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**Probable Link Evaluation for Non-infectious Lung Disease (Asthma and Chronic Obstructive Pulmonary Disease - COPD)**

*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 asthma or chronic obstructive airways disease (COPD).

*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 (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 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.”

Background information for Asthma and COPD

Asthma and COPD (chronic obstructive pulmonary disease or chronic obstructive airways disease) are both inflammatory lung diseases and although acute exacerbations may be triggered by viral or bacterial infections, the etiology of the diseases is thought to be primarily non-infectious. Asthma is an immune-mediated inflammatory disease. Patients have been found to have higher levels of serum immunoglobulin E (IgE), a surrogate marker for allergen sensitivity (Sears et.al. 1991) and immune responses in young children may affect the development of asthma (Celedon et.al 2002; Prescott, et.al, 2003). Similarly, while the primary risk factor for COPD is smoking, there is increasing evidence that there may be an autoimmune component to the disease which is triggered by smoking (Agusti et. al, 2003). Furthermore, active inflammation persist in the lungs of many patients long after they have stopped smoking (Rutgers, et. al, 2000).

Mouse studies suggest that PFOA may augment total IgE response to environmental allergens (i.e. potentially causing an increase in allergy/asthma type disease) (Fairley, et. al, 2007). Other studies of PFOA exposure on immunity and allergy have shown
immunosuppression and suppression of IgM antibody production (Dewitt, et.al, 2008; Peden-Adams, et. al, 2007).

Cross sectional analyses by the science panel of IgE in relation to PFOA has found an association of decreased IgE with increasing PFOA (Fletcher, et. al, 2011).

**Epidemiologic Studies on Other Populations:**

A prospective cohort study of pregnant women in Japan found cord levels of IgE decreased significantly with high maternal levels of PFOA among female infants, however no relationship was found between maternal PFOA and infant asthma at the age of 18 months. To our knowledge, no data has been collected on adult asthma and PFOA exposure.

Based on the United States National Health and Nutrition Examination Survey (NHANES) data collected between 1999-2000 and 2005-2006, a statistically significant negative association between COPD and PFOA was reported in a cross sectional analysis (RR=0.58, 95%CI: 0.43, 0.76, p=0.0003) (Melzer, et. al, 2010).

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

Community Residents - adults

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 aged 20 years 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., 2011). From 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 also 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 3,713 (84%) of these 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%.

The main statistical approach was a multivariate survival analysis, which modeled disease risk as a function of the cumulative exposure index at that time (as a sum of yearly modeled serum PFOA concentration estimates), controlling for gender, race, education, smoking, and alcohol use.

Analyses were done which either included or excluded the time with no exposure to PFOA contaminated drinking water, before these study participants moved into the study area or started employment in the plant. Further analyses considered applying a lag which focuses on exposures up to 5 or 10 years prior to diagnosis. 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.

The main analyses considered all cases through the study period, with most of them occurring prior to enrollment into the C8 Health Project in 2005-6. We also conducted prospective analyses which applied the same method, but was restricted to community cohort members and the time after the date of enrollment into the C8 Health Project. It also
excluded people who had developed disease before 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 enrollment.

Children

A sample of 878 mothers who provided blood samples during or close to the time of their pregnancy was interviewed concerning diseases among their children, including asthma. Information was gathered from the mothers of a child born between 2004 and 2007 and who participated in the C8 Science Panel Study. The interview was focused on the index child in the household only, including questions about whether they had ever had asthma and whether they had had asthma attacks in the past 12 months. In total, information was gathered on 878 children.

Asthma (ever vs never) was assessed in relation to the serum levels of PFOA in their mothers during pregnancy. Where the serum sample was taken after pregnancy, the levels were adjusted for time trends in this population (Shin, et.al 2011), and also took into account how long they breast-fed the child which can also affect serum levels of PFOA. For recent asthma attacks, the frequency during the 12 months preceding interview was also examined in relation to PFOA.

Results of C8 Science Panel Studies

Asthma in Children

Among the 878 children there were 185 reporting asthma ever and among these there was a pattern of decreasing asthma risk by quartile of in utero PFOA (RRs by quartile 1.0, 1.11, 0.82, 0.55, p value for decreasing trend across quartile of 0.016. For frequency of asthma episodes reported in the previous 12 months among children, there was also evidence of an association with PFOA levels: by the same quartiles of in utero PFOA the RR per episode fell with increasing exposure (1.0, 0.70, 0.55, 0.49, pvalue for trend 0.025).

Chronic Obstructive Pulmonary Disease and Asthma in Adults

A diagnosis of COPD was self-reported by 3,755 participants and a diagnosis of asthma by 2,055 participants in the cohort study. Of these 2959/3755 (79%) COPD cases and 1609/2055 (78%) asthma cases consented to have their medical records accessed. After reviewing medical records, a diagnosis of COPD was validated for 1726/3755 (46%) and a diagnosis of asthma was validated for 1321/2055 (64%). This analysis includes information
on 1,614 cases who had confirmed COPD on medical record review, were born on or after 1920, were age 20 years or older at diagnosis and for whom complete information on education was available.

Survival analysis was used to investigate the relationship between serum PFOA and the risk of developing COPD over time. This was done both retrospectively, with person time at risk beginning at birth (or 1920 for those born before 1920), and prospectively with person time at the time of the C8 Health Project survey. In the overall results including all cases, those with higher cumulative PFOA exposure had a lower risk of being diagnosed with COPD (adjusted relative risk (RR) by quintile of increasing cumulative modeled PFOA: 1.0, 0.8, 1.0, 0.8, 0.8) p value for trend =0.02). The prospective analysis did not show such a clear picture with an overall downward trend in relation to the logged exposure measure (pvalue <0.01) but no clear pattern by quintiles (1.0, 1.3, 1.6, 1.9, 0.8).

For asthma, there was also a tendency of lower risk with increasing exposure, with the pattern of RR by cumulative modeled PFOA quintile in the overall analysis being 1.0, 0.7, 0.7, 0.7, 0.6, with a pvalue for trend of 0.14). There was not suggestion of a trend in either direction in the prospective analysis, (RR by quintiles 1.0, 1.3, 1.1, 1.2, 0.9, pvalue for trend >0.2).

Evaluation

In none of the science panel studies is there evidence of any increased risk of asthma or COPD in relation to measured or estimated PFOA exposure. Several results point to an inverse relationship for one or other of these conditions. Therefore on the basis of epidemiological 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 an increased risk of either asthma or COPD.

References:


Shin HM, Vieira VM, Ryan PB, Steenland K, Bartell SM. Retrospective exposure estimation and predicted versus observed serum perfluorooctanoic acid concentrations for participants in the C8 Health Project. Environmental Health Perspectives 2011;119:1760-5.