

October 29, 2012

## **Probable Link Evaluation for Parkinson's 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 Parkinson's 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 Parkinson’s Disease

Parkinson's disease is a disorder of the brain that leads to shaking (tremors) and difficulty with walking, movement, and coordination, and although it is rare it is the one of the most common of the neurodegenerative disorders. Other major neurodegenerative diseases were not evaluated: amyotrophic lateral sclerosis (AML, also known as Lou Gehrig’s disease) is quite rare and Alzheimer’s disease could not be assessed effectively using any of the study designs that were available.

The evidence to evaluate the probable link between PFOA exposure and Parkinson’s disease comes only from the Science Panel studies in the Mid-Ohio Valley, specifically the community and worker follow-up study examining the association between PFOA exposure and incidence of Parkinson’s disease. In addition, the toxicological evidence has been considered.

### Mechanistic and Toxicologic Evidence

There are several reports suggesting potential adverse effects of PFOA on behavior and neurological function in animal models. PFOA (as well as PFOS) was reported to reduce activity in adult mice (Johansson et al., 2008) and alterations were found in brain proteins related to normal brain development (Johansson et al., 2009). The more extensive evidence indicating neurobehavioral effects of PFOS (Lau et al., 2007; Stahl et al., 2011) may have relevance to PFOA as well.

### Epidemiologic Studies on Other Populations

To our knowledge, Parkinson's disease has not been evaluated in other epidemiologic studies.

### Epidemiologic Studies on Mid-Ohio Valley Populations

#### Studies Conducted by the Science Panel

The Science Panel community and worker follow-up study has examined the association between PFOA exposure and incidence of diagnosed Parkinson's 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.

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 diagnosed Parkinson's disease, community residents and workers who were interviewed in 2008-2011 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.

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 [check] gender, race, education, smoking, 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 quintiles (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 worker and community sub-cohorts, 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 through the study period, with most of them occurring prior to enrolment into the C8 Health Project in 2005-6. 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. Numbers 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 reported disease at enrolment.

### Results of Science Panel Studies

The Science Panel community and worker follow up study (described above) examined the association between PFOA exposure and reported incidence of Parkinson's disease among adult community residents and plant workers who were interviewed by the Science Panel.

All subjects were interviewed during 2008-2011 regarding their medical history. Participants reporting Parkinson's disease were asked to provide consent for the Science Panel to review their medical records. . Further they reported the age at diagnosis and whether they had received medication for the disease.

A total of 138 participants reported Parkinson's disease. The Science Panel sought medical records to confirm these cases, and was able to validate the diagnoses for 78 cases (57%). Because the diagnosis can be subtle, and a modest proportion of reported cases could be validated, our principal analysis was restricted to the validated cases.

In the main analysis looking at the cumulative exposure to PFOA, there is no evidence of a trend of increasing risk with increasing exposure, with relative risks of 1.0, 0.8, and 1.0 for the 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> quartiles of exposure compared to the 1<sup>st</sup> quartile (p-value for trend = 0.61). There was no evidence of an association with serum PFOA level in the year of diagnosis either (RRs = 0.8, 1.0, 0.9 for 2<sup>nd</sup> through 4<sup>th</sup> quartiles compared to 1<sup>st</sup> quartile, p-value for trend = 0.66). This lack of association was not affected by excluding exposure in the 10 years prior to disease onset to allow for a latency period between exposure and disease, nor were the results affected by excluding background exposure that occurred prior to residing in the study area or restricting analysis to the community cohort and excluding the workers. Supplemental analyses of all reported cases were similar to those of validated cases in showing no associations between higher exposure and higher risk.

Prospective analyses were limited by a small number of cases (N=36) and applied the same method following the baseline survey to estimate RRs for disease onset after the

time of the C8 Health Project and excluded people who had developed Parkinson's disease before that age. Subject to the small numbers of cases, the relative risks were 1.2, 1.2, and 2.7 across the 2<sup>nd</sup> through 4<sup>th</sup> quartiles relative to the first; the p-value for trend was 0.06. There was little effect of discounting exposure in the 10 years prior to diagnosis, but the elevated risk for the 4<sup>th</sup> quartile was not apparent when the exposure was calibrated to consider measured blood levels (p=0.12) or when the blood levels at the time follow-up started were used as the exposure measure (p=0.26). Given the small number of cases and isolated finding of an elevated result using just one of the approaches to assigning exposure, the support for a positive association from the prospective analyses is limited.

### Evaluation

From our studies of patterns of diagnosed Parkinson's disease there is no evidence of any increased risk of in the retrospective study and limited support for an association in the prospective study. Given the lack of any corroborating evidence from other studies, the Science Panel does not find a probable link between exposure to C8 (also known as PFOA) and Parkinson's disease.

### References

Frisbee, S. J., A. P. Brooks, Jr., et al. (2009). "The C8 health project: design, methods, and participants." Environ Health Perspect **117**(12): 1873-1882.

Johansson N, Eriksson P, Viberg H. Neonatal exposure to PFOS and PFOA in mice results in changes in proteins which are important for neuronal growth and synaptogenesis in the developing brain. Toxicol Sci 2009;108(2):412-8.

Johansson N, Fredriksson A, Eriksson P. Neonatal exposure to perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA) causes neurobehavioural defects in adult mice. Neurotoxicology 2008; 29(1):160-9.

Lau, C., K. Anitole, et al. (2007). "Perfluoroalkyl acids: a review of monitoring and toxicological findings." Toxicol Sci **99**(2): 366-394.

Shin, H. M., V. M. Vieira, et al. (2011). "Environmental Fate and Transport Modeling for Perfluorooctanoic Acid Emitted from the Washington Works Facility in West Virginia." Environ Sci Technol.

Shin, H. M., V. M. Vieira, et al. (2011). "Retrospective exposure estimation and predicted versus observed serum perfluorooctanoic acid concentrations for participants in the C8 Health Project." Environ Health Perspect **119**(12): 1760-1765.

Stahl T, Mattern D, Brunn H. Toxicology of perfluorinated compounds. *Environ Sci Europe* 2011;23:38.

Woskie, S. R., R. Gore, et al. (2012). "Retrospective Exposure Assessment of Perfluorooctanoic Acid Serum Concentrations at a Fluoropolymer Manufacturing Plant." *Ann Occup Hyg.*