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Probable Link Evaluation of Neurodevelopmental Disorders in Children

Conclusion: On the basis of epidemiologic and other data available to the C8 Science Panel, we conclude that there is a not probable link between exposure to C8 (also known as PFOA) and neurodevelopmental disorders in children, including attention deficit disorders and learning disabilities.

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, a general term that includes specific measures such as rate ratios, odds ratios, hazard ratios or standardized mortality ratios) 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 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 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 less likely 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." Measures of neurobehavioral function often are in the form of scales, such as IQ, so that the analyses consider the impact of PFOA exposure on the score. These are expressed as regression coefficients which indicate how much the score is predicted to change as PFOA exposure increases and also include 95% confidence intervals.

Background Information on Neurodevelopmental Disorders

Toxicological Data

Toxicology studies demonstrate the potential for perfluorinated compounds (PFCs) to affect fetal growth, development, viability, and postnatal growth (Lau et al., 2004, 2007; Stahl et al., 2011). There are several reports suggesting potential adverse effects of PFOA on behavior and neurodevelopment in animal models. PFOA (as well as PFOS) was reported to reduce activity in adult mice (Johansson et al., 2008) and alterations were found in brain proteins related to normal brain development (Johansson et al., 2009). The more extensive evidence indicating neurobehavioral effects of PFOS (Lau et al., 2007) may have relevance to PFOA as well.

Epidemiologic Studies of Neurodevelopmental Disorders Conducted by Others

There are few published studies of PFOA and child development. A sample of 1400 women who participated in the Danish National Birth Cohort were assayed for PFOA levels in early pregnancy and a number of different outcomes were evaluated. They first analyzed the relationship of PFOA to Apgar score, a measure of neonatal development, as well as maternally reported developmental milestones (Fei et al., 2008). Higher levels of PFOA were not associated with lower Apgar scores or later attainment of developmental milestones or motor skills in children up to age 18 months of age. In a later follow-up of these children at age 7 years, Fei and Olsen (2011) evaluated behavior and motor function in relation to PFOA exposure. There was no evidence that higher PFOA levels were associated with poorer scores on measures reflective of social, behavioral, and motor development in children. Gump et al. (2011) assessed the association between PFOA and an experimental measure of impaired response inhibition, potentially related to attention deficit disorders. Evaluating 79 children, ages 9-11 years, they found little evidence suggesting adverse effects of PFOA, though other PFCs were related to impaired response inhibition.

One study considered the more clinically relevant outcome of parent-reported Attention Deficit Hyperactivity Disorder (ADHD) in children aged 12-15 years (Hoffman et al., 2010). Using data from the National Health and Nutrition Examination Survey from 1999 – 2000 and 2003 – 2004 (n=571), Hoffman et al. found an association of higher risk with higher levels for each of the PFCs examined, including PFOA. The adjusted odds ratio of ADHD per 1 ug/L increase in PFOA was 1.12 (95% CI 1.01-1.23). While this small association is worthy of note, these results are limited by the cross-sectional nature of the data in which past exposures at the time the disorder was developing are unknown and there is the potential for reverse causality if the behavioral effects of ADHD modify serum levels of PFOA through diet or other exposure determinants.

Epidemiologic Studies of Neurodevelopmental Disorders Conducted by the Science Panel

The C8 Health Project population, which has been extensively studied by the C8 Science Panel, was formed from those who live or lived in any of six C8 contaminated water districts that participated in the 2005-2006 baseline survey (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 older) agreed to participate in follow-up studies conducted by the C8 Science Panel, and 82% of these volunteers 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). 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.

Stein et al. (2011) analyzed cross-sectional data from the C8 Health Project on measured serum PFOA levels in children and the prevalence of parents who reported that a doctor diagnosed their child with ADHD or a teacher told them their child had a learning disorder. No association was found between PFOA and ADHD (with or without medication). Those cases of ADHD being treated with medication were assumed to be more likely to valid. With the possible exception of a small increase in risk in the second quartile and a reduced risk in the fourth quartile for ADHD treated by medication, there was also no association between PFOA and learning disorders.

In a study developed specifically to address the possibility that PFOA may affect risk of neurodevelopmental disorders in children, we recruited and evaluated 320 children ages 6-12 years from the C8 Health Project. We assessed IQ; reading and math skills; language, memory and learning; visual-spatial processing; and attention using standardized instruments for measuring these realms. PFOA exposure was associated with a modest *increase* in IQ (1 – 4 points) comparing the highest to lowest exposure quartiles, although there was not a consistent pattern. Results indicated that children with the highest exposure to PFOA were least likely to have profiles similar to children with ADHD. There were essentially no associations between PFOA and reading or math skills or neuropsychological functioning. These results do not suggest an adverse association between the levels of PFOA exposure experienced by the children in this cohort and their performance on neuropsychological tests. The small positive association between PFOA and IQ or attention is unlikely to be causal.

We also asked the children's parents and teachers to complete standardized assessments of the child's behavior. These data evaluated several different aspects of the child's behavior and personality: 1) executive functions (related to making decisions), 2) attention deficits, and 3) emotional disturbances. Behavior scores for both parents' and teachers' reports provide little overall indication of any relationship between PFOA exposure estimated for the time of the pregnancy, or measured in the child's serum, and behavior.

Evaluation

The amount of research on neurobehavioral health of children is very limited, even with the additional work done by the Science Panel. Based on mixed results from studies conducted by others and largely negative results from the studies conducted by the Science Panel, we conclude that there is a not probable link between PFOA and neurodevelopmental disorders in children, including attention deficit disorders and learning disabilities.

References

Fei C, McLaughlin JK, Lipworth L, Olsen J. Prenatal exposure to perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) and maternally reported developmental milestones in infancy. Environ Health Perspect 2008;116(10):1391-5.

Fei C, Olsen J. Prenatal exposure to perfluorinated chemicals and behavioral or coordination problems at age 7 years. Environ Health Perspect 2011;119(4):573-8.

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

Gump BB, Wu Q, Dumas AK, Kannan K. Perfluorochemical (PFC) exposure in children: associations with impaired response inhibition. Environ Sci Technol 2011;45(19):8151-9.

Hoffman K, Webster TF, Weisskopf MG, Weinberg J, Vieira VM. Exposure to polyfluoroalkyl chemicals and attention deficit/hyperactivity disorder in U.S. children 12-15 years of age. Environ Health Perspect 2010;118(12):1762-7.

Johansson N, Eriksson P, Viberg H. Neonatal exposure to PFOS and PFOA in mice results in changes in proteins which are important for neuronal growth and synaptogenesis in the developing brain. Toxicol Sci 2009;108(2):412-8.

Johansson N, Fredriksson A, Eriksson P. Neonatal exposure to perfluorooctanesulfonate (PFOS) and perfluorooctanoicacid (PFOA) causes neurobehavioural defects in adult mice. Neurotoxicology 2008; 29(1):160-9.

Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutchens A, Seed J. Perfluoroalkyl Acids: A Review of Monitoring and Toxicological Findings. Toxicological Sciences 2007; 99:366-394.

Lau C, Butenhoff JL, Rogers JM. The developmental toxicity of perfluoroalkyl acids and their derivatives. Toxicol Appl Pharmacol 2004;198(2):231-41.

Olsen GW, Butenhoff JL, Zobel LR. Perfluoroalkyl chemicals and human fetal development: an epidemiologic review with clinical and toxicological perspectives. Reprod Toxicol 2009;27(3-4):212-30.

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 2011a, 45:1435-42.

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 2011b;119:1760-5.

Stahl T, Mattern D, Brunn H. Toxicology of perfluorinated compounds. Environ Sci Europe 2011;23.

Stein CR, Savitz DA. Serum perfluorinated compound concentration and attention deficit/hyperactivity disorder in children 5-18 years of age. Environ Health Perspect 2011;119(10):1466-71.