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Probable Link Evaluation of Miscarriage and Stillbirths

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 miscarriage or stillbirth.

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

Pregnancy loss refers to miscarriage, defined as loss of pregnancy before 20 weeks of gestation, and stillbirth, defined as loss of pregnancy at 20 weeks gestation or later. The evidence to evaluate the probable link between PFOA exposure and pregnancy loss comes from four Science Panel studies: 1) Measured serum PFOA and self-reported miscarriage among C8 Health Project participants (Stein et al., 2009); 2) Estimated serum PFOA and self-reported miscarriage and stillbirth among C8 Health Project participants (Savitz et al., 2011a, in press); 3) Estimated serum PFOA and stillbirth based on vital records from the West Virginia Health Department for counties with elevated PFOA exposure (Savitz et al., 2011b, under review); 4) Estimated serum PFOA and self-reported miscarriage among C8 Health Project Community Cohort follow-up participants (manuscript in preparation).

Epidemiologic Studies on Mid-Ohio Valley Populations

The first study examined measured serum PFOA and self-reported miscarriage 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 pregnancies 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 (n=1,845). 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 miscarriage (n=249) and measured serum PFOA exposure among these pregnancies. The odds ratios for miscarriage were very close to the null value of 1.0 using both continuous and categorical indicators of measured serum PFOA exposure. Stillbirth was not examined in relation to measured serum PFOA because there were too few stillbirths in this subgroup for reliable statistical analysis.

The second study examined estimated serum PFOA and self-reported pregnancy loss 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 miscarriage (n=1,443) 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. The results for self-reported stillbirths (n=105) were more complicated. There was essentially no indication of an association between estimated serum PFOA and stillbirth based on continuous exposure, but there was an irregular pattern across categorical exposure groups. The adjusted odds ratios for the 3rd, 4th, and 5th quintiles were 1.2 (95% CI = 0.7-2.0), 1.7 (95% CI = 1.0-2.8), and 1.0 (95% CI = 0.5-1.8), reflecting an increased risk in the 4th quintile as compared to the 1st and 2nd quintiles combined, but no increased risk among the highest exposure group.

The third study examined estimated serum PFOA and stillbirths identified from West Virginia fetal death records for women who resided in Mason or Wood Counties in West Virginia from 1990-2005 (Ohio did not provide information on stillbirths) (Savitz et al., 2011b, under review).

Parts of these two counties had elevated PFOA levels in municipal water supplies. Estimated serum PFOA at the time of pregnancy was determined using the residential address listed on the fetal death certificate. There was essentially no association between stillbirth (n=106) and estimated serum PFOA using continuous or categorical exposure indicators. The results did not change when we restricted the analysis to the 66% of pregnancies for which 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 fourth study addressed pregnancies to Class Members that occurred from 2005-2010, after enrollment in the C8 Health Project. This follow-up Community Cohort Study estimated serum PFOA levels at the time of pregnancy (n=1,808) by correcting serum PFOA measured in 2005-2006 for the estimated decline after removal of PFOA from municipal water supplies (manuscript in preparation). There was essentially no association between estimated serum PFOA and self-reported miscarriage (n=321) based on either continuous or categorical exposure indicators.

Epidemiologic Studies on Other Populations

To our knowledge, there are no other epidemiologic studies that address PFOA exposure and pregnancy loss.

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 neonatal 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 of an association between PFOA exposure and pregnancy loss is insufficient to conclude that PFOA has a probable link with miscarriage or stillbirth among Class Members. The evidence for assessing the link between PFOA and miscarriage or stillbirth comes from C8 Science Panel analyses of data from the C8 Health Project and vital records data in West Virginia. The absence of increasing risk with increasing exposure, the failure of more refined exposure estimates to show an association, the lack of consistent results across exposure measures, and the absence of directly supportive toxicologic data lead us to conclude that there is not a probable link between PFOA (C8) and miscarriage or stillbirth.

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