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Probable Link Evaluation of Diabetes

Conclusion: On the basis of epidemiologic 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 Type II (adult-onset) diabetes.

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.

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 or standardized mortality ratios (SMRs)) was the primary measure of association that we examined. The RR is a marker 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.

The mid-Ohio 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 in any of six C8 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 C8 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 age 20 or above) consented to participate in follow-up studies conducted by the C8 Science Panel, and 82% of these 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 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 also 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 these workers.

Combined population studied by the Science Panel in its follow-up study of diabetes
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 these consented for the Science Panel to review their medical records, and of these we were able to review 84%.

<u>Toxicologic data</u>

We found no animal (toxicological data) concerning PFOA and diabetes. We found one report (Hines et al. 2009) noting an increase in female mice in mid-life obesity following low-dose in utero exposure to PFOA, which was longer evident among adult mice, and which was not apparent in the high dose group. No differences were seen in glucose-tolerance tests between dose groups.

<u>Epidemiologic studies of diabetes conducted by others</u>

Lundin et al. (2009) studied mortality among 3993 workers at a 3M plant in Minnesota, and found a two-fold excess of diabetes among the 'probably exposed' (42% of the workers) compared to the Minnesota population (RR 2.0, 1.2-3.2, 18 diabetes deaths). There were no

diabetes deaths in the 'definitely exposed' (13% of the workers), and a deficit of diabetes mortality in the 'never-exposed' (RR 0.5, 5 deaths)(45% of the workers). Probably and definitely exposed workers compared to the never-exposed have a relative risk of diabetes death of 3.7 (1.4-10.1, 18 deaths vs. 5 deaths). However, there was little trend of increased risk with increased exposure in a second analysis using years of exposure weighted by a qualitative judgment of exposure intensity. It should be noted that mortality is not the most sensitive way to study diabetes, which is often not fatal. Furthermore, diabetes mortality rates may be influenced by the quality of treatment in addition to the rate of occurrence of the disease.

Leonard et al. (2008) found a deficit of diabetes mortality in comparing 6,027 PFOA-exposed Dupont workers at the Washington Works plant to the US population, with follow-up through 2002. However, these authors found a two-fold increase in diabetes mortality in comparison with other non-exposed Dupont workers (RR 2.0, 1.2-3.0, 22 deaths), a possibly more suitable comparison group because workers tend to be more healthy than the general population.

There are two recent studies with indirect relevance to diabetes. Lin et al. (2011) found no relation between PFOA levels and glucose homeostasis in a cross-sectional study of a sample young Taiwanese (aged 12-30). Halldorsson et al. (2012) conducted a prospective study of offspring of 665 Danish women who had been pregnant 20 years earlier. These authors found higher obesity in 20-year old women (but not men) who had had higher levels of in utero exposure to PFOA. Both these studies involved low general population levels of PFOA. Neither concerned diabetes directly, although obesity and high blood sugar are risk factors for diabetes.

Epidemiologic studies of diabetes conducted by the Science Panel

In a Science Panel study, Steenland and Woskie (2012, in press) conducted a further mortality follow-up through 2008 of the same population of DuPont workers studied by Leonard et al. (2008), extending follow-up by 6 years. They again found no excess of underlying-cause diabetes mortality comparing workers to the US population (RR 1.1), but found the same two-fold excess in comparing them to other DuPont workers in the region (RR 1.9, 1.4-2.6, 38 deaths). The authors estimated occupational PFOA serum levels over time for these workers. Dividing workers into four groups based on their cumulative (summed over time) serum levels, there was no positive trend with increased exposure (RR 1.9, 1.5, 2.3, 1.9 by increasing quartile of cumulative PFOA serum level). Analyses based on any occurrence of diabetes anywhere on the death certificate (not just underlying cause) were also conducted using the US population as the comparison group. These analyses found an overall deficit of diabetes mortality (SMR 0.8), and no trend of increased risk by quartile of cumulative PFOA serum level (also found no trend of increased risk with increased exposure (SMRs of 0.7, 1.1, 0.8, and 0.5 by increasing cumulative PFOA serum level).

In another earlier Science Panel study, McNeil et al. (2009) studied 54,000 adults in the mid-Ohio valley who participated in the C8 Health Project (described above) in 2005-2006. This study was based on data available from 2005/2006 [consistent use of 2005-2006 or 2006/2006], including medical history, serum PFOA and blood glucose. Diabetes prevalence in this population was 8%, about what was expected based on state prevalence data in Ohio and West Virginia. In the principal analysis, data were restricted to long-term residents (>=20 years residence, n=14,000) of the six PFOA-contaminated water districts. Cases were restricted to those with Type II (adult-onset) diabetes, with at least 10 years residence before diabetes occurrence, and whose diabetes was confirmed via medical record review; there were 1055 in this sub-group. Analyzed by decile of PFOA measured in 2005/2006, there was no positive trend for increased diabetes with increased PFOA. In a second analysis of blood glucose

among non-diabetics, there was also no relation between PFOA and glucose after excluding diabetes.

In its most recent and most comprehensive study of diabetes conducted by the Science Panel, the Science Panel studied a population of 32,254 described above. We excluded Type I diabetes (early onset) from this analysis, as this type of diabetes is an auto-immune disease which will be the subject of a separate Science Panel report; type I diabetes represents about 5%-10% of all diabetes. After excluding Type 1 diabetes, 4883 study subjects reported having diabetes during interviews in 2009-2011; of these the Science Panel was able to validate 3899 diagnoses through medical record review. Estimated cumulative PFOA serum levels (summed over time) prior to disease occurrence was the exposure used in the analysis; ten exposure groups were formed with increasing cumulative serum level (decile). In analyses based on cases confirmed through medical records, there was no trend of increased risk with increased cumulative PFOA serum levels, comparing the nine highest PFOA groups with the lowest (RRs of 1.0, 0.9, 1.1, 1.0, 0.9, 1.1, 1.1, 1.0). Analyses discounting the last 10 years of exposure yielded similar results. Analyses based on all self-reported cases also found similar results. All these analyses were adjusted for the major factors which can increase the risk of diabetes, such as age, gender, race, body mass index, family history, and educational level. A sub-group analysis of confirmed new cases occurring after the C8 Health Project in 2005/2006 (n=771) also showed no trends of increased risk with increasing cumulative exposure (RRs of 1.1, 0.7, 1.2, 1.1, 1.1, 1.0, 1.1, 1.2. 1.0). We considered estimated serum level at the time of disease occurrence, instead of cumulative exposure, and this way to measure exposure also did not show any increased risk with increased exposure. We also separated out the workers within out cohort and analyzed them separately; their results were quite similar to the cohort as a whole. In a supplementary analysis of fasting glucose levels in 2005-2006 among those who participated in the C8 Health Project, we found no trend of higher glucose with greater cumulative serum levels of PFOA, after excluding diabetics.

Evaluation

In our opinion, the evidence for an association between PFOA exposure and diabetes (Type II) is insufficient to conclude that PFOA has a probable link to this disease among class members.

While two mortality studies of highly exposed workers found a two-fold excess of diabetes mortality, mortality is not the best way to study diabetes, which is usually not fatal. Mortality also involves effects of treatment as well as disease occurrence. Death certificate coding practices also may differ in different places. A recent study of 540 patients with diabetes who subsequently died found that only 39% had diabetes listed anywhere on their death certificate, and only 10% had diabetes listed as an underlying cause (McEwen et al. 2006). Furthermore, the one worker mortality study with the most thorough evaluation of past exposure to PFOA found no trend of increased risk of death from diabetes with increased exposure (estimated cumulative serum level).

In a comprehensive analysis of diabetes incidence in the mid-Ohio valley, combining community residents and exposed workers, and controlling for other risk factors known to influence diabetes, the Science Panel found no trend of increased risk of diabetes with increasing exposure to PFOA. This study included 4900 cases of diabetes, with an accurate estimate of exposure prior to disease occurrence, and could reasonably be expected to detect an elevated risk of diabetes due to PFOA if such a risk existed. The lack of any indication of increased risk with more exposure in these data does not support a probable link finding.

References

Halldorsson TI, Rytter D, Haug LS, Bech BH, Danielsen I, Becher G, Henriksen TB, Olsen SF. Prenatal Exposure to Perfluorooctanoate and Risk of Overweight at 20 Years of Age: A Prospective Cohort Study. Environ Health Perspect. 2012

Frisbee SJ, Brooks AP, Maher A, Flensborg P, Arnold S, Fletcher T, Steenland K, Shankar A, Knox SS, Pollard C, Halverson JA, Vieira VM, Jin C, Leyden KM, Ducatman A. 2009. The C8 Health Project: Design, Methods, and Participants Environ Health Perspect 2009;117:1873-1882

Hines EP, White SS, Stanko JP, Gibbs-Flournoy EA, Lau C, Fenton SE. Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: Low doses induce elevated serum leptin and insulin, and overweight in mid-life. Mol Cell Endocrinol. 2009 May 25;304(1-2):97-105.

Lin CY, Wen LL, Lin LY, Wen TW, Lien GW, Chen CY, Hsu SH, Chien KL, Sung FC, Chen PC, Su TC. Associations between levels of serum perfluorinated chemicals and adiponectin in a young hypertension cohort in Taiwan. Environ Sci Technol. 2011 Dec 15;45(24):10691-8.

Leonard RC, Kreckmann KH, Sakr CJ, Symons JM. Retrospective cohort mortality study of workers in a polymer production plant including a reference population of regional workers. Ann Epidemiol. 2008 ;18:15-22

Lundin JI, Alexander BH, Olsen GW, Church TR. Ammonium perfluorooctanoate production and occupational mortality. Epidemiology. 2009;20:921-8.

MacNeil J, Steenland K, Shankar A, Ducatman A, A Cross-Sectional Analysis of Type II Diabetes in a Community with Exposure to Perfluorooctanoic acid (PFOA), Environ Res 2009;109:997-1003

McEwen LN, Kim C, Haan M, Ghosh D, Lantz PM, Mangione CM, Safford MM, Marrero D, Thompson TJ, Herman WH; TRIAD Study Group. Diabetes reporting as a cause of death: results from the Translating Research Into Action for Diabetes (TRIAD) study. Diabetes Care. 2006;29:247-53.

Shin HM, Vieira VM, Ryan PB, Detwiler R, Sanders B, Steenland K, Bartell SM. Environmental Fate and Transport Modeling for Perfluorooctanoic Acid Emitted from the Washington Works Facility in West Virginia. Environ Sci Technol 2011 epub ahead of print.

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.

Steenland K and Woskie S, Cohort mortality study of workers exposed to PFOA (perfluorooctanoic acid), in press 2012

Woskie S, Gore R, Steenland K, Retrospective exposure assessment of perfluorooctanoic acid (PFOA) serum concentrations at a fluoropolymer manufacturing plant , in press 2012