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### **Probable Link Evaluation of Autoimmune Disease**

Conclusion: On the basis of epidemiological and other data available to the C8 Science Panel, we conclude that there is a probable link between exposure to C8 (also known as PFOA) and ulcerative colitis, and find no probable link between PFOA and any of the other autoimmune diseases (rheumatoid arthritis, lupus, type1 diabetes, Crohn's disease, or multiple sclerosis).

### **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 ratios or standardized mortality ratios (SMRs)) 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 differences 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.”

#### The Mid-Ohio Valley Population Studied by the Science Panel

##### *Community Residents*

The Mid-Ohio population which has been extensively studied by the C8 Science Panel was formed from those who live or lived in any of six PFOA contaminated water districts and participated in a baseline survey called the C8 Health Project in 2005-2006 (Frisbee 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 thyroid hormones, cholesterol, uric acid, etc. Most C8 Health Project participants (74% of adults age 20 or above) consented to participate in follow-up studies

conducted by the C8 Science Panel, among whom 82% were subsequently interviewed by the C8 Science Panel in 2009-2011, and in 2010, a sample of 755 provided second blood samples.

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 et al., 2011a, b). 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, 4391 past and current workers at the Washington Works plant were interviewed by the Science Panel. This group is a subset of a cohort of 6027 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 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 3713 (84%) of the interviewed workers.

#### *Combined Community and Worker Population*

Community residents and workers were combined to form a final population of 32,254 people for whom we could study the relationship between past PFOA serum levels and subsequent disease. Of these approximately 60% reported some chronic disease; 79% of whom consented for the Science Panel to review their medical records, and of these we were able to review 84%.

#### Background Information on Autoimmune Disease

Autoimmune diseases are diseases in which one's body's immune system attacks oneself. These diseases are generally relatively rare. They are not usually fatal but are incurable diseases which cause serious chronic discomfort and may be disabling. We considered the five most common autoimmune diseases that occur in the Mid-Ohio Valley. It should be noted that some of these diseases, such as inflammatory bowel disease, are likely to involve both auto-immunity and other non-autoimmune processes.

Inflammatory bowel disease (combining ulcerative colitis and Crohn's disease) is a chronic disease characterized by chronic inflammation of the lining of the digestive tract, probably brought on by a response to bacteria which does not subside properly. Diagnosis depends on excluding other diagnoses for inflammation in the digestive tract. The prevalence in the US is not known precisely but appears to be around 5/1000 ([www.cdc.gov/ibd/](http://www.cdc.gov/ibd/)). Ulcerative colitis and Crohn's disease are clinically distinct conditions, with distinguishing clinical, anatomical, and histological findings. However, there is no definitive diagnostic method to distinguish between them. These conditions probably represent a continuum of diseases, with ulcerative colitis and Crohn's disease at opposite ends (Hanauer 2006).

Rheumatoid arthritis is a chronic disease characterized by inflammation of the small joints, typically in the hands and feet, but can have effects on the lung and kidneys. It differs from the more common osteoarthritis which is characterized by loss of cartilage in the joints due to wear and tear. Rheumatoid arthritis is a systemic autoimmune disease which can be diagnosed by x-ray and blood tests; it is more common in women. The prevalence of rheumatoid arthritis is about 10/1000 ([www.cdc.gov/arthritis/basics/rheumatoid.htm](http://www.cdc.gov/arthritis/basics/rheumatoid.htm)).

Type 1 diabetes is a chronic disease. It is also known as juvenile diabetes or insulin-dependent diabetes, because it primarily affects young people and destroys the insulin producing cells of the pancreas. However, Type 1 diabetes is now diagnosed in adults as well. The destruction of the insulin-producing cells is due to a disorder of the immune system. Type 1 diabetes represents about 5% of diabetes, with a prevalence of about 4 per 1000 ([www.cdc.gov/diabetes/](http://www.cdc.gov/diabetes/)). It can be diagnosed via persistently high blood sugar, low insulin levels, and often by the presence of specific antibodies in the blood.

Lupus (systemic lupus erythematosus) is a chronic disease that has a variety of clinical manifestations and can affect joints, skin, brain, lungs, kidneys, and blood vessels. People with lupus may experience fatigue, pain or swelling in joints, skin rashes, and fevers. The disease is rarely, but sometimes, fatal. It is more common in women. The prevalence of lupus is not well known but may be about 1-2/1000 ([www.cdc.gov/arthritis/basics/lupus.htm/](http://www.cdc.gov/arthritis/basics/lupus.htm/)). Diagnosis is difficult and requires a review of medical history and some testing of the immune system.

Multiple sclerosis (MS). Multiple sclerosis is an inflammatory disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of neurological signs and symptoms. Disease onset usually occurs in young adults, and prevalence is around 1/1000

([www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/multiple\\_sclerosis/](http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/multiple_sclerosis/)). Diagnosis is difficult and relies on neuroimaging to view de-myelination and analysis of cerebral spinal fluid for inflammation. MS has a strong familial component, and is more common in women. There is no cure for MS and it is sometimes, although rarely, fatal.

Other autoimmune diseases are rare and we do not have sufficient data to analyze them. Because diagnoses for all the autoimmune disease listed above are difficult, we rely exclusively on cases validated via medical records, which typically are only a minority of self-reported cases.

Evidence linking autoimmune diseases to environmental agents remains limited, but there are some examples (Miller et al. 2012). Further data on the prevalence of autoimmune diseases can be found in Cooper et al. (2009).

#### Toxicological Data

There are no toxicological data specifically regarding PFOA and autoimmune disease.

#### Epidemiologic Studies of PFOA and Autoimmune Diseases by Others

There are no prior studies of PFOA and autoimmune disease.

#### Epidemiologic Studies of Autoimmune Disease Conducted by the Science Panel

Regarding the five autoimmune diseases of interest, the number of self-reported and validated (based on medical record review) cases of inflammatory bowel disease, rheumatoid arthritis, lupus, and multiple sclerosis were 747 reported/245 validated, 2872 reported/348 validated, 183 reported/71 validated, and 150 reported/98 validated, respectively. Rheumatoid arthritis, often confused with osteoarthritis, had the lowest validation rate. The self-reported/validated cases of Type 1 diabetes were 347/160. However, upon more detailed review of the 160 validated cases, we found that only 85 specifically were validated specifically for Type 1 diabetes, while the remained were validated as 'insulin-dependent'. We conducted analyses for both the group of 160 validated cases and the sub-group of 85 validated cases. For all five diseases, the prevalence in the Mid-Ohio Valley conforms broadly with that expected from US population statistics, although data on the expected prevalence of these diseases is imprecise.

Analyses were conducted using the entire experience of the cohort (main analysis), while other analyses were restricted to the experience of the cohort after participating in the C8 Health Project in 2005-2006 (prospective analysis). For some analyses there were insufficient cases to conduct a prospective analysis.

**Inflammatory Bowel Disease (IBD).** Inflammatory bowel disease showed a positive trend of increased risk with increasing cumulative exposure in our main analyses based on 245 cases, which was statistically significant. Results by quartile of cumulative exposure were RRs of 1.00, 1.74 (95% CI: 1.14 to 2.65), 1.80 (1.18-2.73), and 2.20 (1.43-3.39), respectively. These RRs indicate that those in the top 25% of cumulative exposure to PFOA had a risk of inflammatory bowel disease twice that of the lowest 25%. A test of trend in these RRs were statistically significant ( $p=0.001$ ). Prospective analyses based on 44 cases, however, showed no positive trend (RRs of 1.0, 0.69, 0.92, and 1.00, respectively).

Among the validated inflammatory bowel disease cases, we conducted separate analyses for ulcerative colitis (161 cases) and Crohn's disease (96 cases), based on the subject's self-report of the type of inflammatory bowel disease. The positive trend with PFOA exposure was found primarily for ulcerative colitis, for which there was a strong dose-response gradient. RRs by quartile of increasing exposure were 1.0, 1.89 (1.08-3.31), 2.58 (1.52-4.38), and 3.18 (1.84-5.51),  $p$  value test for trend  $<0.0001$ ). The analogous RRs for Crohn's disease were 1.0, 1.36, 1.22, and 1.10 ( $p$  value for trend 0.39). Prospective analyses (from 2005-2006 onwards) were restricted to 30 cases for ulcerative colitis. These analyses also showed a positive although non-statistically significant trend by quartile of increasing exposure, with RRs of 1.0, 1.49, 1.84, 2.18 ( $p$  value for trend 0.28). There were too few cases of Crohn's disease ( $n=14$ ) to do a prospective analysis.

**Rheumatoid Arthritis.** Rheumatoid arthritis showed no positive trend with increasing exposure in the main analysis (RRs by increasing quartile of exposure, 1.0, 1.24, 1.40, 0.99). Prospective analyses based on 56 cases also did not show any positive trend with increasing exposure (RRs of 1.0, 0.81, 2.10, 0.52).

**Systemic Lupus Erythematosus.** Lupus did not show any positive trend with increasing quartile of cumulative exposure in the main analysis (RRs of 1.0, 1.48, 1.00, 0.69). Prospective analyses also showed no positive trend, but were limited due to small numbers of cases ( $n=18$ ).

**Type 1 Diabetes.** Type 1 diabetes did not show any positive trend with increasing exposure in analyses of all 160 validated cases (validated for either “Type 1 diabetes” or “insulin dependent diabetes”), in the main analysis (RRs of 1.0, 0.67, 0.53, and 0.59, by increasing quartiles of cumulative exposure). After restricting to cases specifically validated via medical records for ‘Type 1 diabetes’ (excluding those with ‘insulin dependent diabetes’), analyses also showed no positive trend (RRs of 1.0, 0.83, 0.90, 0.61). For either type of validation, cases were too few for prospective analyses (n=10 and n=3, respectively).

**Multiple Sclerosis (MS).** Multiple sclerosis did not show any consistent positive trend with increasing exposure for the 99 validated cases, in main analysis (RRs for quartiles by increasing cumulative exposure of 1.00, 0.85, 1.56, 1.26, p value for trend 0.22).

### Evaluation

We found a probable link between PFOA and ulcerative colitis based on the strong positive trend in the main analyses, and a similar but slightly weaker trend in prospective analyses based on a small number of cases. Because there is no other relevant epidemiologic research and virtually no toxicology on this topic, we made this judgment based solely on the Science Panel cohort study, which found a very clear and positive dose-response relationship, with a large elevation in risk in the highest exposure group.

We found no probable link between PFOA and any of the other autoimmune diseases (rheumatoid arthritis, lupus, type1 diabetes, Crohn’s disease, or multiple sclerosis).

### References

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