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Probable Link Evaluation for heart disease (including high blood pressure, high cholesterol, coronary artery disease)

Conclusion: On the basis of epidemiological and other data available to the C8 Science Panel, we conclude that

- 1) there **is not** a probable link between C8 (also known as PFOA) and diagnosed and high blood pressure (hypertension)
- 2) there **is** a probable link between exposure to PFOA and diagnosed high cholesterol (hypercholesterolemia)
- 3) There **is not** a probable link between exposure to PFOA and coronary artery disease, including its manifestations as myocardial infarction, angina, and coronary bypass surgery.

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. The Science Panel recognizes that, given the many diseases we are studying, some may appear to be associated with exposure simply through chance, but we have to judge these associations individually and acknowledge the uncertainty inherent in making these judgments.

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 or bias, and plausibility based on experiments in laboratory animals. The relative risk (RR – which can include specific measures such as rate ratios, odds ratios, hazards or standardized mortality ratios) was the primary measure of association that we examined. The RR is a measure 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. The RRs discussed below are generally ‘adjusted’ for demographic variables such as age and gender, so that difference in disease risk between exposed and non-exposed are not the result of age and gender differences. We also examined 95% confidence intervals (95% CI) as a measure of the statistical precision of the RR. The 95% CI shows a range of plausible values taking chance into account. Where there are a range of RRs across exposure groups, statistical measures of trend are conducted to determine if RRs are increasing with increasing exposure. These tests of trend generate p-values, which reflect the statistical chance of getting such a result by chance alone. The lower the p-value the more unlikely it is that the observed trend resulted from chance, with many in the scientific community treating p-values less than 0.05 as being “statistically significant.”

Below we review the evidence and evaluate it with regard to high blood pressure, high cholesterol, and coronary artery disease. The evaluation is focused on epidemiologic studies of humans. Toxicologic evidence is scant for most of these outcomes, while there is relatively abundant human data.

Review of Evidence for High Blood Pressure with Medication

By high blood pressure, we mean above blood pressure sufficiently high to result in a doctor prescribing medication. That often means a diastolic pressure above 80 mmHg and/or a systolic pressure above 140 mmHg, but doctors will take into account a number of factors in determining whether to prescribe medication for high blood pressure. For our analysis in the community/worker cohort study we have focused on the outcome where people have reported receiving both a doctor’s diagnosis of high blood pressure and subsequent treatment for it.

People with blood pressure do not have any adverse symptoms as a direct result of their high blood pressure. Symptoms may never develop, but high blood pressure is an indicator of being at an increased risk of subsequent development of symptomatic disease. This condition is unlike other diseases with symptoms about which we have made probable link judgments. However, high blood pressure is a disease in the sense that it is a medical condition and it is amenable to treatment. Having high blood pressure over many years can lead to an increased risk of atherosclerosis, which in turn can increase the risk of diseases such as coronary heart disease and stroke.

Studies Conducted by Others

Min et al. (2011) studied serum PFOA and blood pressure in 2934 adults in the NHANES population, a representative sample of the non-institutionalized US population. These authors found a statistically significant although small association between increased PFOA in the serum and increased systolic blood pressure observed in the low exposure range typical of the US population (mean 4 ng/ml). These findings are limited by the cross-sectional nature of the study, not indicating whether PFOA levels preceded increases in blood pressure.

Studies Conducted by the Science Panel

Community/Worker Cohort Study

The Science Panel community and worker follow-up study has examined the association between PFOA exposure and incidence of coronary artery disease, high cholesterol, and hypertension in adult community residents and plant workers exposed to high levels of PFOA in the Mid-Ohio Valley.

This cohort combines 28,541 community residents in the Mid-Ohio Valley near the DuPont plant, and 3,713 DuPont workers. We interviewed all members of the cohort, or proxies in case they had died (4%), in 2008-2011, with regard to their medical history. About 90% of the cohort had participated in the 2005/2006 C8 Health Project, at which time their serum PFOA levels were measured.

The principal route of exposure for this population was through drinking water contaminated with PFOA coming from the DuPont plant. Historical serum PFOA estimates for community residents over time were developed by the Science Panel, based on the estimated intake of contaminated drinking water. Estimates of drinking water concentrations, in turn, were based on the amount of PFOA released from the DuPont plant, wind patterns, river flow, groundwater flow and the residential address history provided by study participants (Shin, Vieira et al. 2011a; Shin, Vieira et al. 2011b). Estimates of serum PFOA levels over time for the DuPont workers

incorporated both modelled residential exposure and occupational exposure (Woskie et al. 2012).

Participants in this study were asked whether they had ever been told by a doctor that they had coronary artery disease, high cholesterol, or high blood pressure. For coronary artery disease, the Science Panel sought medical record verification of self-report, and analyses were limited to validated disease. For the last two outcomes, we also asked whether they were currently taking prescription medication as a more reliable indicator of the presence of the disease, and analyses were limited to those who indicated they were taking medication.

The data were analysed to determine whether those with higher cumulated serum PFOA levels over time were more likely to have had coronary artery disease, high blood pressure, or high cholesterol, compared to those with lower cumulated serum levels. The main analysis covered the entire study period, while a sub-analysis was a prospective analysis of the population which was disease free in 2005/2006 at the time of the C8 Health Project.

There were no suggestions of an association between PFOA and hypertension with prescription medication (11,798 cases) in the main analysis (RRs by increasing quintile of cumulative serum level of PFOA, 1.00, 1.10, 1.10, 1.05, and 0.98) (p value for negative trend, $p=0.003$), nor in any sub-analyses by age or gender, or with different measures of PFOA exposure. There was also no association in the prospective analysis (2226 cases), with RRs of 1.00, 1.00, 0.86, 0.87, and 0.81, nor in any prospective supplemental analyses.

Cross Sectional Study of Blood Pressure in 753 Adults

The Science Panel assessed the relationship between PFOA and blood pressure in 753 community participants who provided repeat blood samples in 2010. PFOA, which had already been measured in 2005-6 was measured again in 753 participants in 2010. Blood pressure in 2010 was taken using a manual sphygmomanometer by a trained nurse. First the relationship of blood pressure and PFOA as continuous measures, was investigated and there was some evidence of small positive slope, with systolic BP rising 0.5 units per increasing 100 ng/ml increase in serum PFOA ($p=0.07$). This trend was more pronounced in females, ($p=0.05$). Hypertension, defined as systolic BP >140 mm Hg d/or diastolic >90 mm Hg, was present in 124 people (16.5% of the population in 2010). The risk of hypertension was analysed by quartile of PFOA, using the average of the 2005/6 and 2010 measurements to reflect exposure prior to the blood pressure measurement. Relative risks in models with adjustment for age, sex, BMI and hypertension treatment, varied by quartile: 1.00, 1.54, 1.31, 1.18, but confidence intervals were wide and none of these were close to statistical significance. There was no strong evidence of an overall trend ($p=0.22$ for continuous relationship).

Evaluation of high blood pressure

There is one positive cross-sectional study associating PFOA at low levels with systolic blood pressure. However, there was only weak support for that association in the C8 Science Panel's own cross sectional study, and no support in that study for an association of PFOA with clinically defined hypertension. The substantial cohort study data gathered by the C8 Science Panel do not show an association with diagnosed and treated hypertension. Weighing the evidence together, we conclude there is not a probable link between PFOA and hypertension.

Review of Evidence for High Cholesterol

By high cholesterol we mean above serum concentrations sufficiently high to result in a doctor prescribing medication. That often means total cholesterol above 240 mg/dL, but doctors will take into account the subtypes of cholesterol, including HDL (good cholesterol) and LDL (bad cholesterol) in guiding treatment advice. For our analysis in the community/worker cohort study we have focused on the outcome where people have reported receiving both a doctor's diagnosis of raised cholesterol and subsequent treatment for it.

People with high cholesterol do not have any adverse symptoms as a direct result of their high cholesterol. Symptoms may never develop, but high cholesterol is an indicator of being at an increased risk of subsequent development of symptomatic disease. This condition is unlike other diseases with symptoms about which we have made probable link judgments. However, high cholesterol is a disease in the sense that it is a medical condition and it is amenable to treatment. Having high cholesterol over many years can lead to an increased risk of atherosclerosis and narrowing of the arteries, which in turn can increase the risk of coronary heart disease.

Animal Studies

Animal evidence for rodents dosed at high levels shows a decrease in cholesterol compared to rodents not treated, the opposite of the human findings (Lau et al. 2007). While this evidence is not supportive of the human data (see below), other pathways may be operating between different species at different dose ranges, so the relevance of the animal data to human exposure is uncertain.

Human Studies Conducted by Others

Aside from Science Panel studies discussed below, a positive association of PFOA with cholesterol has been observed in six occupational studies, one study of a highly exposed community, and one general population study (see review, Steenland et al. 2010). Four of these eight studies showed a statistically significant association (at

the $p=0.05$ level). Five of these studies were cross-sectional, making it difficult to determine if PFOA preceded an increase in cholesterol, but three were longitudinal, with PFOA measured before the assessment of cholesterol. The magnitude of effect of PFOA on cholesterol was greatest in the general population low exposure setting, and lowest in the occupational high exposure setting. A more recent occupational study (Olsen et al. 2012) was longitudinal and showed no association between PFOA and lipids, but was limited in time of follow-up (mean 5.5 months) and sample size ($n=179$).

Studies Conducted by the Science Panel

Cross Sectional Studies in the Mid-Ohio Valley

The Science Panel participated in a study with West Virginia University investigators which analysed lipids and PFOA in a cross-sectional study of 12,000 highly exposed children and adolescents in the mid-Ohio valley (Frisbee et al. 2010). There was a steady increase in cholesterol with increasing serum PFOA after adjustment for confounders (age, BMI, fasting, gender, and exercise). All lipid fractions except HDL showed an increasing pattern with increasing exposure.

The Science Panel conducted a study of lipids and PFOA in a cross-sectional study of 46,000 adults in the Mid-Ohio Valley, who were not taking lipid-lowering drugs (Steenland et al. 2010). There was a steady increase in cholesterol with increasing PFOA after adjustment for confounders (age, gender, education, smoking, BMI, alcohol, exercise). All lipid fractions except HDL showed an increasing pattern with increasing exposure. Analysing the people with raised cholesterol (>240 mg/dL) also showed a significantly increased risk of hypercholesterolemia in relation to serum levels of PFOA (RR rose by quartiles of PFOA 1.0, 1.21, 1.33, 1.38, test for linear trend $p<0.0001$).

There are large differences in C8 exposure between the six exposed water districts in the mid-Ohio valley. In a supplementary analysis, the C8 Science Panel also examined whether LDL cholesterol (the form thought to be most harmful) levels in 2005/2006 were associated with average measured PFOA in 2005/2006 by water district. Adjusted for age, sex, BMI, fasting status, smoking, alcohol, exercise, home-grown vegetables, and work at DuPont, there was a significant positive association between LDL and average water district PFOA, although the association was weaker than the association observed using individual measurements.

Longitudinal Study of Lipids in 560 Adults

A sub-group of the adult population was invited by the Science Panel to provide further blood samples in 2010, an average of 4.4 years after the C8 Health Project. On average, the level of PFOA 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 to 30.8 at the second survey. After excluding those who had been taking medications to control lipids, a total of 560 adults aged 20-60 at entry were analysed, to investigate the association between the amount of decrease in PFOA and change in lipids, i.e., to see whether those whose PFOA levels changed the most also had the greatest change in their lipid levels. Specific lipids measurements assessed were total cholesterol, LDL and HDL cholesterols and triglycerides.

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 modelling the relationship between the change in PFOA and change in LDL cholesterol, was that the greater the decrease in PFOA during the study period, the greater the decrease in LDL cholesterol. We found a 50% drop in PFOA predicted a 3.6% decrease in LDL cholesterol. This was statistically significant with a 95% confidence interval of 1.5% to 5.7%. 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.

Community/Worker Cohort Study

The community/worker cohort study was described above. There was some indication of an increase in 'high cholesterol with prescription medication' (9653 cases) with increasing cumulative PFOA exposure in the main analysis, although without any consistent increasing trend, with RRs by increasing quintile of cumulative serum PFOA levels of 1.00, 1.24, 1.17, 1.19 and 1.19 (test for positive trend, $p=0.005$). This trend was more pronounced in males RRs 1.00, 1.32, 1.32, 1.24, 1.28), particularly males in the age group 40-60 ($n=3134$), with RRs of 1.00, 1.38, 1.32, 1.31, 1.44 (p value for positive trend <0.001), although again without showing a steady increase with increasing exposure. Rate ratios using PFOA serum levels estimated for each year instead of cumulative serum levels, were 1.00, 1.07, 1.11, 1.05, 1.20 (p -value for positive trend <0.001). For males 40-60, the corresponding RRs by increasing yearly serum levels were 1.00, 1.16, 1.19, 1.16, 1.38 (p -value for positive trend <0.001). Considering only that exposure which was above background level, or only exposure that occurred after the year of qualification for being in the C8 Health Project, produced slightly lowered RRs.

Prospective analyses (1825 cases) showed a modest decrease in risk of high cholesterol with increasing quintiles of cumulative exposure, with RRs of 1.00, 0.92, 0.95, 0.89, and 0.84 (p value for negative trend 0.04). Restriction to males did not suggest any higher risks, with RRs of 1.00, 1.03, 0.92, 0.93, 0.83 (p -value for negative trend 0.10); restriction to the specific age groups also changed these

results very little. No other supplemental analyses (e.g., measured levels in 2005) changed these results appreciably.

Evaluation of high cholesterol

There is positive evidence that serum PFOA is associated with serum cholesterol in several cross sectional studies and a small number of longitudinal studies, although a few studies do not show any association. There is evidence of both a shift in average cholesterol and increased risk of high cholesterol in relation to PFOA. In C8 Science Panel work in the Mid-Ohio Valley, both analyses of exposure level by water district, and longitudinal follow-up of cholesterol analysed in relation to the degree of drop in PFOA serum levels, suggested that the association of PFOA and cholesterol is due to PFOA rather than confounding factors distorting the PFOA/cholesterol relationship or by cholesterol levels affecting PFOA level.

There was mixed evidence in the overall analysis of the C8 Science Panel's large community/worker cohort study of an increase in self-reported incidence of a medical diagnosis of high cholesterol with reported use of medication, in relation to estimated levels of PFOA in the blood. The effect was particularly evident in males age 40-60, an age at which cholesterol tends to increase. However, there was a slight decrease in diagnosed high cholesterol (with medication) in relation to either the modelled or measured PFOA levels in the prospective analysis of this cohort from 2005/2006 onwards. While it is possible that those who were most likely to have been affected by high PFOA levels had already been diagnosed with high cholesterol by 2005/2006, these results are contradictory.

The evidence is inconsistent, but given the evidence from a variety of different studies with different study designs, including several different studies by the C8 Science Panel in the mid-Ohio valley, we judge that there is a probable link between exposure to PFOA and diagnosed high cholesterol.

Review of Evidence for Coronary Artery Disease

Studies Conducted by Others

Mortality from coronary artery disease has been studied in two occupational cohorts. Workers (n=6207) at a DuPont plant that used PFOA were studied by Leonard et al. (2008) and Sakr et al. (2009). Serum PFOA Levels among all workers at this plant in 2004 averaged 240 ng/ml, with an average of 490 ng/ml among workers in the PFOA areas (Sakr et al., 2007). There was no overall excess of ischemic heart disease mortality at this plant compared to several external populations (Leonard et al. 2008). Sakr et al. (2009) conducted dose-response analyses of these same data using a job-exposure matrix. A number of different analyses for ischemic heart disease mortality using different ways to categorize exposure showed no significant positive

trends, though one analysis showed a suggestion of a positive trend (RRs = 1.0, 1.0, 1.4, and 1.6, p for trend=0.06). A second occupational cohort of workers (n=3922) at the 3M plant in Minnesota was studied by Lundin et al. (2009) included analyses of ischemic heart disease mortality and did not show any excess risk of ischemic heart disease overall or in exposure-response analyses when workers were assigned likely levels of PFOA exposure.

In a cross-sectional general population study with low levels of PFOA, Melzer et al. (2010) found no trend in self-reported history of heart disease (defined as coronary heart disease and/or angina and/or heart attack) in NHANES data, which are representative of the US population. However, these data are limited by the low range of exposure (background levels in the general population), the cross-sectional nature of the data, and the lack of validation of self-reported data.

Shankar et al. also conducted a general population study of 1200 adults with low levels of PFOA in another data set (National Health Examination Survey, 1999-2003) that is representative of the US general population. These authors found significant positive trends in risk for both self-reported cardiovascular disease (defined as coronary heart disease, heart attack or stroke) and for measured ankle blood pressure (peripheral artery disease). These data are again limited by the low range of exposure (background levels in the general population), the cross-sectional nature of the data, and the lack of validation of self-reported data.

Studies Conducted by the Science Panel

Worker Cohort Mortality Study

Steenland and Woskie (2012) studied the mortality of 6027 workers at the DuPont plant in West Virginia, with follow-up through 2008. This was an update of a prior mortality study of this cohort by Leonard et al. (2009), with follow-up through 2002. Steenland and Woskie (2012) used newly developed estimates of exposure for these workers (Woskie et al. 2012), to determine whether higher levels of PFOA from occupational exposure were associated with more ischemic heart disease. Results showed no increase in ischemic heart disease mortality (287 ischemic heart disease deaths) compared to other DuPont workers or the US population. Furthermore there was no suggestion of a trend of increased ischemic heart disease mortality by quartile of increasing cumulative serum PFOA level. These data are somewhat limited by being restricted to coronary artery disease mortality rather than disease incidence.

The Community/Worker Cohort Incidence Study

The community/worker cohort study was described above. There were 2,468 validated cases of coronary artery disease in the main analysis (including coronary

artery disease, myocardial infarction, angina and other indications of coronary artery disease like bypass surgery). The main analysis found no increasing trend of coronary artery disease incidence in relation to PFOA level. Rate ratios by increasing quintile of cumulative serum PFOA were 1.00, 1.26, 1.17, 0.99, 1.07 (test for trend log cumulative exposure, $p=0.08$ (protective)). Other analyses using serum level estimated for each year or using a 5-year lag also showed no trend. Separation of the data by gender also did not show any trends with exposure, and there was no suggestion of differences by age.

Prospective analyses of coronary artery disease (515 validated cases) also showed no evidence of a positive trend (Rate ratios 1.00, 0.75, 0.68, 0.76, 0.71, p -value for trend 0.15), and again supplemental analyses also showed no suggestion of a positive trend.

Further, we note that the probable link for raised cholesterol would not necessarily result in an observed increase in heart disease in the mid-Ohio valley, given that coronary artery disease is associated with many causes, of which high cholesterol is only one, and the risk of high cholesterol related to PFOA was small in magnitude.

Evaluation of coronary artery disease

Despite some acknowledged limitations in the data, given the overall negative pattern in the epidemiologic studies, the C8 Science Panel concludes there is not a probable link between PFOA and coronary artery disease.

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