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Probable Link Evaluation for Chronic Kidney Disease

Conclusion: On the basis of epidemiological and other data available to the C8 Science Panel, we conclude that there is not a probable link between exposure to C8 (also known as PFOA) and chronic kidney disease.

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 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 to 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.”

Review of Evidence for Chronic Kidney Disease

Chronic kidney disease is diagnosed when the kidneys lose their ability to effectively remove wastes and excess water from the body. Chronic kidney disease slowly gets worse over time. In the early stages, there may be no symptoms. The loss of function usually takes months or years to occur. It may be so slow that symptoms do not appear until kidney function is less than one-tenth of normal. The final stage of chronic kidney disease is called end-stage renal disease. At this stage, the kidneys are no longer able to remove enough wastes and excess fluids from the body. The patient needs dialysis or a kidney transplant. Chronic kidney disease and end-stage renal disease are rare conditions. They affect about 1 out of every 500 people in the United States. Diabetes and high blood pressure are the two most influential risk factors.

Mechanistic and Toxicologic Evidence

There are few toxicologic data implicating PFOA as damaging to the kidney. Cui et al. (2009) have shown kidney hypertrophy in PFOA-treated rats. In animals the kidney is exposed to PFOA as it is a major route of excretion and reabsorption of PFOA in the

body. Hence the kidney is a potential target organ. The C8 Science Panel has previously determined there is a probable link between kidney cancer and PFOA

Epidemiologic Studies on Mid-Ohio Valley Populations

Studies Conducted by Others

Shankar et al. (2011) conducted a cross sectional study of kidney function in 4,587 participants in the NHANES population, a probability sample of the US population. These authors defined chronic kidney disease as an estimated glomerular filtration rate of $<60 \text{ ml/minute}/1.73\text{m}^2$; about 6% of the population had chronic kidney disease by this definition, the majority without symptoms. The odds of having chronic kidney disease increased with increasing level of PFOA in the blood, up to an odds ratio of 1.73 (1.01-3.27) in the highest quartile (p for trend = 0.02). This study is limited by the lack of knowledge of whether the PFOA serum levels were increased prior to the development of kidney disease or after it. There is the possibility of reverse causality in which poor filtration rate due to compromised kidney function could result in reduced PFOA excretion and thus lead to higher measured levels of serum PFOA.

Studies Conducted by the Science Panel

1.) Cross Sectional Studies of Kidney Function

The science panel has carried out two cross sectional analyses of chronic kidney disease using blood measurements taken in the C8 Health project in 2005-6. Estimated Glomerular Filtration Rate (eGFR) is a marker of kidney function that can be calculated from serum creatinine levels, taking into account age and sex. The relationship between eGFR and PFOA has been investigated for both children and adults. We found a significant statistical relationship, with higher PFOA associated with reduced eGFR in both children and adults. If this was due to PFOA exposure then it would indicate a risk of reduced eGFR and perhaps an increased risk of chronic kidney disease due to PFOA. However, these analyses were cross sectional and thus the direction of the association is unknown. Specifically, these analyses do not tell us whether higher exposure to PFOA leads to lower kidney function or whether lower kidney function leads to higher levels of PFOA in the blood, which is a plausible pathway. The Mid-Ohio Valley exposure situation offers an opportunity to investigate these different interpretations as there are large differences in exposure between water districts, and if PFOA is affecting kidney function we would find people with higher exposure (based on higher concentrations in drinking water rather than relying only on blood PFOA levels) to show differences in kidney function. Among 50,308 adult participants of the C8 Health

Project we do not find any evidence of a relationship between kidney function and average level of contamination by water district. The results are presented as the %change in eGFR per log unit of PFOA and for individuals serum level the association is significant -0.26%(95%CI -0.36%, -0.17%) but for the PFOA as area averages there is little or no evidence of an association -0.02%(-0.17%,0.13%).

Among 9,660 children in the C8 Health Project, we investigated eGFR in relation to predicted levels of serum PFOA, based on the estimated patterns of concentrations in drinking water and residence history (Shin et al., 2011a,b) and again there was no evidence of an association. Specific results are presented below as the difference in eGFR comparing someone at the 25th percentile versus someone at the 75th percentile of predicted PFOA levels, referred to as the interquartile range or IQR. All regression models were adjusted for potential confounding factors. Specifically, this study found a statistically significant 0.73 ml/minute/1.73m² decrease (95% confidence interval: -1.38, -0.08; p=0.03) in eGFR per IQR increase in measured serum PFOA levels. However, the same analyses in relation to predicted serum PFOA levels showed almost no association (-0.12 ml/minute/1.73m²; 95% confidence interval:-0.81, 0.58; p=0.75). These results suggest that the cross-sectional association apparent between measured blood levels of PFOA and kidney function, is likely to be primarily explained by lower kidney function leading to higher blood levels of PFOA. Thus damaged kidney function appears to directly affect the serum levels of PFOA, leading to higher PFOA concentrations in the blood because of poorer PFOA elimination. This same phenomenon may well explain the positive association reported from the NHANES analysis (Shankar et al., 2011).

2.) Community/Worker Cohort Study

The Science Panel community and worker follow-up study examined the association between PFOA exposure and incidence of diagnosed chronic kidney disease among adult community residents and plant workers.

Community Residents

The Mid-Ohio population, which has been extensively studied by the C8 Science Panel, was formed from those who were living or had lived in any of six PFOA contaminated water districts and participated in a baseline survey called the C8 Health Project in 2005-2006 (Frisbee, Brooks et al. 2009). The principal route of exposure for this population was via drinking water contaminated with PFOA. In 2005/2006, participants in the C8 Health Project (n=69,030) had their PFOA serum levels measured, provided a medical history, and also had a panel of blood measurements, including liver enzymes, cholesterol, uric acid, etc. Most C8 Health Project participants (74% of adults aged 20 or above) consented to participate in follow-up studies conducted by the C8 Science

Panel, of whom 82% were subsequently interviewed by the C8 Science Panel in 2009-2011.

Historical serum PFOA estimates for community residents over time were developed by the Science Panel, based on the estimated intake of contaminated drinking water. These 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). Among those interviewed we were able to estimate historical serum concentrations for 28,541 community residents who had never worked at the DuPont plant.

Workers at the DuPont Plant

In addition, 4,391 past and current workers at the Washington Works plant were interviewed by the Science Panel. This group is a subset of a cohort of 6,027 Washington Works workers studied by the Science Panel to evaluate their patterns of death (see below for results of the mortality study).

An estimate of serum levels over time for workers in different jobs in the plant was developed by the C8 Science Panel (Woskie, Gore et al. 2012). These estimates were combined with estimated serum levels from residential exposure to contaminated drinking water. We were able to estimate combined residential and occupational exposure for 3,713 (84%) of the interviewed workers.

Combined Community and Worker Population

For the study of chronic kidney disease, community residents and workers who were interviewed in 2008-2011, and had complete data on PFOA serum levels over time, were combined to form a final population of 32,254 people for whom we could study the relationship between past PFOA serum levels and disease.

Analysis

The main statistical approach was a multivariate survival analysis, which modelled disease risk as a function of the estimated serum PFOA levels at the time or a cumulative exposure index at that time (as a sum of yearly modelled serum PFOA concentration estimates), controlling for gender, race, education, smoking, BMI, hypertension, hypercholesterolemia, coronary artery disease, congestive heart failure, and alcohol use. For each analysis, overall trend of risk with increasing exposure was assessed and, to explore the pattern of risk with exposure, the risk by increasing

exposure quartiles (compared to the lowest exposure group) was calculated. Because the exposure prediction model is more uncertain at the lower exposure levels, we are especially interested in the presence or absence of trends of risk across the whole range of exposure categories. Additional analyses were done including considering a lag which focuses on exposures estimated prior to 10 years before year of diagnosis, separating out a community-only sub-cohort, and restricting the analysis to the time after they moved into the study area or started working at the plant.

The main analyses considered all cases of chronic kidney disease (see disease definition below) occurring through the study period, with most of them occurring prior to enrolment into the C8 Health Project in 2005-2006. We also conducted prospective analyses among the community cohort members restricted to the time and disease development after the date of enrolment into the C8 Health Project (2005-2006). Numbers for this prospective analysis are thus smaller, but this allowed us to make use of the measured PFOA levels in 2005-6 and assess risk of subsequent disease in the 5 years since among those without a history of reported disease at enrolment.

Results from Community/Worker Cohort Study

Cases were defined as those reporting chronic kidney disease, renal failure, or 'other kidney disease' with a written comment noting renal insufficiency or renal failure. There were 727 such cases, of whom we obtained medical record information for 80%. Of those with medical record information, 75% were confirmed for chronic kidney disease. Analyses were restricted to these medically confirmed cases, and further restricted to those who had complete information on exposure and age (n=397). A second analysis was restricted to the subset of the cases who reported they were currently being treated (n=273). In both case groups, we analyzed separately cases who had no self-report of diabetes (n=187, n=118 for treated cases), under the hypothesis that if PFOA were linked to chronic kidney disease, it might be linked only among cases which had not developed kidney disease subsequent to diabetes.

Relative risks by quartile of increasing exposure in the main analysis (397 cases) were 1.00, 1.34, 1.16, and 1.19 (p-value for trend 0.57). When restricted to non-diabetic cases (n=187), the RRs were 1.00, 0.93, 0.89, and 1.37 (p for trend 0.26). Among the cases who reported treatment for kidney disease (n=273), the RRs were 1.00, 1.58, 1.36, 1.36 (p=.23); for non-diabetic treated cases (n=118) the RRs were 1.00, 1.27, 1.14, and 1.66 (p=.11).

Prospective analyses (212 cases) among cases reporting kidney disease, with or without reported treatment, yielded RRs across increasing exposure quartiles of 1.00,

1.23, 1.00, 1.22 ($p=0.67$); when restricted to non-diabetics (106 cases) these RRs were 1.00, 0.83, 0.74, and 1.10 ($p=0.83$). Prospective analyses restricted to cases reporting treatment for kidney disease ($n=136$) were 1.00, 1.25, 1.07, 1.42 ($p=.38$); when restricted to non-diabetics ($n=64$) the RRs were 1.00, 1.03, 0.89, 1.28 ($p=0.58$).

Results from Follow Up Worker 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) in order to determine higher levels of PFOA from occupational exposure were associated with a higher risk of chronic kidney disease.

There were 13 deaths from chronic kidney disease as an underlying cause in this cohort, and 73 deaths with any mention of chronic kidney disease on the death certificate. In comparing chronic kidney disease in this cohort to other DuPont workers in the same region of the country, the relative risk of chronic kidney disease as an underlying cause of deaths was 3.11 (95% CI: 1.66, 5.32). Furthermore, in exposure-response analyses there was a trend of increased risk with increased estimated cumulative exposure ($p=0.001$). In multiple cause analyses of chronic kidney disease, with a 20-year lag, there was again a significant positive exposure-response trend ($p=0.03$).

Evaluation

There is one report of kidney toxicity in animals. In humans there is one cross-sectional study linking kidney dysfunction with PFOA in the general US population, which suffers from the limitation that one cannot tell if PFOA exposure preceded disease and the strong possibility that kidney dysfunction leads to increased serum PFOA. Two cross sectional studies of kidney dysfunction in relation to PFOA in the Mid-Ohio Valley both showed a significant relationship with measured serum PFOA, but not estimated exposure to PFOA based on their residence. These results suggest that the cross-sectional associations between serum PFOA and kidney function are unlikely to be caused by the PFOA. The Science Panel's worker mortality study provides some evidence of a link between PFOA and kidney disease, but it is based on small numbers and mortality is not the ideal endpoint for studying a disease, which may be not fatal. The Science Panel's community/worker incidence study is based on a large number of medically confirmed incident cases of kidney disease. There is no evidence from the incidence study of an association between kidney disease and PFOA. Overall, based

on the strength of the community/worker cohort study, we conclude that there is not a probable link between kidney disease and PFOA.

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