December 5, 2011

Probable Link Evaluation of Birth Defects

Conclusion: On the basis of epidemiologic studies 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 birth defects.

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

Birth defects are structural malformations in the infant that arise during fetal development. These structural changes can cause severe morbidity and often require corrective action. Birth defects are rare and require large populations for meaningful research. The evidence to evaluate the probable link between PFOA exposure and birth defects comes from three studies, two of which are Science Panel Studies: 1) ZIP Code-based PFOA exposure and birth defects from birth certificates (Nolan et al., 2010); 2) Measured serum PFOA and self-reported birth defects among C8 Health Project participants (Stein et al., 2009); 3) Estimated serum PFOA and self-reported birth defects among C8 Health Project participants (Savitz et al., 2011a, in press). The Science Panel did not conduct a study of birth defects based on birth certificates because of the poor quality of the birth defects information contained on the birth certificate.

Epidemiologic Studies on Mid-Ohio Valley Populations

The first study examined the relationship between water service area and birth defects for Ohio births 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 birth defects. Only 3 birth defect cases were found among births in ZIP Codes fully contained in the water service area for Little Hocking Water Association and 4 birth defect cases among residents of ZIP Codes partially within the Little Hocking Water Association service area, so little information can be obtained from this study. No meaningful associations were found between water service area and birth defects.

The second study examined measured serum PFOA and self-reported birth defects 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 1,589 live births 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. Although there was no overall support for an association between measured serum PFOA and birth defects among these pregnancies, above the 90^{th} percentile of exposure there was a suggested elevation in risk (adjusted odds ratio = 1.7, 95% CI = 0.8-3.6). There were, however, only 12 birth defects in this highest exposure group. We could not examine specific types of birth defects in this study because of the small population size.

The third study examined estimated serum PFOA and self-reported birth defects 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 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). There was no evidence of an association between estimated serum PFOA and birth defects (n=449). This finding remained true when data were restricted to pregnancies with the highest quality exposure estimates (pregnancies among 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 results did not change with the alternative estimation method. We also considered specific types of birth defects, despite the limited

numbers available for analysis. We observed limited evidence for an increased risk of congenital heart defects with increased estimated serum PFOA, which we consider most likely to be due to chance. The adjusted odds ratio comparing the 75th to the 25th percentiles of exposure was 1.31 (95% CI = 0.95-1.79). The adjusted odds ratio was 1.5 (95% CI = 0.9-2.4) comparing those above to below the 40th percentile of exposure.

Epidemiologic Studies on Other Populations

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

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 of an association between PFOA exposure and birth defects is insufficient to conclude that PFOA has a probable link with birth defects among Class Members. The most informative data on PFOA and birth defects comes from the data collected in the C8 Health Project. There was little support for an overall effect of PFOA on risk of birth defects based either on measured serum PFOA or estimated serum PFOA. Results for individual birth defects varied, with some support for an association with congenital heart defects, but not with sufficient strength or clarity to infer a probable link. We believe that the small elevation in risk found for congenital heart defects most likely represents a chance finding. Therefore the Science Panel concludes that there is not a probable link between PFOA (C8) and birth defects.

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