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Probable Link Evaluation of Stroke

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 stroke.

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 – a general term that includes 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 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 greater than 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 is 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 obtaining 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 on Stroke

This report considers stroke, also referred to as a cerebrovascular accident, which is defined as the sudden death of brain cells resulting from inadequate blood flow. This can result from blockage of an artery supplying blood to the brain or leakage of blood into the brain tissue. Symptoms vary and may include paralysis, loss of speech or memory, and loss of consciousness.

Toxicological Data

We are not aware of any toxicological data that would have relevance to the potential association between PFOA and stroke.

Epidemiologic Studies of Stroke Conducted by Others

Previous work directly exploring the relation between PFOA and stroke is limited to two mortality studies among worker populations (Leonard et al. 2008; Lundin et al. 2009). Leonard et al.

(2008) compared the mortality experience of 6,027 potentially PFOA-exposed DuPont workers at the Washington Works plant with that of 72,882 presumably non-exposed DuPont workers from 7 nearby states (Ohio, Virginia, Kentucky, Indiana, Pennsylvania, Tennessee, and North Carolina) and found that Washington Works employees died from stroke less often than expected compared to out-of-state workers (RR = 0.86; 95% CI, 0.60–1.20; 35 deaths).

Lundin et al. (2009) compared the mortality experience of 3,993 workers at a 3M manufacturing facility in Cottage Grove, Minnesota with that of Minnesotans in general and found an upward trend in cerebrovascular mortality across never exposed, ever probably exposed but never definitely exposed, and definitely exposed workers [RRs of 0.5 (95% CI, 0.3–0.8; 13 deaths), 0.7 (0.4–1.1; 17 deaths), and 1.6 (0.5–3.7; 5 deaths), respectively; no test for trend was presented]. When workers were instead categorized by estimated cumulative exposure (using weights of 1, 30, and 100 for time spent in never, probably, and definitely exposed positions, respectively), an internal comparison of the cohort yielded relative risks of 1.0 (23 deaths), 0.6 (95% CI, 0.2–2.2; 3 deaths), and 2.1 (95% CI, 1.0–4.6; 9 deaths) for the equivalent of <1 year, 1–5 years, and >5 years in a definitely exposed position, respectively. These results offer modest support for a possible association, though the number of stroke deaths is limited.

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 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., 2011a, b). 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.

We studied the mortality of 5,791 workers exposed at a DuPont chemical plant, using a newly developed job-exposure matrix based on serum data for 1308 workers from 1979-2004 (Steenland & Woskie, 2012). These results extend those of Leonard et al. (2008) by continuing follow-up to 2008 (versus 2002 in the previous study) and using a refined and presumably more accurate method of assigning exposure. Comparing PFOA-exposed workers to a referent population of DuPont workers employed outside the area, there was no association between estimated exposure and stroke mortality. From lowest to highest quartile of exposure, relative risks were 0.6 (95% confidence interval 0.9-1.3), 0.8 (0.4-1.4), 1.3 (0.8-2.1), and 0.7 (0.3-1.3). The relative risk comparing exposed workers to other DuPont workers or the US population was <1.0, reflecting modestly decreased risk of stroke mortality.

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 stroke 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.

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, and worker cohort members who were not in the community cohort, followed forward after 2006... This prospective approach 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.

Stroke cases were individuals who self-reported a stroke or transient ischemic attack on at least one of the Battelle surveys and whose self-report was validated through a review of medical records. Both ischemic and hemorrhagic stroke were counted; 1,596 individuals reported a stroke, of which 919 individuals (57.6%) had this self-report validated. After omitting those who were born before 1920, strokes reported before age 20, and cases with missing date of diagnosis or essential covariates, 825 cases were included in the retrospective analysis. In the prospective analysis, with follow-up from the time of enrollment in the C8 Health Project through 2010, 302 cases of stroke were reported and included in the analysis.

In the main analysis, there was no overall relationship between cumulative estimated serum level of PFOA and stroke incidence. Comparing the upper quintiles of exposure to the lowest one, adjusted relative risks were 1.4 (1.1-1.8), 1.4 (1.1-1.7), 1.5 (1.2-1.8), and 1.1 (0.9-1.4) for the 2nd through 5th quintiles. While the 2nd to 4th quintiles were raised relative to the lowest, the exposure predictions are less certain in the very low exposure category, and there was no evidence of a trend overall (p=0.59). Restricting the study to the time after moving to the study area or starting work at the plant, results were similar with small increases in the relative risks

for the 2nd through 4th quintiles, but not in the 5th quintile, and there was no suggestion of a trend of increasing risk with increasing exposure (p= 0.84).

Because recent exposure might be less important than past exposure, the data were also analyzed ignoring the exposures that occurred in the most recent 10 years. With this 10-year lag, comparing the upper quintiles of exposure to the lowest one, the adjusted relative risks were 1.1 (0.8-1.4), 1.0 (0.8-1.4), 1.1 (0.9-1.5), and 1.0 (0.7-1.3), with a p-value for the trend of 0.70. Thus, the modest association in the middle quintiles disappeared when the most recent exposure was discounted.

The results from the prospective analysis were also not reflective of an association. Comparing the upper quintiles of exposure to the lowest one, the adjusted relative risks were 1.1 (0.7-1.6), 1.1 (0.7-1.6), 1.2 (0.8-1.8), and 0.9 (0.6-1.3) for the 2nd through 5th quintiles, with essentially no evidence of a linear trend (p = 0.41). Discounting the most recent 10 years of exposure information had little effect on the results. Restriction to hospitalized cases, presumably the most serious events, did not change the pattern of results summarized above.

Evaluation

The only support for an association between PFOA and stroke comes from the follow-up study of stroke mortality among 3M workers (Lundin et al., 2009), and that evidence is limited. On the other hand, the extended follow-up of DuPont workers (Steenland & Woskie, 2012) showed no indication of an association with stroke mortality. While there were some indications of elevated risk in the middle range of exposure in the main study of C8 Health Project participants, there was no evidence of positive trend of stroke with higher PFOA exposure in the in either the main or prospective C8 Science Panel cohort follow-up study. Based on the totality of the evidence, we conclude that there is not a probable link between PFOA and stroke.

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