA typically occurs through transfer from food packaging, bioaccumulation in the food chain, and inhalation of household dust [4]. PFOA is almost always detectable in serum [5] and has been found in amniotic fluid [6, 7], maternal and umbilical cord blood [8–10], and breast milk [11–15]. Toxicology studies highlight the potential for PFAS to affect fetal growth, development, viability, and postnatal growth (reviewed in [3, 16–18]). The U.S. Environmental Protection Agency has initiated a voluntary phase-out of PFOA emissions and product content by 2015 [19], but human exposure will persist for some time because of the chemical's global dispersion and 2 to 4 year serum half-life [20, 21].

PFAS are not thought to be teratogens below doses causing maternal toxicity [16]. Depending on the specific PFAS and animal model, however, there have been positive results at the highest exposure levels for cleft palate [22, 23], cardiac abnormalities [22, 24, 25], and delayed ossification [22, 26]. Combined with cross-species differences in elimination, observed developmental toxicity, and ubiquitous human exposure, study of PFAS and birth defects in human is warranted.

Epidemiological information on PFOA and birth defects in humans is limited to three published reports based on data from a single region with PFOA exposure from contaminated drinking water leading to serum PFOA concentrations approximately 5 times higher than the national average. Two of these reports are based on the C8 Health Project [27], as is the current study (C8 is another name for PFOA, denoting its 8-carbon chain). The first report examined maternal serum PFOA concentration measured in 2005 – 2006 in relation to maternal report of birth defects in 1,590 singleton live births from 2000 – 2006 [28]. There was an increased odds of birth defects (analyzed in the aggregate) above the 90th percentile of exposure as compared to below the 50th percentile (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI) 0.8 – 3.6) [28]. The second report examined predicted maternal prenatal serum concentration based on an environmental pharmacokinetic model in relation to maternal report of birth defects in 10,189 singleton live births from 1990 – 2006 [29]. Birth defects in the aggregate were unrelated to PFOA, but there was a weak, imprecise association with heart defects for exposure above as compared to below the 40th percentile (adjusted OR 1.5, 95% CI 0.9 – 2.4). The third report observed no association between an ecological measure of PFOA exposure and report of birth defects from birth certificates, analyzed by group or in the aggregate, for 1,548 singleton live births [30].

We sought to explore the relation between PFOA and birth defects in more detail using the now-complete resources of the C8 Health Project, which included coding of an open-ended birth defects field. The addition of this detailed birth defect information and more detailed examination of specific types of birth defects distinguishes the current study from previous reports [28, 29].

2. Materials and Methods

2.1 Study Population

In 2001, a group of residents from the West Virginia and Ohio communities surrounding a chemical plant near Parkersburg, West Virginia filed a class action lawsuit alleging health damage from drinking water supplies drawing from PFOA-contaminated groundwater [27]. Geometric mean PFOA levels in this population were approximately 5 times the national average; exposure to most other PFAS reflected typical background levels.

The settlement of the class action lawsuit included a baseline health survey, the C8 Health Project, that enrolled 69,030 people from 2005 – 2006 [27]. Individuals were eligible to participate if they could prove they had consumed water for at least one year since 1950 while living, working, or going to school in one of six PFOA-contaminated water districts or private wells within the area of documented contamination. The Project collected health data through self-administered questionnaires and blood tests.

Women in the C8 Health Project reported 10,960 live singleton or multiple births from 1990 – 2006. We excluded women aged <14 or >45 years at delivery (n=11), women with self-reported pre-pregnancy diabetes (n=206), women who worked at the chemical plant, which would make the exposure estimate based on drinking water inaccurate (n=404), women missing data on potentially important covariates (race, smoking, education, infant sex; n=54), and births with reported genetic birth defects (n=23), leaving 10,262 (94%) live singleton or multiple births for analysis. Women could contribute more than one birth to the analysis.

2.2 Exposure Assessment

Serum PFOA was measured at study enrollment in 2005 – 2006. To make the exposure temporally relevant to historical outcomes, we used an environmental pharmacokinetic model to estimate historical serum PFOA concentration. Considerable variation in PFOA exposure across calendar year and water district informed an exposure reconstruction model based on documented PFOA releases, environmental fate and transport modeling, human exposure and excretion pharmacokinetics, geocoded residential history, and maps of public water supply networks [31]. Exposure modeling generated individual estimates of serum PFOA levels for C8 Health Project participants. The model-based exposure predictions correlated well with the serum measurements obtained at study enrollment (r=0.67) [32]. For these analyses, we assigned the estimated serum PFOA for the calendar year of conception. We restricted the epidemiologic analysis to pregnancies from 1990 through study enrollment because this time period was when exposure substantially exceeded background levels.

2.3 Outcome Assessment

For each self-reported live birth, women were asked, “Did the baby have any major birth defects, something that required medical treatment?” and then were asked to specify the birth defect. The questionnaire contained 10 checkboxes for specific defects or conditions (congenital heart defect; club foot or other foot defect; Down syndrome; eye defect; genital or urinary tract defect; nose defect; oral clefts; Sickle Cell Disease; spina bifida; Marfan

Syndrome) plus a checkbox labeled “other” followed by an open-ended field for study participants to write in a description of the defect. Working as a group, we (CRS, PGT, SMG) coded the open-ended birth defects field without knowing exposure status and then broadly grouped both checkbox and described defects into 10 body system categories [brain (neural tube defects, hydrocephalus, reduction deformities); craniofacial (oral clefts, ear defects, craniosynostosis); eye; gastrointestinal; genitourinary; heart; kidney; limb; other–specified (musculoskeletal, skin, thyroid, vessel); other–unspecified]. The “other-unspecified” category indicated cases where the box for “other” was checked, but additional descriptive information was not provided by the mother. While we report descriptive results for the two “other” categories we do not analyze them as distinct outcomes given the heterogeneity of the groupings. We did not consider reports of heart murmurs or patent ductus arteriosus without mention of corrective surgery to be heart defects. Birth defects were considered isolated defects (n=325) when only one body system was affected. Birth defects were considered multiple defects (n= 63) when more than one body system was affected.

2.4 Statistical Analysis

We analyzed each birth defect system as a separate outcome, excluding births with any defect from the denominator. The primary analysis was among babies with isolated defects (n=10,232). A secondary analysis included babies with either isolated or multiple defects (n=10,262). We used two metrics of estimated prenatal PFOA concentration: a log transformed interquartile range (IQR) increase and a three-level categorical variable with cut points at the 40^{th} and 70^{th} percentiles, comparing those in the 40^{th} – $<70^{th}$ percentile and those at or above the 70^{th} percentile to a common referent of those $<40^{th}$ percentile. These cutpoints were selected because exposure estimates below the 40^{th} percentile largely reflect background exposures, with little ability to discriminate in the background range based on the models. Above background, we divided pregnancies approximately evenly using the 70^{th} percentile as the cutpoint to be able to examine a dose gradient with maximum statistical power. To evaluate the association between PFOA and birth defects, we used generalized estimating equations regression models with a logit link function and an independent correlation structure to account for the dependence among siblings. We estimated crude ORs and ORs adjusted for year (continuous) of conception relating continuous measures of PFOA to maternal report of birth defects. Categorical measures of PFOA were adjusted for year of conception only for outcomes with ≥20 cases. Adjusting for additional factors was not feasible because of the small numbers of specific types of birth defects. Analyses were performed using SAS 9.3 (Cary, NC).

3. Results

This was a relatively young group of pregnant women (mean (standard deviation) 25.6 (5.4) years) and births were evenly divided over the study period. The racial-ethnic homogeneity of this region of the United States was evidenced by 97% of the population identifying as non-Hispanic white. Over half of the women had at least some college education (58%) and were multiparous (55%); almost half reported never smoking (47%). The mean (standard

deviation) and median (quartile 1, quartile 3) estimated serum PFOA concentrations were 61.3 (123.1) ng/mL and 10.4 (5.0, 44.8) ng/mL, respectively.

The prevalence of reported isolated birth defects was 3.2% (n=325; Table 1). Among specified birth defects categories, heart defects were the most commonly reported defects. There was minimal variation in estimated prenatal PFOA concentration across birth defect systems, with the exception of brain defects with a median of 86.2 ng/mL as compared to 10.4 ng/mL for births without defects.

With an IQR increase in estimated prenatal PFOA concentration, women were 2.6 (95% CI 1.2 – 5.4) times more likely to report that their child was born with a brain defect (Table 2). This increase in odds of brain defects was also evident above the 70^{th} percentile of estimated prenatal PFOA exposure as compared to below the 40^{th} percentile (OR 16.1, 95% CI 0.8 – 325), although this estimate was extremely imprecise.

There was little evidence of an association between PFOA and heart defects with either the continuous (OR 1.2, 95% CI 0.8 – 1.7) or categorical (OR for $\geq 70^{th}$ percentile vs. $<40^{th}$ percentile 1.4, 95% CI 0.4 – 5.3) metrics of estimated prenatal PFOA exposure.

Craniofacial defects also showed essentially no association with estimated prenatal PFOA exposure for an increase from the 25^{th} to 75^{th} percentile (OR 0.6, 95% CI 0.3 – 1.2). We conducted a separate analysis (data not shown) of just oral clefts (n=13) pulled from this broader craniofacial defects group because of the toxicological data suggesting an association between PFOA exposure and cleft palate. The association with oral clefts when PFOA was treated continuously (OR 0.5, 95% CI 0.2 – 1.4) was imprecise enough to be considered essentially null. With the categorical treatment of PFOA, there was an elevated odds ratio in the middle (40^{th} – $<70^{th}$ percentile) as compared to lowest ($<40^{th}$ percentile) exposure category, but the estimate was also imprecise (OR 2.8, 95% CI 0.2 – 37.8). There were only 2 cases of oral clefts among births in the highest ($\geq 70^{th}$ percentile) exposure category.

Adjustment for year of conception made little difference in the association between estimated prenatal PFOA concentration and any reported birth defect system (Table 2). Examining the associations between PFOA exposure and multiple defects did not alter the pattern of results (data not shown).

4. Discussion

Using a cohort of over 10,000 live births, we applied quantitative predictive modeling estimates to examine the association between estimated maternal prenatal PFOA concentration and maternal report of birth defects across several body systems. The distinctive environmental source of exposure – contamination of public water supplies by known quantities of PFOA – made this type of modeling possible.

While increased exposure appeared to be related to brain defects based on the continuous exposure metric, the absolute number of these types of defects in this population was small – just 13 – and the prevalence of spina bifida (n=2 isolated; n=3 multiple) was below the

national prevalence estimate of 3.5 per 10,000 live births [33]. Previous investigations in this population reported suggestive associations with congenital heart defects [28, 29], but we did not observe any compelling association between estimated prenatal PFOA concentration and congenital heart defects in the present examination. This difference may be due to the more rigorous indication of congenital heart defects required for the present investigation, such as our exclusion of heart defects associated with Down syndrome under the general exclusion of genetic birth defects, and of heart murmurs or patent ductus arteriosus without mention of corrective surgery.

This is the largest, most comprehensive investigation to date of PFOA exposure and birth defects. Even with the large sample size, however, the number of cases of specific types of birth defects was modest and our power to detect associations with PFOA exposure was low. Our reliance on maternal report of birth defects from checkboxes and open-ended fields limited our ability to classify defects beyond very basic, broad categories. The use of broad categories rather than specific defects led to heterogeneity within the outcome groupings. The open-ended fields often contained vague descriptions of birth defects, and the quality of the maternal report was likely poor compared to data obtained from medical records or birth defects surveillance programs. We also had little ability to discriminate between major and minor defects, and because birth defect information was only collected for live births we were unable to include pregnancies ending in spontaneous or induced abortion or stillbirth. Additionally, at the time of the C8 Health Project the community was aware of which water districts had higher concentrations of PFOA, although we do not know whether this knowledge biased maternal report of birth defects. All of these limitations in outcome assessment would make a true association more difficult to identify and underestimate the magnitude of the association, if an association exists.

The low prevalence of specific birth defects also impacted our ability to adjust for confounders. However, given the origins of the exposure, confounding would arise only if risk factors for birth defects, such as social, behavioral or medical characteristics, differed by residential location or time period, which are the primary determinants of exposure in this population. Levels of PFOA were not known until rather recently and were unlikely to have negatively affected property values or be related to other indicators of socioeconomic status. For instance, in this population educational attainment was not associated with estimated serum PFOA concentration.

Our use of modeled, rather than measured, PFOA is both a strength and limitation. The implementation of a rigorous environmental pharmacokinetic model allowed us to greatly expand our sample size beyond the initial investigation using measured PFOA and to examine defects across 10 different body systems [28]. These historical serum estimates, however, are derived from complex prediction models with many assumptions needed for the environmental fate and transport models [31] and pharmacokinetic adsorption, distribution, metabolism, and excretion models [32].

In toxicological studies, dosing at which terata were observed ranged from 1 mg/kg for cardiac abnormalities in chicken embryos [24], to 10 mg/kg for cleft palate, cardiac abnormalities, and delayed ossification in rats [22], and 13 mg/kg for cleft palate in mice

[23]. In female CD-1 mice, a dose of 20 mg/kg PFOA for 7 and 17 days resulted in mean (± standard error) serum concentrations of 178 (± 19) μg/mL and 171 (± 15) μg/mL, respectively [34]. Comparisons of exposure, internal dose, and effect across species are complex, but the exposures that resulted in teratogenicity in these animals were markedly higher than the exposures evaluated in the present study.

5. Conclusions

We observed an association between estimated maternal prenatal PFOA concentration and defects of the brain among live births, but the number of reported defects was small and within the range of what would be expected. In contrast to the weak indications for increased risk at the highest exposure in previous studies, we observed little evidence of an association with congenital heart defects [28, 29]. In addition, essentially no association with oral clefts was observed despite prior toxicological support from animal studies. Findings were largely null for the remaining defects.

Acknowledgments

We thank Hyeong-Moo Shin for developing the environmental pharmacokinetic models.

This research was funded by the C8 class action settlement agreement [Jack W. Leach, et al. v. E.I. du Pont de Nemours & Company (no. 01-C-608 W.Va., Wood County Circuit Court, West Virginia, USA] between DuPont and plaintiffs. Funds were administered by the Garden City Group (Melville, New York) that reports to the court. Our work and conclusions are independent of either party to the lawsuit. Cheryl Stein was supported by the National Institute of Environmental Health Sciences (K01 ES019156).

ABBREVIATIONS

CI	confidence interval
IQR	interquartile range
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PFAS	perfluoroalkyl substance
PFOA	perfluorooctanoate

References

1. U.S. Environmental Protection Agency. Perfluorooctanoic Acid (PFOA) and Fluorinated Telomers. Washington, DC: 2009.
2. U.S. Environmental Protection Agency. Perfluorooctanoic Acid (PFOA). Washington, DC: 2009.
3. Stahl T, Mattern D, Brunn H. Toxicology of perfluorinated compounds. Environ Sci Europe. 2011; 23
4. D'Eon JC, Mabury SA. Is Indirect Exposure a Significant Contributor to the Burden of Perfluorinated Acids Observed in Humans? Environ Sci Technol. 2011; 45:7974–84. [PubMed: 21630688]
5. Kato K, Wong LY, Jia LT, Kuklenyik Z, Calafat AM. Trends in Exposure to Polyfluoroalkyl Chemicals in the U.S. Population: 1999–2008. Environ Sci Technol. 2011

6. Jensen MS, Norgaard-Pedersen B, Toft G, Hougaard DM, Bonde JP, Cohen A, et al. Phthalates and Perfluorooctanesulfonic Acid in Human Amniotic Fluid: Temporal Trends and Timing of Amniocentesis in Pregnancy. Environ Health Perspect. 2012
7. Stein CR, Wolff MS, Calafat AM, Kato K, Engel SM. Comparison of polyfluoroalkyl compound concentrations in maternal serum and amniotic fluid: A pilot study. Reprod Toxicol. 2012
8. Inoue K, Okada F, Ito R, Kato S, Sasaki S, Nakajima S, et al. Perfluorooctane sulfonate (PFOS) and related perfluorinated compounds in human maternal and cord blood samples: assessment of PFOS exposure in a susceptible population during pregnancy. Environ Health Perspect. 2004; 112:1204–7. [PubMed: 15289168]
9. Midasch O, Drexler H, Hart N, Beckmann MW, Angerer J. Transplacental exposure of neonates to perfluorooctanesulfonate and perfluorooctanoate: a pilot study. Int Arch Occup Environ Health. 2007; 80:643–8. [PubMed: 17219182]
10. Monroy R, Morrison K, Teo K, Atkinson S, Kubwabo C, Stewart B, et al. Serum levels of perfluoroalkyl compounds in human maternal and umbilical cord blood samples. Environ Res. 2008; 108:56–62. [PubMed: 18649879]
11. Kuklenyik Z, Reich JA, Tully JS, Needham LL, Calafat AM. Automated solid-phase extraction and measurement of perfluorinated organic acids and amides in human serum and milk. Environ Sci Technol. 2004; 38:3698–704. [PubMed: 15296323]
12. So MK, Yamashita N, Taniyasu S, Jiang Q, Giesy JP, Chen K, et al. Health risks in infants associated with exposure to perfluorinated compounds in human breast milk from Zhoushan, China. Environ Sci Technol. 2006; 40:2924–9. [PubMed: 16719092]
13. Tao L, Kannan K, Wong CM, Arcaro KF, Butenhoff JL. Perfluorinated compounds in human milk from Massachusetts, U.S.A. Environ Sci Technol. 2008; 42:3096–101. [PubMed: 18497172]
14. Tao L, Ma J, Kunisue T, Libelo EL, Tanabe S, Kannan K. Perfluorinated compounds in human breast milk from several Asian countries, and in infant formula and dairy milk from the United States. Environ Sci Technol. 2008; 42:8597–602. [PubMed: 19068854]
15. Volkel W, Genzel-Boroviczeny O, Demmelmair H, Gebauer C, Koletzko B, Twardella D, et al. Perfluorooctane sulphonate (PFOS) and perfluorooctanoic acid (PFOA) in human breast milk: results of a pilot study. Int J Hyg Environ Health. 2008; 211:440–6. [PubMed: 17870667]
16. Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutchens A, Seed J. Perfluoroalkyl acids: a review of monitoring and toxicological findings. Toxicol Sci. 2007; 99:366–94. [PubMed: 17519394]
17. Lau C, Butenhoff JL, Rogers JM. The developmental toxicity of perfluoroalkyl acids and their derivatives. Toxicol Appl Pharmacol. 2004; 198:231–41. [PubMed: 15236955]
18. Olsen GW, Butenhoff JL, Zobel LR. Perfluoroalkyl chemicals and human fetal development: an epidemiologic review with clinical and toxicological perspectives. Reprod Toxicol. 2009; 27:212–30. [PubMed: 19429401]
19. U.S. Environmental Protection Agency. 2010/2015 PFOA Stewardship Program.
20. Bartell SM, Calafat AM, Lyu C, Kato K, Ryan PB, Steenland K. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect. 2010; 118:222–8. [PubMed: 20123620]
21. Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, et al. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect. 2007; 115:1298–305. [PubMed: 17805419]
22. Thibodeaux JR, Hanson RG, Rogers JM, Grey BE, Barbee BD, Richards JH, et al. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. I: maternal and prenatal evaluations. Toxicol Sci. 2003; 74:369–81. [PubMed: 12773773]
23. Era S, Harada KH, Toyoshima M, Inoue K, Minata M, Saito N, et al. Cleft palate caused by perfluorooctane sulfonate is caused mainly by extrinsic factors. Toxicology. 2009; 256:42–7. [PubMed: 19041924]
24. Jiang Q, Lust RM, Strynar MJ, Dagnino S, DeWitt JC. Perflurooctanoic acid induces developmental cardiotoxicity in chicken embryos and hatchlings. Toxicology. 2012; 293:97–106. [PubMed: 22273728]

25. Cheng W, Yu Z, Feng L, Wang Y. Perfluorooctane sulfonate (PFOS) induced embryotoxicity and disruption of cardiogenesis. Toxicology in vitro: an international journal published in association with BIBRA. 2013; 27:1503–12. [PubMed: 23562911]
26. Case MT, York RG, Christian MS. Rat and rabbit oral developmental toxicology studies with two perfluorinated compounds. Int J Toxicol. 2001; 20:101–9. [PubMed: 11354466]
27. Frisbee SJ, Brooks AP Jr, Maher A, Flensborg P, Arnold S, Fletcher T, et al. The C8 health project: design, methods, and participants. Environ Health Perspect. 2009; 117:1873–82. [PubMed: 20049206]
28. Stein CR, Savitz DA, Dougan M. Serum levels of perfluorooctanoic acid and perfluorooctane sulfonate and pregnancy outcome. Am J Epidemiol. 2009; 170:837–46. [PubMed: 19692329]
29. Savitz DA, Stein CR, Bartell SM, Elston B, Gong J, Shin HM, et al. Perfluorooctanoic Acid exposure and pregnancy outcome in a highly exposed community. Epidemiology. 2012; 23:386–92. [PubMed: 22370857]
30. Nolan LA, Nolan JM, Shofer FS, Rodway NV, Emmett EA. Congenital anomalies, labor/delivery complications, maternal risk factors and their relationship with perfluorooctanoic acid (PFOA)-contaminated public drinking water. Reprod Toxicol. 2010; 29:147–55. [PubMed: 19897029]
31. Shin HM, Vieira VM, Ryan PB, Detwiler R, Sanders B, Steenland K, et al. Environmental Fate and Transport Modeling for Perfluorooctanoic Acid Emitted from the Washington Works Facility in West Virginia. Environ Sci Technol. 2011; 45:1435–42. [PubMed: 21226527]
32. Shin HM, Vieira VM, Ryan PB, Steenland K, Bartell SM. Retrospective exposure estimation and predicted versus observed serum perfluorooctanoic acid concentrations for participants in the C8 Health Project. Environ Health Perspect. 2011; 119:1760–5. [PubMed: 21813367]
33. Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, et al. Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004–2006. Birth Defects Res A Clin Mol Teratol. 2010; 88:1008–16. [PubMed: 20878909]
34. Lau C, Thibodeaux JR, Hanson RG, Narotsky MG, Rogers JM, Lindstrom AB, et al. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicol Sci. 2006; 90:510–8. [PubMed: 16415327]

Highlights

- Perfluorooctanoate (PFOA) is detectable in umbilical cord blood and amniotic fluid.
- Some toxicological findings suggest that perfluoroalkyl substances may be teratogenic.
- while increased prenatal exposure to PFOA appeared to be related to brain defects, the number of reported defects was small and within the range of what would be expected.
- There was generally no association between estimated PFOA concentration and other reported birth defects.

Table 1

Live births by maternal characteristics and reported isolated birth defect system, C8 Health Project, mid-Ohio Valley, 1990 – 2006 (n=10,232)

Birth Defect System	**None**	**Gastrointestinal**	**Kidney**	**Brain**	**Craniofacial**	**Eye**	**Limb**	**Genitourinary**	**Heart**	**Other – specified[a]**	**Other – unspecified**
Maternal Characteristic	**N (percent)**	**N (percent)**	**N (percent)**	**N (percent)**	**N (percent)**	**N (percent)**	**N (percent)**	**N (percent)**	**N (percent)**	**N (percent)**	**N (percent)**
Cases [N (Row Percent)]	9907 (96.8)	11 (0.11)	11 (0.11)	13 (0.13)	21 (0.21)	24 (0.24)	27 (0.26)	31 (0.30)	60 (0.57)	20 (0.19)	107 (1.05)
Estimated Prenatal Serum PFOA [Median ng/mL (Q1, Q3)]	10.4 (5.0, 44.6)	14.0 (4.7, 28.2)	9.3 (5.1, 64.5)	86.2 (15.1, 247)	8.0 (4.7, 19.3)	9.2 (4.9, 46.4)	10.1 (5.3, 61.8)	12.3 (4.5, 63.1)	13.4 (5.1, 64.5)	6.2 (4.5, 34.9)	9.8 (5.2, 34.1)
Estimated Prenatal Serum PFOA percentiles (ng/mL)											
<40th percentile (3.9 to <6.79)	3962 (40)	4 (36.4)	4 (36.4)	3 (23.1)	9 (42.9)	10 (41.7)	11 (40.7)	13 (41.9)	23 (38.3)	11 (55)	45 (42.1)
40th – <70th percentile (6.79 to <31.70)	2974 (30)	5 (45.5)	6 (54.5)	2 (15.4)	9 (42.9)	7 (29.2)	6 (22.2)	8 (25.8)	17 (28.3)	4 (20)	33 (30.8)
≥70th percentile (31.70 to 934.33)	2971 (30)	2 (18.2)	1 (9.1)	8 (61.5)	3 (14.3)	7 (29.2)	10 (37)	10 (32.3)	20 (33.3)	5 (25)	29 (27.1)
Year of Conception											
1990 – 1994	3338 (33.7)	3 (27.3)	3 (27.3)	6 (46.2)	9 (42.9)	9 (37.5)	10 (37)	14 (45.2)	18 (30)	7 (35)	34 (31.8)
1995 – 1999	3210 (32.4)	3 (27.3)	4 (36.4)	5 (38.5)	6 (28.6)	7 (29.2)	6 (22.2)	11 (35.5)	23 (38.3)	6 (30)	40 (37.4)
2000 – 2006	3359 (33.9)	5 (45.5)	4 (36.4)	2 (15.4)	6 (28.6)	8 (33.3)	11 (40.7)	6 (19.4)	19 (31.7)	7 (35)	33 (30.8)
Maternal Age (years)											
14 – 19	1279 (12.9)	4 (36.4)	3 (27.3)	6 (46.2)	3 (14.3)	4 (16.7)	5 (18.5)	5 (16.1)	5 (8.3)	2 (10)	16 (15)
20 – 24	3323 (33.5)	2 (18.2)	3 (27.3)	4 (30.8)	7 (33.3)	7 (29.2)	12 (44.4)	7 (22.6)	21 (35)	7 (35)	42 (39.3)
25 – 29	2905 (29.3)	3 (27.3)	3 (27.3)	2 (15.4)	5 (23.8)	9 (37.5)	4 (14.8)	5 (16.1)	21 (35)	5 (25)	26 (24.3)
30 – 45	2400 (24.2)	2 (18.2)	2 (18.2)	1 (7.7)	6 (28.6)	4 (16.7)	6 (22.2)	14 (45.2)	13 (21.7)	6 (30)	23 (21.5)
Maternal Race/Ethnicity											
Other	277 (2.8)	1 (9.1)	2 (18.2)	0	1 (4.8)	2 (8.3)	0	1 (3.2)	2 (3.3)	1 (5)	3 (2.8)
Non-Hispanic White	9630 (97.2)	10 (90.9)	9 (81.8)	13 (100)	20 (95.2)	22 (91.7)	27 (100)	30 (96.8)	58 (96.7)	19 (95)	104 (97.2)
Maternal Education (years)											
≤12	4121 (41.6)	4 (36.4)	5 (45.5)	7 (53.8)	15 (71.4)	11 (45.8)	13 (48.1)	6 (19.4)	18 (30)	13 (65)	46 (43)
>12	5786 (58.4)	7 (63.6)	6 (54.5)	6 (46.2)	6 (28.6)	13 (54.2)	14 (51.9)	25 (80.6)	42 (70)	7 (35)	61 (57)
Parity											
0	4425 (44.7)	8 (72.7)	8 (72.7)	9 (69.2)	6 (28.6)	6 (25)	17 (63)	17 (54.8)	32 (53.3)	14 (70)	46 (43)
≥1	5482 (55.3)	3 (27.3)	3 (27.3)	4 (30.8)	15 (71.4)	18 (75)	10 (37)	14 (45.2)	28 (46.7)	6 (30)	61 (57)
Plurality											
Multiple	248 (2.5)	1 (9.1)	0	1 (7.7)	0	2 (8.3)	1 (3.7)	0	5 (8.3)	0	10 (9.3)
Singleton	9659 (97.5)	10 (90.9)	11 (100)	12 (92.3)	21 (100)	22 (91.7)	26 (96.3)	31 (100)	55 (91.7)	20 (100)	97 (90.7)

Birth Defect System Maternal Characteristic	None N (percent)	Gastrointestinal N (percent)	Kidney N (percent)	Brain N (percent)	Craniofacial N (percent)	Eye N (percent)	Limb N (percent)	Genitourinary N (percent)	Heart N (percent)	Other – specified[a] N (percent)	Other – unspecified N (percent)
Cigarette Use											
Never	4672 (47.2)	3 (27.3)	5 (45.5)	5 (38.5)	10 (47.6)	13 (54.2)	5 (18.5)	9 (29)	26 (43.3)	11 (55)	44 (41.1)
Former	1988 (20.1)	2 (18.2)	2 (18.2)	2 (15.4)	2 (9.5)	3 (12.5)	6 (22.2)	9 (29)	13 (21.7)	2 (10)	21 (19.6)
Current	3247 (32.8)	6 (54.5)	4 (36.4)	6 (46.2)	9 (42.9)	8 (33.3)	16 (59.3)	13 (41.9)	21 (35)	7 (35)	42 (39.3)

[a]Other – specified includes musculoskeletal, skin, thyroid, and vessel defects

PFOA = perfluorooctanoate; Q1 = quartile 1; Q3 = quartile 3

Table 2

Crude and adjusted[a] odds ratios and 95% confidence intervals for the association between estimated maternal prenatal serum perfluorooctanoate concentration and isolated only birth defect system, C8 Health Project, mid-Ohio Valley, 1990 – 2006 (n=10,105)

Birth Defect System	Crude OR (95% CI)	Adjusted[a] OR (95% CI)	Crude OR (95% CI)			Adjusted[a] OR (95% CI)		
PFOA	IQR increase[b]	IQR increase[b]	<40th percentile	40th – <70th percentile	≥70th percentile	<40th percentile	40th – <70th percentile	≥70th percentile
Gastrointestinal	0.7 (0.4, 1.4)	0.7 (0.3, 1.4)	1.0	3.1 (0.2, 54.6)	0.4 (0.01, 17.1)	NC	NC	NC
Kidney	0.7 (0.3, 1.6)	0.7 (0.3, 1.8)	1.0	4.6 (0.3, 73.2)	0.1 (0.001, 11.0)	NC	NC	NC
Brain	2.6 (1.2, 5.4)	2.6 (1.3, 5.1)	1.0	0.8 (0.02, 38.9)	16.1 (0.8, 325)	NC	NC	NC
Craniofacial	0.6 (0.3, 1.2)	0.6 (0.3, 1.3)	1.0	1.9 (0.3, 14.2)	0.2 (0.01, 3.0)	1.0	2.4 (0.3, 19.1)	0.2 (0.01, 4.0)
Eye	1.1 (0.6, 2.1)	1.1 (0.6, 2.1)	1.0	0.9 (0.1, 7.1)	0.9 (0.1, 7.2)	1.0	0.9 (0.1, 8.7)	0.9 (0.1, 7.8)
Limb	1.2 (0.7, 2.0)	1.2 (0.7, 2.0)	1.0	0.5 (0.1, 4.4)	1.5 (0.2, 10.0)	1.0	0.5 (0.1, 4.3)	1.5 (0.2, 9.7)
Genitourinary	1.0 (0.6, 1.7)	1.0 (0.6, 1.7)	1.0	0.7 (0.1, 4.5)	1.1 (0.2, 6.6)	1.0	0.8 (0.1, 5.4)	1.3 (0.2, 8.4)
Heart	1.2 (0.8, 1.7)	1.2 (0.8, 1.7)	1.0	1.0 (0.2, 3.8)	1.4 (0.4, 5.3)	1.0	0.9 (0.2, 3.7)	1.4 (0.4, 5.1)

[a] Adjusted for year of conception (continuous); adjusted ORs for categorical PFOA calculated only for defects with n≥20

[b] for IQR increase from 25th (5.0 ng/mL) to 75th (44.6 ng/mL) percentile

PFOA = perfluorooctanoate; IQR = interquartile range; NC = not calculated