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Probable Link Evaluation of Thyroid disease

Conclusion: On the basis of epidemiological and other data available to the C8 Science Panel, we conclude that there is a probable link between exposure to C8 (also known as PFOA) and thyroid disease.

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 ratios 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."

The Mid-Ohio Population Studied by the Science Panel

The Science Panel conducted three studies of the population of the mid-Ohio valley, one of diagnosed thyroid disease based on interviews in 2009-2001, and two of thyroid hormones among adults and children.

1) The Science Panel community and worker follow-up study has examined the association between PFOA exposure and incidence of diagnosed thyroid disease 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 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 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, 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).

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 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 the interviewed workers.

Combined Community and Worker Population

For the study of diagnosed thyroid disease, community residents and workers who were interviewed in 2009-2011 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.

2) The Science Panel studied thyroid hormones in the population of 50,680 adults who participated in the 2005-2006 C8 Health Panel survey. These subjects had measured PFOA levels and hormones in their serum. Further blood tests for thyroid disease were carried out in a subset of 755 adults who participated during 2010 in the Science Panel Short Term Follow-up Study. In both these studies the Science Panel studied hormones in relation to PFOA among those without clinical disease.

3) The Science Panel studied thyroid hormones in 10,725 children who participated in the 2005-2006 C8 Health Panel survey (Lopez-Espinosa et al., 2012). Data on health and disease are available from questionnaires completed by parents. Among 10,725 children (age: 1-17 years) with data on disease, there were 61 cases of reported thyroid disease. This information was recorded in the interviews with parents in the C8 Health Project. There was no validation of these reports using medical records.

Background Information on Thyroid Hormones and Thyroid Disease

Thyroid hormones play important roles in regulating metabolism, growth, and development. Thyroxine (T4) and triiodothyronine (T3) are two thyroid hormones produced in the thyroid gland. These thyroid hormones can be measured in a free or total form as free T3 (FT3), total T3 (TT3), free T4 (FT4) and total T4 (TT4). The free hormones are a better indicator of thyroid function, but are a more expensive measure so less frequently carried out. However, free and total T4 tend to be correlated to some extent. Sometimes another clinical marker, T3 uptake, can be used with TT4 to derive a measure - Free Thyroxine Index (FTI), which we have demonstrated in a Science Panel study to correlate well with FT4. The pituitary gland produces thyroid-stimulating hormone (TSH) which regulates the production of thyroid hormones, as needed.

There are several major disorders of the thyroid gland, but the most common ones are hypothyroidism and hyperthyroidism. Hypothyroidism is a condition in which the thyroid gland does not make enough thyroid hormone, i.e. the thyroid gland is under-active. Hypothyroidism is characterized by elevated serum TSH levels combined with a low serum FT4. In contrast, if the thyroid is too active, it makes more thyroid hormones than the body needs; this disease is known as hyperthyroidism and is characterized by very low TSH levels and raised FT4. Subclinical (mild and in many cases undiagnosed by the doctor) hypo- and hyperthyroidism are characterized by more moderate elevation or depression of TSH level along with FT4 in the normal range (Surks et al., 2004). For the Science Panel study below we identified subclinical hypothyroidism by either raised TSH (>4.5 uiU/ml) and normal FTI (in the 95% range of values), or more severely, TSH>10 and FTI below this normal range. We identified subclinical hyperthyroidism as either having lowered TSH (<0.45 uiU/ml) and normal FTI (in the 95% range of values), or more severely, TSH<0.1 and FTI above this normal range.

Previous Experimental and Toxicological Data

The medical literature shows two experimental studies in animals dosed with PFOA reported measures of thyroid function (with severe toxicity experienced in the higher dose groups in

the monkey study). A study of male cynomolgus monkeys dosed with PFOA for 6 months found no significant changes in TSH, FT4 or TT4; however, FT3 and TT3 decreased over the study period in the highest dosing group (Butenhoff et al 2007) compared to non-exposed controls. A short term study of rats administered high doses of PFOA for up to 5 days showed falls in FT4, TT4 and TT3 (Martin et al 2007).

Previous Epidemiologic Studies of Adult Thyroid Disease and Thyroid Hormones Conducted by Others

The association between PFOA serum levels and reported diagnosed thyroid diseases has been explored in non-occupational populations with low exposure levels. A cross-sectional analysis of PFOA concentrations and self-reported thyroid disease in the NHANES population (n=3,966) showed an odds ratio (OR) of 2.2 (95% CI: 1.4, 3.7) for thyroid disease in association with the highest versus first and second quartiles of serum PFOA in females (PFOA mean=3.77 ng/mL) (Melzer et al. 2010). The age of diagnosis was not given and there is concern that the serum PFOA levels measured at the time of the survey may not accurately reflect levels prior to diagnosis, as the disease had begun many years ago in some cases. In a small study of pregnant Canadian women with hypothyroxinemia (n=96) higher serum PFOA concentrations were not found when compared to matched controls (n=175) (Chan et al., 2011).

There have been several small studies of thyroid hormone levels in workers with occupational exposure to PFOA. They all involve small populations with much higher serum PFOA levels than the average in the community. In the first, Olsen et al. (1998) assessed TSH in two populations of 111 and 80 workers and found no clear evidence of an association between levels of TSH and PFOA category. In a 2000 study including 518 workers from two chemical plants, PFOA was positively associated with increases in T3. Other measured thyroid hormones, such as TSH, TT4 or FT4 were not associated with PFOA (Olsen et al., 2003). A new cross-sectional analysis of data including a male subsample of the 2000 survey and male workers from another plant (n=506) showed a negative association between PFOA and FT4 and positive with T3, but not with TSH or TT4 (Olsen et al., 2003). In the 2000 studies, Olsen et al. reported that results were not of clinical relevance since most hormone measurements were within reference ranges (Olsen and Zobel, 2007). These occupational studies were consistent in showing no associations with TSH, but inconsistent with regard to associations with PFOA.

One small non-occupational study of a community (n=31) of anglers from New York, found no association for serum levels of PFOA and TSH or FT4 (Bloom et al., 2010). Two studies of adults in the Mid-Ohio Valley have been published previously by other investigators. The

smaller study reported no evidence of an association between PFOA and TSH levels in exposed residents (n=371) living in the most contaminated of the 6 water districts in the C8 Health Project area (Emmett et al., 2006). An analysis of the C8 Health Project data carried out by Knox et al (2010), reported associations between TT4 and PFOA particularly among women (as the Science Panel has found and is summarized below). They reported no evidence of association with TSH. The main difference with respect to the Science Panel study is that they divided the population above and below age 50 and they looked for trends across quintile groupings of PFOA. They did not consider sub-clinical thyroid disease.

Epidemiologic Studies of Thyroid Disease and Function Conducted by the Science Panel

1) The Science Panel community and worker follow up study (described above) examined the association between PFOA exposure and incidence of reported diagnoses of thyroid disease 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, including non-malignant thyroid disease. Participants reporting thyroid disease were asked to classify their thyroid disease by type (hypothyroidism, hyperthyroidism, goiter, Grave's disease, Hashimoto's disease, specified other), and to report their age at diagnosis and whether they had received medication for the disease. The analysis was restricted to those born during or after 1920, and thyroid disease occurrence was restricted to age 20 years or older.

A total of 3,633 participants reported 'functional' thyroid disease (which excludes neoplasms, congenital disease, nodules without functional changes, cysts, and unspecified types); and 3,027 (83%) reported taking medication for their disease. The Science Panel sought medical records to confirm these cases, and was able to validate the diagnoses for 2,109 cases (70%), of which 400 were classified as cases of hyperthyroidism and 1,442 cases of hypothyroidism. There were about six times more cases among women than men. Results summarized here are restricted to validated cases of functional thyroid disease.

The main statistical approach was a multivariate survival analysis, which modeled disease risk as a function of the cumulative exposure index up to date of diagnosis time (sum of yearly modeled serum PFOA concentration estimates), controlling for gender, race, education, smoking, and alcohol use. Analyses were performed which either included or excluded the time before they had exposure to elevated PFOA through contaminated drinking water or starting employment in the plant. For each analysis, we assessed the overall trend of risk with increasing exposure and examined the pattern of risk with exposure by grouping PFOA levels into quintiles.

The main analyses considered all cases of thyroid disease 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 restricted to cohort members who participated in the C8 Health Project in 2005-2006 and followed through 2010-2011. For the prospective analyses, analyses were performed both in relation to the measured levels of PFOA in 2005-2006, and cumulative exposure calibrated to the 2005-2006 measured levels. Numbers in this analysis are thus smaller, but this approach allowed us to assess the association between measured PFOA levels in 2005/6 and the risk of new thyroid disease occurring in the next five years.

In the main overall analysis (both sexes together) there was a slight increasing trend of functional thyroid disease with increasing cumulative PFOA in serum (RRs 1.0, 1.2, 1.2, 1.3, and 1.3 across the categories; p-value for trend=0.09). This trend was more pronounced among women (RRs 1.0, 1.2, 1.3, 1.4, 1.4; p-value for trend=0.03), and absent among men (RRs 1.0, 1.1, 0.8, 1.0, 1.1; p-value trend=0.85). Among women, a positive trend was seen for both hypothyroidism (RRs 1.0, 1.3, 1.3, 1.3, 1.5; p-value for trend=0.08) and hyperthyroidism (RRs 1,0, 1.0, 1.3, 1.5, 1.4; p-value for trend=0.07). Part of this trend was driven by the contrast between a lower reported rate for the time prior to entering the cohort and trend was smaller after restricting the analysis to the experience after moving into the study area or starting employment: the trend for functional thyroid disease in women was much weaker (RRs 1.0, 1.0, 1.1, 1.1, 1.1;, p-value for trend=0.18), as was the trend for hyperthyroidism in women (RRs 1.0, 0.9, 1.2, 1.2, 1.2; p-value for trend=0.17). Prospective analyses (878 cases) applied the same method following the baseline survey to estimate RRs for disease onset after the time of the C8 Health Project and excluded people who had developed thyroid disease before that age. Although there were no clear associations for men and women combined for overall functional thyroid disease, in analyses done separately for each sex and type of thyroid disease using cumulative modeled exposure, some positive trends were seen. For hyperthyroidism in women, the RRs were 1.0, 1.3, 2.1, 1.2, and 1.7 (p-value for trend=0.26), while for men there were too few cases for meaningful analysis (n=16). For hypothyroidism in women, RRs were 1.0, 1.4. 0.9. 0.9, and 0.9 (no trend), while for men for hypothyroidism they were 1.0, 1.1, 1.3, 1.5, and 2.0 (p-value for trend=0.02). Using measured exposure in 2005-2006, the hyperthyroidism RRs for women were 1.0, 2.6, 2.3, 2.5 and 2.7 (p-value for trend=0.10), while for male hyperthyroidism there were too few cases to analyze. For hypothyroidism for women the RRs were 1.0, 0.7, 0.7, 0.7, and 0.8 (p-value for inverse trend p=0.15), while for men RRs were 1.0, 0.8, 2.1, 1.8, and 2.2 (p-value for trend=0.10).

Overall, there was some evidence of a relationship between thyroid disease and estimated PFOA exposure, but results were inconsistent across sex, type of thyroid disease, inclusion

or exclusion of experience before onset of elevated exposure, and in the main versus prospective analysis. Subgroup analyses provided some evidence of an association of PFOA exposure with hyperthyroidism among females in both the main and prospective (post 2005-2006) analyses, and for PFOA and hypothyroidism among males in prospective analyses only.

2) A second Science Panel study examined thyroid hormones in relation to measured PFOA serum levels in adult participants in the C8 Health Project, as described above. This examined both shifts in average hormone levels, and shifts in hormone levels of a sufficient magnitude to indicate early thyroid disease.

In the C8 Health Project, 50,680 adult participants surveyed in 2005-2006 provided serum samples which permitted analysis of 3 thyroid markers (TSH, TT4 and FTI), in relation to measured PFOA. As treatment for diagnosed thyroid disease affects these markers, participants who had reported thyroid disease were excluded from the analyses. After adjusting for age and sex, we assessed the overall trend in the relationship between each outcome and PFOA (each log transformed). Results are presented as the estimated change in each hormone across the interquartile range of exposure which contrasts the 75th to the 25th percentile for PFOA exposure estimate for each sex. The interquartile range of exposure for men was 16 to 85 ng/ml of PFOA in serum and for women 11 to 59 ng/ml.

There was some evidence of a positive but very small association between elevated PFOA and elevated TSH for both sexes (1.2% increase for men (95%CI 0.2 to 2.3) and 1.6% for women (95%CI 0.4 to 2.8) for the interquartile range. Both TT4 and FTI also showed small positive associations with exposure for women (1.2% and 0.4% increases respectively) but for males there was no evidence of an association between PFOA and TT4 or FTI. These small changes are generally within the normal range.

A second outcome studied was subclinical thyroid disease among those who had not reported diagnosed thyroid disease, indicated by reduced TSH suggesting hyperthyroidism, or raised TSH suggesting hypothyroidism. We adjusted for age and sex and present the risk for the interquartile contrast in PFOA serum levels. As expected subclinical hypothyroidism was more common (1184 in men and 1235 in women), than subclinical hyperthyroidism (351 in men and 456 in women) but each provide sufficient numbers for analysis. Previous studies have shown that subclinical hypothyroidism indicates a risk of progressing to overt hypothyroidism (2% to 5% per year progress), whereas this is less the case for subclinical hyperthyroidism, (1% to 2% per year progress to develop overt hyperthyroidism) (Surks et al 1994).

Results of analyses for subclinical disease showed a difference between hypothyroidism and hyperthyroidism. RRs for subclinical hypothyroidism were close to 1 (no association) for both men and women with an RR of 0.96 (95%CI CI 0.88-1.04) for men and 0.97 (95%CI CI 0.89 – 1.05) for women for an interquartile rangecontrast in exposure. For hyperthyroidism, there was a significant inverse relationship with PFOA (reduced risk) with an OR of 0.83 (95%CI 0.71 to 0.92) for men and 0.76 (95%CI 0.66 to 0.88) for women for the interquartile contrasts.

These analyses were repeated using the modeled PFOA serum estimates developed by the Science Panel (as opposed to the measured serum values) to remove the potential for reverse causality in which altered thyroid function might affect serum PFOA levels. We used the modeled values estimated at the time of blood sampling (Shin et al., 2011). Associations in the same direction as those reported above were found, but weaker in magnitude.

Overall therefore these results are consistent with a weak positive association between hormone levels and measured TSH, more apparent for women than for men (as this was found in relation to both modeled and measured PFOA). For subclinical thyroid disease, there was consistent evidence of a reduced risk for hyperthyroidism (for women only) in both modeled and measured PFOA. The increase in average TSH could be consistent with either an increased risk of hypothyroidism or a reduced risk for hyperthyroidism.

In a subsample of this study was recruited for further blood testing by the Science Panel. In 2010, 755 adult volunteers, who had been in the first survey in 2005-2006, provided blood samples and, in addition to the same thyroid hormones measured earlier and repeated (TT4, TSH and T3 uptake), additionally FT4, a better marker of thyroid function.

Three further analyses were undertaken to examine associations between PFOA and thyroid function. We assessed i) the association between FT4 and PFOA, ii) whether thyroid hormone levels changed in parallel with changes in PFOA levels between 2005 and 2010, and iii) the association between PFOA and markers of auto-immune thyroid disease. In this subgroup with repeated measurements, there were 679 without reported thyroid disease. We found no evidence of association between FT4 and PFOA. The relationship between the change in PFOA (averaging a 50% drop) and any change in TSH, TT4 or FTI was investigated for the 679 participants without pre-existing reported thyroid disease. There was little evidence of an association between change in these markers being correlated with change in PFOA, for example, the TSH in women rose by 7% (95%CI -4 to +19%) for a halving of PFOA for women and TSH in men rose by 0% (95%CI -6 to +7%).

In the same population, as a marker of auto-immune thyroid dysfunction, two markers TPO and Tg (human thyroid peroxidase and thyroglobulin) were measured and the correlation with serum levels of PFOA investigated. Adjusting for age and sex, the associations were weak with TPO going up slightly and Tg falling, but both were close to null with wide confidence limits. The regression coefficients log outcome vs log PFOA were 0.033 (95%CI -0.064 to 0.129) for TPO and -0.019 (95%CI -0.098 to + 0.060) for Tg.

These results of further tests in this subgroup did not indicate any relationship between PFOA and FT4, TPO or Tg in cross-sectional analyses, nor changes in TT4, TSH or FTI in longitudinal analyses. The sample size is relatively small compared the large study of hormones in the population of over 50,000 people, described above, but larger than the previously published studies in other populations.

3) The Science Panel study of childhood thyroid disease and function found that reported thyroid disease was positively associated with measured PFOA serum levels in the child (RR=1.44, 95% CI: 1.02 to 2.03) for an interquartile contrast of 13 to 68 ng/mL in serum PFOA measured in 2005-2006. Most of the cases were reported as hypothyroidism (n=39), and the association just for hypothyroidism was similar (RR=1.54, 95% CI: 1.00 to 2.37). These associations are consistent in direction and magnitude for the stricter definition of reported thyroid disease combined with reported use of thyroid medication (RR=1.61, 95% CI: 1.07 to 2.51). Numbers of reported cases of hyperthyroidism were too few to be informative. For most of these children, they were paired with their mothers who provided blood samples as well, from which the maternal serum levels during pregnancy were estimated. The risk of thyroid disease by maternal serum levels during pregnancy showed a similar pattern (RR=1.61, 95% CI:0.96 to2.63). The study also reported cross sectional analyses of thyroid hormones T4 and TSH in relation to measured PFOA in serum, including subclinical hypothyroidism derived from raised TSH levels. No association was found with these clinical markers among those without thyroid disease.

Evaluation

Of the evidence summarized above, by far the largest studies are the Science Panel studies of the Mid-Ohio Valley populations. They provided inconsistent suggestions for an association between PFOA and thyroid function or disease.

In the Science Panel study of validated diagnosed thyroid disease (study 1 above), there was some evidence of a positive relationship between thyroid disease and categories of increasing PFOA exposure. This study provided evidence of an association of PFOA exposure with hyperthyroidism among females in both the main and prospective (post 2005-

2006) analyses, and for PFOA and hypothyroidism among males in prospective analyses only.

The other Science Panel studies (studies 2 and 3 above) had results that were inconsistent with study 1. In the cross sectional analysis of hormones there was a modest increase in TSH (and one would expect on average a fall in TSH with hyperthyroidism) and the analysis of subclinical disease found a clear inverse relationship between subclinical hyperthyroidism and PFOA in women, and to a lesser extent in men. The cross-sectional analysis of subclinical hypothyroidism showed no association.

In children (mainly girls) there was a positive association based on (non-validated) reported thyroid disease and PFOA exposure either measured at the time of interview (post diagnosis) or estimated in utero.

We carefully considered how much weight to put on the different studies and analytic approaches, particularly whether it is appropriate to add up the pieces of supportive evidence despite their coming from different subsets of individuals or different indicators of thyroid disease. While each finding in isolation was not compelling, plausibly a result of chance or other errors, the presence of some independent pieces of evidence indicative of an association was not easily dismissed, despite a lack of coherence among them. Among the positive pieces, the strongest was the evidence of increased occurrence of medically validated thyroid disease (hyperthyroidism in women, hypothyroidism in men) with increasing measured PFOA exposure (2005-2006) in the prospective analyses (2005-2010). After taking into account the available evidence in its totality, despite inconsistencies in the evidence, the Panel concluded that there was evidence of a probable link between C8 and thyroid disease.

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