IN THE CIRCUIT COURT OF WOOD COUNTY, WEST VIRGINIA

JACK W. LEACH, et al.,

Plaintiffs,

v.

CIVIL ACTION NO.: 01-C-608
(Judge John D. Beane)

E.I. DU PONT DE NEMOURS AND COMPANY,

Defendant.

STIPULATION REGARDING SCIENCE PANEL STATUS REPORTS

Counsel for plaintiffs and counsel for defendant hereby stipulate and agree that on December 2, 2011, they received the attached Status Report from the Science Panel:

1. Changes in serum PFOA/PFOS and serum lipids between 2005 and 2010 in the Mid-Ohio Valley;
2. PFOA and adult thyroid disease in the mid-Ohio valley;
3. Prospective study of reproductive health outcomes in the mid-Ohio valley.

Stipulated and agreed to on December 2, 2011.

FOR PLAINTIFFS:

Larry A. Winter (WVSB No. 4094)
Winter Johnson & Hill PLLC
United Center, Suite 500
500 Virginia Street, East
P.O. Box 2187
Charleston, WV 25328-2187
(304) 345-7800

FOR DEFENDANT:

Clifford F. Kinney, Jr. (WVSB No. 6220)
Niall A. Paul (WVSB No. 5622)
Spilman, Thomas & Battle, PLLC
300 Kanawha Blvd., East
PO Box 273
Charleston, WV 25321-0273
(304) 340-3874

Status report

Changes in serum PFOA/PFOS and serum lipids between 2005 and 2010 in the Mid-Ohio Valley

The C8 Science Panel: Tony Fletcher, Kyle Steenland, and David Savitz

December 5, 2011

This report summarizes findings relating changes over approximately 4.5 years in PFOA (C8) and changes in lipid measurements in the serum of a sample of adults living in the Mid-Ohio Valley. It also summarizes the findings for another perfluoroalkyl compound, PFOS. High total cholesterol, high LDL cholesterol and low HDL cholesterol are known risk factors for cardiovascular disease.

We have analyzed data from the questionnaires and blood tests collected in the C8 Health Project in 2005-06 and the follow-up study of the Science Panel in which a sample of adults from the 2005-6 survey were invited back and provided blood samples in 2010. On average, the level of both PFOA and PFOS in serum fell by about one half between the two studies, from initial average values (expressed as geometric means) for these participants of 74.8 ng/mL for PFOA and 18.5 ng/mL for PFOS to 30.8 for PFOA and 8.2 for PFOS. The decline in PFOA was due to the ending of contamination of the public drinking water supplies, while PFOS serum levels was falling during the same years at a rate in line with the general decline in the US population. PFOA levels in the US population are approximately 3.9 ng/mL. For 560 adults who did not report taking medicines for lowering cholesterol in either the first or second survey we looked at changes in total cholesterol, LDL, HDL and triglycerides.

Changes in each lipid measurement were analyzed in relation to the change in PFOA and PFOS. In each case measures for main analyses were log-transformed; the log transformation better captures the shape of the relationship between lipids and PFOA in the Science Panel's earlier analyses of the C8 Health Project data. Account was also taken of other potential explanatory factors, such as age, gender, time between measurements and fasting status.

There was little change in lipid levels overall, with mean total cholesterol changing from 196.0 at baseline to 196.3 mg/dL at follow up, and serum LDL cholesterol, from 112.4 mg/dL at baseline to 113.8 mg/dL at follow up. The main finding from modeling the relationship between PFOA and LDL cholesterol was that a decrease in LDL cholesterol was associated with a decrease in PFOA, whereby a 50% drop in PFOA predicted a 3.6% decrease in LDL cholesterol. This was statistically significant with a 95% confidence interval of 1.4% to 5.9%. We also looked at the change in LDL in relation to three equal categories of percent drop in PFOA, comparing the modelled shift in LDL in each group to the group that had changed least (median drop of 36% PFOA). In the category with a median drop of 57%, the LDL fell by a further 1.6% (95% CI -3.4% to 6.4%) and in the category with median drop in PFOA of 72%, the LDL fell by a further 4.5% (95% CI -0.3% to 9.1%).

Similarly, halving PFOS predicted a decrease in LDL cholesterol of 5.1% (95% CI 2.4%-7.9%). It is difficult to distinguish between the effects of PFOA and PFOS as fall in one is highly correlated with a fall in the other, but allowing for the two exposures together, we observed a slightly lower effect of PFOA on LDL levels.

A similar but weaker (not statistically significant) pattern was found for change in total cholesterol. We did not find evidence for associations between changes in HDL cholesterol or triglycerides and changes in PFOA.

Previous analyses of lipids in relation to PFOA in the mid Ohio Valley population have shown significant associations between PFOA (and PFOS) and LDL, total cholesterol and triglycerides in cross sectional analyses. These new results are useful because studying change of outcome in relation to change in exposure is less likely to be readily explained by other causes. Hence these new findings will be helpful for the Science Panel's evaluation of any probable links of C8 to cardiovascular diseases.

Status report

PFOA and adult thyroid disease in the mid-Ohio valley

December 5, 2011

C8 Science Panel: Kyle Steenland, Tony Fletcher, David Savitz

Background: There are a number of reports of studies of PFOA (or C8) in relation to thyroid hormones or thyroid disease among populations with low PFOA exposure levels or among workers with higher exposures, with contradictory results. There is one report of a significant positive association between PFOA levels and increased self-reported thyroid disease among a representative sample of US adults exposed to low background levels of PFOA. The C8 Science Panel has previously reported an association in a cross-sectional study between PFOA and thyroid disease in children based on a small number of cases in the mid-Ohio valley, but no association with thyroid hormones in children. Researchers at W. Virginia University have studied the same mid-Ohio valley adult population studied here, cross-sectionally, and found a positive association between PFOA blood levels and thyroid hormones. Here we report on thyroid disease incidence in a longitudinal (follow-up) study of a large adult population in the mid-Ohio valley exposed to relatively high levels of PFOA.

Methods: We have studied approximately 32,200 mid-Ohio valley residents exposed to PFOA in drinking water. Approximately 28,500 were community residents who participated a community survey during 2005-2006 (the C8 Health Project), while the remaining 3,700 were workers who worked in the DuPont plant (of whom about 1,800 also participated in the C8 Health Project). All subjects were interviewed during 2008-2011 regarding their medical history, including non-malignant thyroid disease. Participants reporting thyroid disease were asked to classify their thyroid disease by type (hypothyroidism, hyperthyroidism, goiter, Grave's disease, Hashimoto's disease, specified other), and to report their age at diagnosis and whether they had received medication for the disease. The analysis was restricted to subjects born during or after 1920, and thyroid disease occurrence was restricted to age 20 or older.

Self-reported thyroid disease was classified as 'functional' thyroid disease (disease potentially affecting thyroid function) after a review of the interview data. 'Functional' thyroid disease

included goiter, thyroiditis, hyperthyroidism, hypothyroidism, or a thyroid function problem of unknown type, but excluded nodules with no noted functional abnormality, cysts, tumors, thyroidectomy without one of the above listed, congenital thyroid anomalies, or thyroid disease without a reported type. People who reported thyroid disease that was not considered 'functional' disease were excluded from the analysis. Any thyroid disease, with data on age at diagnosis, was reported by 3900 subjects (12%), with a median age at diagnosis of 43; 3600 (90% of those reporting disease) were considered to have had 'functional' thyroid disease. Of these 3100 had a reported age at diagnosis in the eligible range, including 2000 with an initial functional diagnosis of hypothyroidism, and 700 with an initial functional diagnosis of hyperthyroidism, and 400 with other conditions or both types of conditions reported. There were about 5 times as many cases among women as men.

In addition, we sought medical records for all people who self-reported thyroid disease with medication, and who gave us consent to seek their records. We were able to obtain medical records for 64% of self-reported 'functional' thyroid disease, of which 91% were confirmed by the medical record. We conducted supplemental analyses limited to the validated cases. Exposure in our study was each person's cumulative blood level of PFOA (yearly estimated levels summed over all years of exposure). Past blood levels were estimated based on air and water emission data from the DuPont plant over time, residential histories from subjects, and a model which predicted how much PFOA entered the drinking water and was then taken into the body. Predicted blood levels based on this exposure model were well correlated with observed measurements of PFOA blood levels among C8 Health Project participants in 2005-2006.

Primary analyses were restricted to 'functional' thyroid disease (hereafter simply called thyroid disease). We analyzed whether subjects with higher cumulative PFOA blood levels were more likely to report developing thyroid disease, compared with subjects with lower cumulative PFOA levels. Analyses controlled for age, year of birth, race, gender, education, smoking, and alcohol consumption. The average time of follow-up (after age 20) until the end of follow-up was 33 years.

Results

There was a positive trend of increasing thyroid disease with increasing cumulative blood levels that was statistically significant for women, and nearly significant for men and women combined. Analyses by categories of cumulative exposure showed that the ratios of rates for thyroid disease, by increasing decile of cumulative exposure (<42, ng/ml-years, 42-93, 94-127, 128-167, 168-238, 238-400, 401-821, 822-2,226, 2,227-6,028, 6,029+) versus the lowest decile (<42), were 1.00 (lowest) 1.04, 1.44, 1.34, 1.31, 1.26, 1.36, 1.33, 1.42, and 1.47 (highest decile) for women, and 1.00 (lowest decile) 0.89, 2.41, 1.35, 1.35, 1.50, 1.52, 1.72, 1.61, and 1.39 (highest decile) for men. These positive trends were statistically significant for women (p=0.03, trend test using the log of cumulative exposure) but not for men; the magnitude of association for men was similar to women, but results were based on smaller numbers of cases. In separating disease types, a significant positive trend was found only for hypothyroidism for women (p=0.05, log cumulative exposure).

Analyses restricted to validated cases of thyroid disease (based on medical records) were consistent with, and slightly stronger than, overall results. For women rate ratios for validated thyroid disease by decile of cumulative blood levels were 1.00 (lowest decile), 1.10, 1.46, 1.37, 1.56, 1.35, 1.65, 1.47, 1.65, and 1.65 (highest decile), which was a significant positive trend (p=0.007). For men they were 1.00 (lowest decile), 1.46, 3.65, 2.40, 2.32, 2.17, 2.39, 2.55, 2.37, and 2.15 (highest decile), a positive trend which was not statistically significant (p=0.75, based on the log of cumulative exposure). Again, a significant positive trend was found for hypothyroidism among women (p=0.03, log cumulative exposure), but not men.

Sub-analyses restricted to new thyroid disease occurring after the C8 Health Project in 2005-2006, i.e., in 2006-2008, again considering cumulative blood levels as the measure of exposure, were generally consistent with results of analyses using the entire follow-up period, although the number of cases was smaller and positive trends were not statistically significant.

Conclusions

Our data show a positive association between cumulative blood levels of PFOA and thyroid disease occurrence, using all cases or restricting to validated cases. Positive trends were

statistically significant only for women. The risk of disease increased above the lowest exposure categories, but then did not increase after that.

Status report

Prospective study of reproductive health outcomes in the mid-Ohio valley

December 5, 2011

C8 Science Panel: Kyle Steenland, Tony Fletcher, David Savitz

Background: PFOA reduces birth weight in mice and causes neonatal death in rats. There are few studies of adverse reproductive outcomes in humans to date, with the exception of a number of cross-sectional studies of birthweight and blood PFOA levels in populations exposed to low levels of PFOA, and the previous reports from the C8 Science Panel. The previous reports of the C8 Science Panel were retrospective analyses (prior to 2005-2006) of birth outcomes in the same highly exposed population in the mid-Ohio valley which is studied here.

Methods: The C8 Science Panel has conducted a prospective study, in which we interviewed approximately 15,000 women from the mid-Ohio valley in 2009-2010 about their reproductive outcomes since 2005. All women had participated in the C8 Health Project in 2005-2006, at which time their serum PFOA levels were measured. C8 Health Project participants were exposed to relatively high levels of PFOA coming from a DuPont chemical plant in the area.

The C8 Science Panel studied miscarriages that occurred after enrollment the C8 Health Project, based on interviews. Exposure was defined as measured blood levels of PFOA in 2005-2006, which were adjusted downward for pregnancies occurring in 2008-2010 given that drinking water in all study areas was filtered by the end of 2007.

In addition, self-reported births from 2005 onward among these women were matched to birth records for 2005-2010 from Ohio and West Virginia. We studied preterm births (<37 weeks), pregnancy-induced hypertension, and low-birth weight based on data from state birth records, in relation to PFOA blood levels.

Analyses were restricted to white women since there were few births among non-white women (less than 5%). Pregnancies were restricted to women ages 14-45, and twin births were excluded. Results were adjusted for mother's age, education, smoking, number of prior births, self-reported diabetes, and body-mass index.

PFOA exposure was considered as a continuous variable, either as serum concentration or log of serum concentration, in order to perform statistical tests of trend in risk with increasing concentration. It was also considered by exposure categories, with exposure groups formed by quintiles. The lowest quintile was <6.9 ng/ml in the blood, and the next four quintiles were 6.9-11.0, 11.1-18.8, 18.9-37.1, and greater than or equal to 37.2 ng/ml.

Results: There were 1808 reported pregnancies in our analysis of miscarriage, of which 321 (18%) ended in miscarriage (after excluding induced abortion, stillbirths, ectopic and tubal pregnancies, and missing data). We were able to match 83% of self-reported births from 2005-2010 with state birth records in Ohio and West Virginia (some births occurred in other states). In analyses restricted to births with state birth records, pregnancy-induced hypertension was indicated on birth records for 7% of births (2% was chronic hypertension which was excluded as the hypertension preceded the pregnancy), while preterm birth (<37 weeks) was indicated for 10% of births, low birth weight (<2500 grams, or <5.5 pounds) was indicated for 5% of births, and low birth weight for full term babies (37+ weeks) was indicated for 2% of births.

There was little evidence supporting an association between blood PFOA levels at time of birth and self-reported **miscarriage,** with no statistically significant positive relationship between miscarriage and blood PFOA considered as a continuous or categorical variable. For the latter analysis, the risk of miscarriage comparing those in the highest PFOA group (80%-100% highest levels) vs. those in the lowest levels (0%-20%) was 1.21, with a 95% confidence interval of 0.78-1.88, indicating the 21% excess risk in this group may well have occurred by chance.

There was little evidence supporting an association between blood PFOA levels at time of birth and **preterm birth (<37 weeks)**, for PFOA considered as a continuous or categorical variable. Considering PFOA as a continuous variable, increased PFOA appeared associated with a lower risk of a preterm birth, although this result was likely due to chance. For the latter analysis, the risk of preterm birth for the highest 20% of exposure vs. the lowest 40% was 0.78, with a 95% confidence interval of 0.47-1.29, indicating the decreased risk associated with highest exposure may well have occurred by chance.

There was some evidence supporting an association between blood PFOA levels at time of birth and **pregnancy-induced hypertension (PIH)**, for PFOA considered as a continuous or

categorical variable. Considering PFOA as a continuous variable, increased PFOA appeared to be associated with an increased risk of PIH. However, trends fell somewhat short of statistical significance, indicating that the association may have been due to chance (we did find a significant positive trend with the log of PFOA serum level, after excluding diabetics from the analysis). The relative risk of PIH by increasing quintiles of PFOA exposure were 2.25 (95% CI 0.99-5.11), 2.89 (95% CI 1.30-6.44), 2.61 (95% 1.16-5.87), and 2.82 (95% CI 1.25-6.37), all compared to the lowest exposure quintile. Thus, all four exposure groups above the lowest one had a 2-3 fold increased risk of PIH, but there was little trend among these four groups.

There was little evidence supporting an association between blood PFOA levels at time of birth and **low birthweight** (<2500 grams, or <5.5 lbs). Considering PFOA as a continuous variable, increased PFOA showed no relation to increased risk of preterm birth. The highest quintile of exposure had a risk of 1.12 vs. the lowest quintile, with a 95% CI of 0.53-2.36, indicating no significant difference in risk between the two groups.

There was a small decrease in birthweight with increasing PFOA as a continuous variable. For each 100 ng/ml increase in the serum there was a decrease of 33 grams in birthweight. Change in birthweight for each increasing quintile of PFOA blood level, compared to the first quintile, were 23, -14, -9, and -9, well within the range of random error. None of the observed associations for birthweight were statistically significant.

Conclusions: There was suggestive evidence that pregnancy-induced hypertension among mothers giving birth in 2005-2010 in Ohio and W. Virginia was associated with increasing levels of PFOA in the blood measured in 2005-2006. However, positive trends fell just short of statistical significance and categorical analyses did not indicate a continually increasing trend in risk as exposure increased. There was little evidence of an association of PFOA blood levels for other adverse reproductive outcomes, including preterm birth and low birthweight.

Pregnancy-induced hypertension is defined as an elevation in blood pressure into the range considered hypertensive (systolic over 140 or diastolic over 90) that begins after the 20th week of pregnancy. Preeclampsia refers to the same elevation in blood pressure when it is accompanied by leakage of protein into the urine. Both types of pregnancy induced hypertension, preeclampsia and hypertension without protein in the urine, are common complications of

pregnancy, and preeclampsia in particular can cause serious problems for the mother and for the fetus. Preeclampsia can cause severe maternal health problems that can only be ended by delivering the fetus. Blood pressure and protein in the urine are routinely monitored during pregnancy in order to detect and manage these conditions.

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JACK W. LEACH, et al.,

Plaintiffs,

v.

Civil Action No. 01-C-608
(Judge John D. Beane)

E. I. DU PONT DE NEMOURS AND COMPANY,

Defendant

CERTIFICATE OF SERVICE

I, Clifford F. Kinney, Jr., do hereby certify that on this 5th day of December, 2011, the foregoing **"STIPULATION REGARDING SCIENCE PANEL STATUS REPORTS"** was served upon counsel of record via Facsimile and via United States First Class Mail, postage prepaid, and addressed as follows:

VIA FACSIMILE & U.S. MAIL
R. Edison Hill, Esq.
Harry G. Deitzler, Esq.
Hill, Peterson, Carper, Bee & Deitzler, P.L.L.C.
NorthGate Business Park
500 Tracy Way
Charleston, WV 25311-1261

VIA FACSIMILE & U.S. MAIL
Robert A. Bilott, Esq.
Gerald J. Rapien, Esq.
Taft Stettinius & Hollister, LLP
1800 First Tower
425 Walnut Street, Suite 1800
Cincinnati, OH 45202-3957

VIA FACSIMILE, U.S. MAIL & E-MAIL
Larry A. Winter, Esq.
Winter Johnson & Hill PLLC
P.O. Box 2187
Charleston, WV 25328

Clifford F. Kinney, Jr. (WVSB No. 6220)