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Probable Link Evaluation of Pregnancy Induced Hypertension and Preeclampsia

Conclusion: On the basis of epidemiologic and other scientific data available to the C8 Science Panel, we conclude that there is a probable link between exposure to PFOA (C8) and pregnancy-induced hypertension.

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 as a result of 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

Pregnancy-induced hypertension is defined as an elevation in blood pressure reaching levels considered to be significantly elevated (systolic >140 mmHg or diastolic >90 mmHg) that begins after the 20th week of pregnancy. A specific form of pregnancy-induced hypertension, called preeclampsia, is diagnosed when the elevation in blood pressure is accompanied by leakage of protein into the urine. Both preeclampsia and pregnancy-induced hypertension without protein in the urine are common pregnancy complications, and blood pressure and protein in the urine are routinely monitored during pregnancy in order to detect and manage these conditions. These conditions are associated with reduced fetal growth and an increased risk of preterm birth. Preeclampsia, in particular, can cause serious health problems for the mother and the fetus that can be alleviated only by delivering the fetus.

While these diseases have clear definitions based on detailed clinical evaluations, they are vulnerable to inaccurate or incomplete reporting in both the sources used for this assessment, self-report and birth certificates. Pregnancy-induced hypertension can be confused with hypertension that began before pregnancy started. The self-reported information from the C8 Health Project only asked about "preeclampsia," and among those who reported the condition, an unknown proportion presumably had pregnancy-induced hypertension without protein in the urine. Nonetheless, in referring to those data, we will use the term "preeclampsia." Conversely, the birth certificates only offer an option for "pregnancy-induced hypertension," not a separate option for "preeclampsia," so that resource as well undoubtedly includes women who had protein in the urine and would be diagnosed with preeclampsia. Since hypertensive disorders of pregnancy, with or without protein in the urine, have similar risk factors and we are unable to clearly distinguish them based on the information available, we believe that they should be considered collectively across the data sources available. Thus a determination is made whether or not there is a probable link between PFOA and hypertension that begins during pregnancy, with or without protein in the urine, and refer to this disease generally as "pregnancy-induced hypertension."

To assess the accuracy of the information we obtained directly from the mothers and from the birth certificates, we examined the pattern of reported pregnancy-induced hypertension and preeclampsia in relation to known predictors. We were reassured to see well-established associations for known risk factors: risk was markedly increased in first pregnancies relative to subsequent pregnancies and risk was reduced among women who were smokers relative to non-smokers.

The evidence to evaluate the probable link between PFOA exposure and pregnancy-induced hypertension comes from four studies, three of which are Science Panel studies: 1) ZIP Code-based PFOA exposure and pregnancy-induced hypertension from birth certificates (Nolan et al., 2010); 2) Estimated serum PFOA and pregnancy-induced hypertension based on birth certificate records for Ohio and West Virginia counties with elevated PFOA exposure (Savitz et al., 2011b, under review); 3) Estimated serum PFOA and pregnancy-induced hypertension based on birth certificates for C8 Health Project participants (Savitz et al., 2011b, under review); 4) Prospective study of PFOA and pregnancy-induced hypertension based on birth certificates in births since the C8 Health Project (manuscript in preparation). The evidence to evaluate the probable link between PFOA exposure and preeclampsia comes from two Science Panel studies; 1) Measured serum PFOA and self-reported preeclampsia among C8 Health Project participants (Stein et al., 2009); 2) Estimated serum PFOA and self-reported preeclampsia among C8 Health Project participants (Savitz et al., 2011a, in press).

Epidemiologic Studies on Mid-Ohio Valley Populations

We considered four studies of pregnancy-induced hypertension. The first study examined the relationship between water service area and pregnancy-induced hypertension for Ohio births (n=1,548) in a small part of the affected region from 2003-2005 (Nolan et al., 2010). Birth certificate information was used to determine PFOA exposure by ZIP Code of residence and to identify pregnancy-induced hypertension (n= 157). 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 pregnancy-induced hypertension and 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 of pregnancy-induced hypertension was a Science Panel study. Pregnancy-induced hypertension 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). There was no association between estimated serum PFOA and pregnancy-induced hypertension (n=224). However, we observed a small association 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 highest exposure category, with adjusted odds ratios for the 3rd, 4th, and 5th quintiles of 1.1 (95% CI = 0.7-1.6), 1.0 (95% CI = 0.6-1.6), and 1.3 (95% CI = 0.8-2.1), compared to the 1st and 2nd quintiles combined.

The third study of pregnancy-induced hypertension is a companion to the second 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 pregnancy-induced hypertension (n=250) 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. Analysis of estimated serum PFOA based on the full residential history generated little support for an association with pregnancy-induced hypertension. 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, but there was an irregular dose-response pattern. The adjusted odds ratios for the 3rd, 4th, and 5th quintiles were 1.0 (95% CI = 0.7-1.4), 1.5 (95% CI = 1.1-2.1), and 1.2 (95% CI = 0.8-1.7), compared to the 1st and 2nd quintiles combined.

The fourth study of pregnancy-induced hypertension 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=1,584) reported by participants of the Community Cohort Study to Ohio and West Virginia birth certificate records from 2005-2010. There was evidence of an association between estimated serum PFOA and pregnancy-induced hypertension (n=106) based on the continuous exposure

indicator. The adjusted odds ratio was 1.25 (95% CI = 0.97-1.62) comparing the 75th to the 25th percentiles of exposure. The adjusted odds ratios for the 2nd, 3rd, 4th, and 5th quintiles were 2.2 (95% CI = 1.0-5.1), 2.9 (95% CI = 1.3-6.4), 2.6 (95% CI = 1.2-5.9), and 2.8 (95% CI = 1.2-6.4), as compared to the 1st quintile. These elevated odds ratios indicate a markedly higher risk above the 1st quintile of exposure, although there is no gradient in risk across the 2nd through 5th quintiles of exposure.

The first study of preeclampsia examined measured serum PFOA and self-reported preeclampsia 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 serum PFOA measurement. This restriction helped ensure that the 2005-2006 serum measurement was applicable to the time of pregnancy. Measured serum PFOA was weakly and irregularly associated with preeclampsia (n=156). There was an elevated risk for women above the 50th percentile (median) of exposure (odds ratio = 1.3, 95% CI = 0.9-1.9). This elevated risk above the median was driven by an increased risk in the 50th-75th percentile (odds ratio = 1.5, 95% CI = 1.0-2.3) more than an increased risk in the 75th-90th percentile (odds ratio = 1.2, 95% CI = 0.7-2.1) or above the 90th percentile (odds ratio = 0.9, 95% CI = 0.5-1.8).

The second study of preeclampsia examined estimated serum PFOA 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 preeclampsia (n=730) showed a modest association with estimated serum PFOA at the time of pregnancy. The adjusted odds ratio for the continuous exposure indicator was 1.13 (95% CI = 1.00-1.28), comparing the 75th to the 25th percentiles of exposure. The adjusted odds ratios for the 3rd, 4th, and 5th quintiles were 1.2 (95% CI = 1.0-1.5), 1.1 (95% CI = 0.9-1.4), and 1.2 (95% CI = 1.0-1.6), compared to the 1st and 2nd quintiles combined. These odds ratios do not show a gradient in risk across the 3rd through 5th quintiles of exposure. 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, with adjusted odds ratios across the 3rd, 4th, and 5th quintiles of 1.2 (95% CI = 1.0-1.5), 1.3 (95% CI = 1.1-1.7), and 1.4 (95% CI = 1.1-1.7), compared to the 1st and 2nd quintiles combined. The association between estimated serum PFOA and preeclampsia was also strengthened when we restricted the analysis to more recent pregnancies (2000-2005), with adjusted odds ratios in the upper quintiles ranging from 1.3 to 1.5.

Epidemiologic Studies on Other Populations

To our knowledge, there are no other epidemiologic studies that address PFOA and any type of pregnancy-induced hypertension.

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., 2010), 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

In our opinion, the evidence for an association between PFOA exposure and pregnancy-induced hypertension is sufficient to conclude that PFOA has a probable link to this disease among class members. While few of the individual measures of association are strong or show clear evidence of increasing risk with increasing exposure across the full range of PFOA exposure, there are several reasons why we interpret the pattern of results as supporting a probable link: 1) Associations were observed in several analyses of different sets of pregnancies among women in the C8 Health Project. These analyses used different exposure indicators and health outcomes, each with specific strengths and limitations. While individually the observed associations could have alternative explanations, it is unlikely that the full pattern of findings could be explained by a series of hypothesized biases. 2) The odds ratios were strengthened for the pregnancies that were closest in time to the measured serum PFOA values (both before and after C8 Health Project enrollment) when exposure assignment is likely to be most accurate.

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