Probable Link Evaluation of Preterm Birth and Low Birthweight

Conclusion: On the basis of epidemiologic and other scientific data available to the C8 Science Panel, we conclude that there is not a probable link between exposure to PFOA (C8) and preterm birth or low birthweight.

Introduction - C8 Science Panel and the Probable Link reports

In February 2005, the West Virginia Circuit Court approved a class action Settlement Agreement in a lawsuit about releases of a chemical known as C8, or PFOA, from DuPont's Washington Works facility located in Wood County, West Virginia. The Settlement Agreement had several parts.

One part of the Settlement was the creation of a Science Panel, consisting of three epidemiologists, to conduct research in the community in order to evaluate whether there is a probable link between PFOA exposure and any human disease. A "probable link" in this setting is defined in the Settlement Agreement to mean that given the available scientific evidence, it is more likely than not that among class members a connection exists between PFOA exposure and a particular human disease.

Another part of the Settlement established the C8 Health Project, which collected data from Class Members through questionnaires and blood testing. These data represent a portion of what the Science Panel evaluated to answer the question of whether a probable link exists between PFOA and human disease. Evidence comes from Science Panel research that has been published as well as Science Panel research that has not yet been published. In performing this work, the Science Panel was not limited to consideration of data relating only to Class Members, but examined all scientifically relevant data including, but not limited to, data relating to PFOA exposure among workers, among people in other communities, and other human exposure data, together with relevant animal and toxicological data. The Science Panel has drawn on evidence that has been openly published by other investigators, which means that the detailed evidence used by the Panel to inform its conclusions is available to others.

Criteria used to evaluate the evidence for a probable link included the strength and consistency of reported associations, evidence of a dose-response relationship, the potential for associations to occur by chance, adequacy of control for biases and other causes, and plausibility based on experiments in laboratory animals. The odds ratio was the primary measure of association that we examined. The odds ratio is a marker of the risk in exposed compared to the risk in the unexposed or low-exposed. The null value – indicating no association between exposure and outcome – is 1.0. Values above 1.0 are evidence of increased risk with increased exposure. Values from 0.0 to 0.9 are evidence of decreased risk with increased exposure. We also examined 95% confidence intervals (95% CI) as a measure of the statistical precision of the odds ratios. 95% CI generate a range of plausible values taking chance into account.
Review of Evidence for Preterm Birth

Preterm birth is defined as early delivery of an infant before completing 37 weeks of gestation. Preterm birth is associated with increased risk of infant death and a wide range of health problems in early life and beyond. The earlier the baby is delivered, the more severe the health consequences.

The evidence to evaluate the probable link between PFOA exposure and preterm birth comes from six studies in the Mid-Ohio Valley, five of which are Science Panel studies: 1) ZIP Code-based PFOA exposure and preterm birth from birth certificates (Nolan et al., 2009); 2) Measured serum PFOA and self-reported preterm birth among C8 Health Project participants (Stein et al., 2009); 3) Estimated serum PFOA and self-reported preterm birth among C8 Health Project participants (Savitz et al., 2011a, in press); 4) Estimated serum PFOA and preterm birth based on birth certificate records for Ohio and West Virginia counties with elevated PFOA exposure (Savitz et al., 2011b, under review); 5) Estimated serum PFOA and preterm birth based on birth certificates for C8 Health Project participants (Savitz et al., 2011b, under review); 6) Estimated serum PFOA and preterm birth based on birth certificates for C8 Health Project Community Cohort follow-up participants (manuscript in preparation). Several studies of PFOA and preterm birth in other populations were also considered.

Epidemiologic Studies on Mid-Ohio Valley Populations

The first study examined the relationship between water service area and gestational age for Ohio births (n=1,555) in a small part of the affected region from 2003-2005 (Nolan et al., 2009). Birth certificate information was used to determine PFOA exposure by ZIP Code of residence and to identify gestational age. This study used ZIP Codes overlapping with the Little Hocking Water Association service area to define elevated exposure and the findings were limited by the quality of exposure assignment. There was no association between mean gestational age or preterm birth (n=200) and residence in ZIP Codes that were exclusively or partially served by Little Hocking Water Association as compared to ZIP codes not served by Little Hocking Water Association.

The second study examined measured serum PFOA and self-reported preterm birth among C8 Health Project participants from 2000-2006 (Stein et al., 2009). The C8 Health Project was a survey of Class Members conducted in 2005-2006 that included a health interview and blood collection to measure PFOA levels and clinical health markers. The analysis was restricted to live births (n=1,571) that occurred in the five years prior to enrollment to women who had lived in the same water district from pregnancy through the time of serum PFOA measurement. This restriction helped ensure that the 2005-2006 serum measurement was applicable to the time of pregnancy. There was no support for an association between measured serum PFOA and preterm birth (n=329) among these pregnancies. The adjusted odds ratios for preterm birth were close to the null value of 1.0 using both continuous and categorical indicators of measured serum PFOA.

The third study examined estimated serum PFOA and self-reported preterm birth among C8 Health Project participants from 1990-2005 (Savitz et al., 2011a, in press). The Science Panel generated the historical estimates of serum PFOA among Class Members (Shin et al., 2011a, b) used in this study. This study included a larger number of pregnancies (n=10,189) and greater time span than the study based on measured serum PFOA. The historical serum PFOA estimates were based on the amount of PFOA released from the DuPont plant, wind patterns,
river flow, groundwater flow, and the residential history of C8 Health Project participants (Shin et al., 2011a, b). The results for self-reported preterm birth (n=1,843) showed no evidence of an association with estimated serum PFOA. This finding remained true when data were restricted to pregnancies with the highest quality exposure estimates. Highest quality exposure estimates were available for women with comprehensive residential histories who were served by community water supplies rather than private wells. As an alternative method of estimating serum PFOA levels at the time of pregnancy, we used calibration to the 2005-2006 measured levels. The lack of association between estimated serum PFOA and preterm birth remained when using the calibrated exposure estimates.

In the fourth study, preterm birth was identified from birth records from 1990-2005 for five counties in Ohio and West Virginia (Savitz et al., 2011b, under review). The historical serum PFOA estimates at the time of pregnancy were based on the amount of PFOA released from the DuPont plant, wind patterns, river flow, groundwater flow, and the residential address listed on the birth certificate (Shin et al., 2011a, b). Preterm birth was examined overall (<37 completed weeks gestation) and by degree of prematurity: early preterm birth (<32 completed weeks gestation) and late preterm birth (32–<37 weeks completed gestation). There was no association between estimated serum PFOA and overall preterm birth (n=3,613), early preterm birth (n=491) or late preterm birth (n=3,122) using either continuous or categorical indicators of estimated serum PFOA exposure. However, we observed a small association with overall preterm birth when we restricted the analysis to the 66% of pregnancies where exposure was estimated based on exact street address rather than including those with exposure estimated based on ZIP Code averages. Using exact street address provides a more accurate estimate of serum PFOA exposure from drinking water. This small association was limited to the continuous indicator of estimated exposure (odds ratio = 1.07, 95% CI = 0.99 – 1.15) and there was no gradient of increasing risk across quintiles of exposure.

The fifth study of preterm birth is a companion to the fourth study. This Science Panel study linked birth records from 1990-2005 from 13 counties in Ohio and West Virginia to pregnancies reported by women in the C8 Health Project (Savitz et al., 2011b, under review). This study also examined overall preterm birth (n=405), early preterm birth (n=40), and late preterm birth (n=365) as reported on the birth certificate. PFOA exposure, however, was estimated using the comprehensive residential history recorded in the C8 Health Project rather than just the point-in-time residential address listed on the birth certificate. Estimated serum PFOA was weakly related to overall preterm birth and more strongly related to early preterm birth, although the sample size for early preterm birth was small. As an alternative method of estimating serum PFOA levels at the time of pregnancy, we used calibration to the 2005-2006 measured levels. This alternative estimation method strengthened the association for early preterm birth, with adjusted odds ratios across the 3rd, 4th, and 5th quintiles of 1.5 (95% CI = 0.6-4.1), 2.3 (95% CI = 1.0-5.5), and 2.3 (95% CI = 0.9-5.7), compared to the 1st and 2nd quintiles combined. However these odds ratios were imprecise due to the small number of early preterm births.

The sixth study of preterm birth addressed pregnancies to Class Members that occurred from 2005-2010, after enrollment in the C8 Health Project. This Community Cohort follow-up study estimated serum PFOA levels at the time of pregnancy by correcting serum PFOA measured in 2005 – 2006 for the estimated decline after removal of PFOA from municipal water supplies (manuscript in preparation). This study linked births (n=1,627) reported by participants of the Community Cohort Study to Ohio and West Virginia birth certificate records from 2005 – 2010. There was no association between estimated serum PFOA and overall preterm birth (n= 158) using the continuous indicator of exposure. Using the categorical indicator of exposure there was an isolated increased risk in the 2nd quintile of exposure (adjusted odds ratio = 1.5, 95% CI
= 0.9-2.7) as compared to the 1st quintile, but the adjusted odds ratios in the 3rd, 4th, and 5th quintiles were 1.2 (95% CI = 0.7-2.1), 1.1 (95% CI = 0.6-2.1), and 1.0 (95% CI = 0.5-1.8). There were too few cases of early preterm birth to examine separately.

Epidemiologic Studies on Other Populations

Several studies considered gestational age as a continuous outcome and found no association with measured PFOA in populations with typical background PFOA exposures outside the Mid-Ohio Valley (Apelberg et al., 2007; Fei et al., 2007; Hamm et al., 2009). Continuous gestational age, however, is of limited relevance to the assessment of preterm birth since most births occur at term. In the Danish National Birth Cohort Study (Fei et al., 2007), the risk of preterm birth was elevated above the first quartile of PFOA, but there was no gradient in risk with higher exposure. In contrast, Hamm et al. (2009) found no association between measured serum PFOA and preterm birth, although the number of cases was small.

Mechanistic and Toxicologic Evidence

The toxicology literature examining effects of high doses in rodent models clearly documents the potential for PFOA (and other perfluorinated compounds) to have adverse effects on development, specifically reduced fetal growth (Wolf et al., 2007; Yahia et al., 2020), increased fetal death (Wolf et al., 2007; Suh et al., 2011), delayed developmental milestones (Wolf et al., 2007), and increased risk of neonatal death (Wolf et al., 2007; Yahia et al., 2010). Reviews published by Lau et al., (2004, 2007) summarize a rather substantial body of research through the mid-2000s and find that the evidence for an adverse effect on fetal and postnatal growth is clear, with later health deficits (including mortality) likely to be a product, at least in part, of the reduced growth. Most studies find no effect of PFOA on structural malformations (birth defects) in the offspring of exposed mothers.

Assessment of Evidence for Preterm Birth

In our opinion, the evidence of an association between PFOA exposure and preterm birth is insufficient to conclude that PFOA has a probable link with preterm birth among Class Members. The studies of measured or estimated serum PFOA exposure and self-reported preterm birth were completely negative. The studies of estimated serum PFOA exposure and preterm birth identified from birth certificate records were also negative. The only study with a positive finding used estimated serum PFOA from the C8 Health Project and preterm birth from the birth certificates, and the positive finding was only for early preterm birth (<32 weeks), which had few cases. On balance, the weight of evidence falls short for inferring a probable link between PFOA (C8) and preterm birth in pregnancies among class members.
Review of Evidence for Low Birthweight

Insufficient growth during pregnancy that is clinically significant for the health of the infant can be measured in a variety of ways to identify the babies at greatest risk of health problems. Low birthweight (<2500 grams or 5.5 pounds) and small-for-gestational-age (below the 10th percentile of birthweight for a given duration of pregnancy) are the most common clinical outcomes. In this report we refer generally to “low birthweight” and then note the specific outcome used in a given study. Most of the studies that examined birthweight focused on differences in average birthweight rather than outcomes of medical importance because the populations were too small to study low birthweight or small-for-gestational-age. While shifts in average birthweight may be related to clinically significant reductions in fetal growth, direct information on low birthweight is needed to assess a probable link. The results from studies on small shifts in average birthweight provide data that are relevant to the assessment, but such small shifts do not constitute a disease. The conditions considered for evaluating if there is a probable link with PFOA are low birthweight or small-for-gestational age.

The evidence to evaluate the probable link between PFOA exposure and low birthweight comes from six studies in the Mid-Ohio Valley, five of which are Science Panel studies. 1) ZIP Code-based PFOA exposure and birthweight from birth certificates (Nolan et al., 2009); 2) Measured serum PFOA and self-reported low birthweight among C8 Health Project participants (Stein et al., 2009); 3) Estimated serum PFOA and self-reported low birthweight among C8 Health Project participants (Savitz et al., 2011a, in press); 4) Estimated serum PFOA and birthweight based on birth certificate records for Ohio and West Virginia counties with elevated PFOA exposure (Savitz et al., 2011b, under review); 5) Estimated serum PFOA and birthweight based on birth certificates for C8 Health Project participants (Savitz et al., 2011b, under review); 6) Estimated serum PFOA and birthweight based on birth certificates for C8 Health Project Community Cohort follow-up participants (manuscript in preparation). Several studies in other populations were also considered in the evaluation process.

Epidemiologic Studies on Mid-Ohio Valley Populations

The first study examined the relationship between water service area and birthweight for Ohio births (n=1,555) in a small part of the affected region from 2003-2005 (Nolan et al., 2009). Birth certificate information was used to determine PFOA exposure by ZIP Code of residence and to identify birthweight. This study used ZIP Codes overlapping with the Little Hocking Water Association service area to define elevated exposure and the findings were limited by the quality of exposure assignment. There was lower risk of low birthweight (n=109) and no association with average birthweight among ZIP Codes that were exclusively or partially served by Little Hocking Water Association as compared to ZIP codes not served by Little Hocking Water Association.

The second study examined measured serum PFOA and self-reported low birthweight among C8 Health Project participants from 2000-2006 (Stein et al., 2009). The C8 Health Project was a survey of Class Members conducted in 2005-2006 that included a health interview and blood collection to measure PFOA levels and clinical health markers. The analysis was restricted to live births (n=1,589) that occurred in the five years prior to enrollment to women who had lived in the same water district from pregnancy through the time of serum PFOA measurement. This restriction helped ensure that the 2005-2006 serum measurement was applicable to the time of pregnancy. There was no support for an association between measured serum PFOA and low birthweight (n=80) among these pregnancies.
The third study examined estimated serum PFOA and self-reported low birthweight among C8 Health Project participants from 1990-2005 (Savitz et al., 2011a, in press). The Science Panel generated the historical estimates of serum PFOA among Class Members (Shin et al., 2011a, b) used in this study. This study included a larger number of pregnancies (n=10,189) and greater time span than the study based on measured serum PFOA. The historical serum PFOA estimates were based on the amount of PFOA released from the DuPont plant, wind patterns, river flow, groundwater flow, and the residential history of C8 Health Project participants (Shin et al., 2011a, b). The results for births that were both full term and low birthweight (n=133) showed no evidence of an association with estimated serum PFOA. This finding remained true when data were restricted to pregnancies with the highest quality exposure estimates. Highest quality exposure estimates were available for women with comprehensive residential histories who were served by community water supplies rather than private wells, although there was an isolated increased risk in the 3rd but not the 4th or 5th quintile of exposure, compared to the 1st and 2nd quintiles combined.

In the fourth study, birthweight was identified from birth records from 1990-2005 for five counties in Ohio and West Virginia (Savitz et al., 2011b, under review). The historical serum PFOA estimates at the time of pregnancy were based on the amount of PFOA released from the DuPont plant, wind patterns, river flow, groundwater flow, and the residential address listed on the birth certificate (Shin et al., 2011a, b). We examined term low birthweight (n=918), term small-for-gestational-age (n=353), and average birthweight among term births (n=4,534 term births). Estimated serum PFOA was unrelated to term low birthweight. There was a modest inverse association (lower risk with higher exposure) between estimated serum PFOA and term small-for-gestational-age. There was essentially no association between estimated serum PFOA and average birthweight among term births. The results did not change when we restricted the analysis to the 66% of pregnancies where exposure was estimated based on exact street address rather than including those with exposure estimated from ZIP Code averages. Exact street address provides a more accurate estimate of serum PFOA exposure from drinking water.

The fifth study of birthweight is a companion to the fourth study. This Science Panel study linked birth records from 1990-2005 from 13 counties in Ohio and West Virginia to pregnancies reported by women in the C8 Health Project (Savitz et al., 2011b, under review). This study also examined term low birthweight (n=99), term small-for-gestational-age (n=362), and average birthweight among term births (n=4,043 term births) as reported on the birth certificate. PFOA exposure, however, was estimated using the comprehensive residential history recorded in the C8 Health Project rather than just the point-in-time residential address listed on the birth certificate. Term low birthweight was unrelated to estimated serum PFOA except for an increase in the 4th (adjusted odds ratio = 1.6, 95% CI = 1.0-2.8) but not the 3rd or 5th quintile of exposure, compared to the 1st and 2nd quintiles combined. Small-for-gestational-age showed a weak relationship with a continuous indicator of estimated serum PFOA and a small elevation in only the 5th quintile (adjusted odds ratio = 1.3, 95% CI = 0.9-1.7) compared to the 1st and 2nd quintiles combined. The continuous term birthweight analysis showed a stronger association of reduced birthweight with increasing exposure based on the continuous indicator of estimated serum PFOA and in the 4th and 5th quintiles of the categorical exposure indicator, with average reductions of 25-33 grams. As an alternative method of estimating serum PFOA levels at the time of pregnancy, we used calibration to the 2005-2006 measured levels. The results did not change with the alternative estimation method.
The sixth study of birthweight addressed pregnancies to Class Members that occurred from 2005-2010, after enrollment in the C8 Health Project. This Community Cohort follow-up study estimated serum PFOA levels at the time of pregnancy by correcting serum PFOA measured in 2005–2006 for the estimated decline after removal of PFOA from municipal water supplies (manuscript in preparation). This study linked births (n=1,452) reported by participants of the Community Cohort Study to Ohio and West Virginia birth certificate records from 2005-2010. There was no association between estimated serum PFOA and term low birthweight (n= 34) using the continuous indicator of exposure or quintiles of exposure. When comparing risk for those above the 40th percentile versus below the 40th percentile of estimated PFOA exposure, there was limited evidence of increased risk of term low birthweight. The continuous term birthweight analysis showed a small association of reduced birthweight with increasing exposure based on the continuous indicator of estimated serum PFOA for both comparing the 75th to the 25th percentiles of exposure (-19 grams, 95% CI = -45 to 8) and with a 100 ng/ml shift in exposure (-33 grams, 95% CI = -70 to 4).

**Epidemiologic Studies on Other Populations**

Several studies have examined the relationship between measured PFOA exposure and continuous birthweight in populations with typical background PFOA exposures outside the Mid-Ohio Valley (Inoue et al., 2004; So et al., 2006; Apelberg et al., 2007; Fei et al., 2007; Monroy et al., 2008; Hamm et al., 2009; Washino et al., 2009). Two studies reported clear evidence of decreased average birthweight in relation to increased PFOA (Apelberg et al., 2007; Fei et al., 2007). Smaller decrements were reported in two other studies (Hamm et al., 2009; Washino et al., 2009). The magnitude of association ranged from a decrement of 37 to 104 g per log unit increase in PFOA exposure with varying degrees of statistical precision. One study (Fei et al., 2007) reported a reduction of 10.6 g per ng/ml PFOA. Three smaller studies reported no association between PFOA and birthweight (Inoue et al., 2004; So et al., 2006; Monroy et al., 2008).

Risk of low birthweight was elevated in the upper three quartiles of measured PFOA relative to the lowest quartile in the analysis of the Danish National Birth Cohort Study (Fei et al., 2007), but the same study showed no association with small-for-gestational-age. Small-for-gestational-age was also unrelated to PFOA in a study from Alberta, Canada (Hamm et al., 2009).

Cumulatively, these studies on populations outside the Mid-Ohio Valley provide inconsistent evidence of small reductions in average birthweight associated with PFOA exposure. While an adverse impact of PFOA on birthweight could suggest that the fetus is sensitive to PFOA, the magnitude of the shifts reported in these studies are within the normal birthweight range are of little or no clinical significance.

**Mechanistic and Toxicologic Evidence**

The toxicology literature examining effects of high doses in rodent models clearly documents the potential for PFOA (and other perfluorinated compounds) to have adverse effects on development, specifically reduced fetal growth (Wolf et al., 2007; Yahia et al., 2020), increased fetal death (Wolf et al., 2007; Suh et al., 2011), delayed developmental milestones (Wolf et al., 2007), and increased risk of neonatal death (Wolf et al., 2007; Yahia et al., 2010). Reviews published by Lau et al., (2004, 2007) summarize a rather substantial body of research through the mid-2000s and find that the evidence for an adverse effect on fetal and postnatal growth is
clear, with later health deficits (including mortality) likely to be a product, at least in part, of the reduced growth. Most studies find no effect of PFOA on structural malformations (birth defects) in the offspring of exposed mothers.

**Assessment of Evidence for Low Birthweight**

In our opinion, the evidence of an association between PFOA exposure and low birthweight is insufficient to conclude that PFOA has a probable link with low birthweight among Class Members. While there is some evidence suggesting small decrements in average birthweight at the highest PFOA exposure levels, the findings across studies are inconsistent and it is not clear that these shifts are truly a result of PFOA exposure. Furthermore, such small shifts in average birthweight do not constitute a medically significant condition. There is little support of an association between PFOA (C8) and low birthweight for the extreme values that are of medical significance.
References


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. Environmental Health Perspectives, epub http://dx.doi.org/10.1289/ehp.1103729, 2011b.

