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Probable Link Evaluation for Osteoarthritis

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 osteoarthritis.

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 Osteoarthritis

Osteoarthritis is a progressive disorder of the joints caused by gradual loss of cartilage, resulting in joint pain and stiffness. It is quite common as people age and affects to varying degrees a sizable proportion of the population. While there were no prior epidemiologic studies prior to 2011, the hypothesized metabolic effects of PFOA on lipids, thyroid function, immune function, and liver enzymes may affect the risk of osteoarthritis, so that we chose to consider a possible Probable Link with this condition.

The evidence to evaluate the probable link between PFOA exposure and osteoarthritis comes primarily 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 osteoarthritis. There is also a previously conducted analysis of the C8 Health Project participants (Innes et al., 2011) that we considered, along with the toxicological evidence.

Mechanistic and Toxicologic Evidence

The evidence for a possible effect of PFOA on osteoarthritis is indirect, as reviewed by others (Innes et al., 2011). Several of the postulated effects of PFOA on hormones, immune regulation, and liver enzymes may affect the development of osteoarthritis.

Epidemiologic Studies on Other Populations

To our knowledge, osteoarthritis has not been evaluated in epidemiologic studies outside the Mid-Ohio Valley.

Epidemiologic Studies on Mid-Ohio Valley Populations

Studies Conducted by Others

The data collected for the C8 Health Project were analyzed by Innes et al. (2011) to evaluate the association between serum levels of PFOA and prevalence of osteoarthritis. A weak positive association was found, with odds ratios of 1.0 (95% CI = 0.9-1.1), 1.0 (95% CI = 0.9-1.1), and 1.2 (95% CI = 1.1-1.3) across the 2nd through 4th quartiles relative to the first (adjusted for age and body mass index). More extensive adjustment for possible confounding factors increased the magnitude of association, yielding odds ratios of 1.3-1.4 in the uppermost quartile of exposure. In contrast, there was a notable inverse association between PFOS and osteoarthritis using the same methods. This study is limited by being cross-sectional in design, which means that exposure (serum level of PFOA) and arthritis were ascertained at the same time, without being able to determine what level of PFOA preceded the development of arthritis.

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 osteoarthritis 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 osteoarthritis, 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 incidence of reported diagnoses of osteoarthritis 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 osteoarthritis were asked whether a doctor had ever told them they had arthritis, and if yes, whether it was osteoarthritis or rheumatoid arthritis. Further they reported the age at diagnosis and whether they had received medication for the disease. For these analyses we excluded any self-reported rheumatoid arthritis, and any self-reported disease where the subject did not indicate the type of arthritis. (Rheumatoid arthritis was the subject of any earlier Science Panel Probable Link report regarding autoimmune disease.)

A total of 6,641 participants reported osteoarthritis, of whom 2,268 indicated that they were taking medication for the condition. We considered both the results for all reported cases and results restricted to those who said they were using medication, a subset that is more certain to have osteoarthritis and to represent more severe cases of disease.

In the main analysis using the cumulative exposure to PFOA in the blood, we examined the risk of self-reported osteoarthritis across deciles of exposure and found a small

increase (relative risks of 1.1-1.2) in going from the 1st to the 2nd deciles but no increase in risk in the 2nd through 10th deciles, and no overall pattern of increasing risk with increasing exposure ($p=0.13$). Restriction to cases taking medication yielded a slightly greater increase comparing the 2nd through 10th deciles (relative risks of 1.2-1.4), again with no evidence whatsoever of a trend of increasing risk beyond the second decile and again, no overall pattern of increasing risk with increasing exposure dose-response gradient overall ($p=0.73$). Considering exposure as the predicted PFOA serum level at time of disease occurrence (rather than cumulatively), again there was a small increase from the 1st to 2nd decile for all reported cases and there was evidence of increasing risk with increasing exposure ($p=0.01$); this was not found for the subset of cases of osteoarthritis who took medication ($p=0.18$). Imposing a 10-year lag between exposure and disease onset had no discernible effect on the association.

The prospective analysis of 1345 self-reported new cases and 430 self-reported cases with medication yielded less suggestion of a possible association between PFOA and osteoarthritis. Using cumulative exposure, there was no pattern of increasing risk across deciles of exposure using either self-reported or medicated cases. Discounting the previous 10 years of exposure before onset of disease, use of estimated exposure at the time of disease onset, and exclusion of workers had little impact on the results of the prospective analysis.

Evaluation

The evidence from the C8 Science Panel studies of PFOA and osteoarthritis is mixed, with some weak suggestions of an increased risk based on one cross-sectional study of the mid-Ohio Valley population, and a tendency for risk to increase from the lowest to the next level of exposure in the Science Panel cohort study of this same population. However, there is no suggestion of a pattern of increasing risk with increasing exposure in the main cohort analysis and only no suggestion of elevated risk with increasing exposure in the prospective component of the study. Considering the overall set of research findings and the absence of supportive evidence from other studies, we do not find a probable link between exposure to C8 (also known as PFOA) and osteoarthritis

References

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