April 15, 2012

Probable Link Evaluation of Cancer

Conclusion: On the basis of epidemiologic 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 testicular cancer and kidney cancer but not any of the other cancers that were considered.

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. 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,

ED_001670_00006710-00001

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

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 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 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 estimate 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 for mortality by the Science Panel.

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 so that 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 cancers
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 59% reported some chronic disease triggering a request to review their medical records; 77% of these consented for the Science Panel to review their medical records, and of these we were able to review 92%. Medical record review included linkage to Ohio and W. Virginia cancer registries. In the end we reviewed the medical record for 71% of those reporting chronic disease.

Toxicologic data

Toxicologic data shows that PFOA causes liver tumors, testicular tumors, and pancreatic tumors in rodents. There was some animal data suggesting it might also induce breast tumors (EPA 2005), but a re-review of the pathology has shown no effect on breast tumors (Hardisty et al. 2010). In animals, PFOA is a strong peroxisome proliferator in the liver. Peroxisome proliferation and the resulting

ED_001670_00006710-00002

activation of a nuclear receptor (PPAR alpha) has been proposed as a mechanism for tumor induction (Lau et al. 2007). However, it is not known if this mechanism is relevant to humans, where peroxisome proliferation is generally less apparent (Dewitt et al. 2008). While animal carcinogen data is suggestive, "site concordance for carcinogenicity between rats and mice, and between rodent species and humans, is generally not sufficiently consistent to allow reliable prediction of potential site(s) of carcinogenesis in humans from bioassay data in rodents" (Rice J, Human Relevance of Animal Neoplasms: Site Concordance between Humans and Experimental Animals for Cancers Caused by Exposures to Chemical Carcinogens review prepared for the International Programme on Chemical Safety, WHO, Geneva, 2005).

Epidemiologic studies of cancer conducted by others

Epidemiologic studies outside of the Science Panel's research are limited to two U.S. occupational cohorts (retrospective cohort studies), one follow-up study of the general population in Denmark, and one small case-control study of breast cancer.

In a mortality study at the DuPont Washington Works plant, Leonard et al. (2008) found no statistically significant ($p<0.05$) excesses for any cancers reported. However, numbers of specific cancers were small (8 liver, 11 pancreas, 12 kidney, 3 thyroid, 1 testis, 2 breast). A suggestive elevation in risk was found for kidney cancer (RR=1.8, 95% CI 0.9-3.2, 12 deaths) when comparing workers with other DuPont workers in the region. The kidney cancer RR was slightly lower compared to the US population (RR 1.5, 0.8-2.6), than when the comparison was to other workers. Liver cancer showed also some excess compared to other DuPont workers (RR = 1.6, 0.6-2.8).

Lundin et al. (2009) similarly found no excesses of any cancer deaths comparing 3M workers to the Minnesota population, although results were limited due to the small number of cancers among definitely or probably exposed workers (n=138). Workers were classified into no, low, moderate, and high exposure according to expert opinion by industrial hygienists, without defining exact levels of exposures for these categories. Internal analyses comparing low exposed workers to those with moderate or high exposure to PFOA were presented for only three cancers (liver, prostate, and pancreas). Among these, a trend of increased risk for higher exposure was seen for prostate based on small numbers (non-exposed, probably exposed, definitely exposed) (RRs of 1.0, 3.0 (0.9-9.7), and 6.6 (1.1-37.7), based on 4, 10, and 2 cases respectively.

A general population study in Denmark followed 55,053 adults aged 50-65 from enrollment in 1993-1997 until 2006 through linkage with the Danish cancer registry (Eriksen et al., 2009). PFOA was measured in the serum of all cases and a sample of non-cases. There were 713, 332, 128, and 67 incident cases of prostate, bladder, pancreatic, and liver cancers found in this period. Dividing the population into quartiles of serum PFOA (based on the cases), no significant ($P<0.05$) linear trends by quartile were seen for any of the four cancers studied, although modest positive associations with prostate and pancreas cancers were reported (RR for highest quartile vs. lowest quartile, 1.18 (0.84-1.65) for prostate cancer, and 1.55 (0.85-2.80) for pancreatic cancer). P-values for linear trends were of 0.06 and 0.18 for prostate cancer and pancreatic cancer. Trends were absent or negative for bladder and liver cancer. This study, while much larger than the occupational studies cited above had much lower ranges of PFOA exposure (mean 6-7 ng/ml), typical of a general population.

Finally a small case-control study of 31 breast cancer cases and perfluorinated compounds (PFCs) measured in the serum was conducted by Bonefeld-Jorgensen et al. (2011). These authors found no

evidence of a relationship between breast cancer and PFOA, although there were some positive findings for other PFCs.

Epidemiologic studies of cancer conducted by the Science Panel

The Science Panel has conducted several studies of cancers among residents of the Mid-Ohio Valley, and among workers at the Washington works plant. In each study, where numbers permit, the Science Panel has assessed the risk in relation to PFOA exposure for specific cancer sites. While all cancer sites were considered, special attention was devoted to the cancer sites of concern based on animal or epidemiologic studies: pancreas, liver, testis, prostate, breast, and kidney.

1) In a Science Panel study, Steenland and Woskie (2012, in press) conducted a mortality follow-up through 2008 of the same population of DuPont workers studied by Leonard et al. (2008), extending follow-up by 6 years. No new cases of kidney cancer had occurred since the Leonard et al. study; the RR for kidney cancer was less elevated than reported by Leonard (RR=1.28 (0.66-2.24), when comparing Washington Works workers with other DuPont workers. The authors estimated occupational PFOA serum levels over time for the Washington Works workers. Dividing workers into four groups based on their cumulative (summed over time) estimated serum levels, there was a positive trend for kidney cancer with increasing exposure (RRs 1.07, 1.37, 0.0, and 2.66, p-value test for trend 0.02) across quartiles of cumulative PFOA serum level. Few cancer deaths occurred at other sites of interest (liver, pancreas, breast), so that this study was not informative for those sites.

2) A recent Science Panel study of geographical patterns of cancer in the Mid-Ohio Valley compared cancer rates in exposed vs. unexposed areas of Ohio and West Virginia (Vieira et al. 2012). Analyses included all incident cancer cases diagnosed from 1996-2005 in five Ohio counties and from 1996-2005 in eight West Virginia counties. Ohio addresses at time of diagnosis were geocoded and prior Science Panel work (Shin et al. 2011a, b) was used to estimate PFOA serum levels for residents at that location and time.

Exposure assessments for West Virginia cancers were less detailed due to restrictions in data use. As a result analyses using West Virginia data together with the Ohio data were limited to analyses of exposed water districts, ranked by level of exposure, in relation to non-exposed areas. Analyses restricted to Ohio used more detailed exposure rankings, based on either estimated exposure at residence.

Two different analytical approaches were used, one modeling incidence rates across exposure groups based on small geographical areas, or alternatively, based on water districts; the other was a case-control approach which estimated exposure-related risk comparing each cancer to all other cancers acting as a control. This second method had the advantage that the risks could be adjusted for other information available for the cases (such as smoking and socio-economic indicators).

Using these two different types of exposure estimation, and two different analytic approaches, three sets of analyses were conducted: 1) in Ohio using an individual-level (case-control) approach with estimated serum levels based on residence (categorized into very high, high, medium, low, no exposure) in the time period before cancer occurrence, or 2) in Ohio comparing rates of cancer in different small geographical areas, again divided into very high, high, medium, low, and no exposure categories by estimated serum levels for each area, and 3) combining Ohio and West Virginia data and analyzing risk by water district of residence, in order of descending exposure level: Little Hocking,

ED_001670_00006710-00004

Lubeck, Belpre, Tupper Plains, Pomeroy, and Mason. For analyses (3) individual-level case-control analyses were conducted.

The most notable finding across all four types of analyses was that of an elevated risk for testicular cancer in higher exposure areas, although the findings were based on small numbers since testicular cancer is rare. The RR for testicular cancer in the highest exposure category in the Ohio analyses (6 highest exposed cases) was 3.0 (0.9-9.4) (individual-level approach), and 6.7 (2.3-19.7) (geographical area-level approach), compared to non-exposed subjects. Tests for trend of increased RR with increasing exposure gave low p-values, with p=0.08 using the individual-level and p=0.0003 using the geographical area-level approach. Comparing exposed water districts to non-exposed areas, the RR for testicular cancer in Little Hocking (most highly exposed water district, 8 cases) was 5.9 (2.2-15.7)(individual-level approach). The p-value for test for trend of increased RR with increasing exposure was p=0.002.

There were also some inconsistent trends of increased risk in kidney cancer in higher exposure categories across different types of analyses. In Ohio, the RRs for kidney cancer based on estimated individual exposure (individual-level approach) were 2.0, 2.0, 1.2, 0.8, 1.0 for very high, high, medium, low and no exposure categories. The Ohio RRs for kidney cancer using the area-level approach for the same categories showed a less consistent trend (1.2, 2.6, 1.0, 1.2, 1.0 respectively). P-values for these trends of increasing RRs by increasing exposure, were p=0.01 using the individual-level approach, and p=0.32 for the geographical area-level approach. Using water district as the exposure variable, and including both Ohio and West Virginia, the kidney RRs for Little Hocking, Lubeck, Belpre, Tuppers Plains, Pomeroy, Mason, and non-exposed areas respectively for the geographical area-level approach, and were 1.6, 0.8, 1.3, 2.1, 0 (no cases), and 1.0 for the individual-level approach. Evidence of a trend was reasonably strong (p=0.07).

For prostate cancer, there was an increase in the highest water district (RR = 1.4, 0.9-2.1) (test for trend across water district p=0.27) using the individual-level approach, and also an elevated RR for highest exposure category using the individual-level approach (RR = 1.7, 1.0-2.7) (test for trend across exposure groups p=0.11). However the RR using the geographical area-level approach was not elevated the for highest exposure category (RR=1.0, 0.6-1.7)(test for trend p=0.97).

There were no suggestions of positive findings for other cancers of interest, including liver, pancreas, or breast.

This study has many different types of analyses. Table 1 below attempts to provide an overview of the four types of analyses used for three cancers with the most positive findings. The table shows p-values for trend tests evaluating a trend of increased risk of cancer with increasing PFOA exposure, with lower p-values indicating a stronger trend. Of interest is the degree to which the different types of analyses are consistent for a given cancer.

Table 1. P-values for trends* for increasing cancer risk by increasing PFOA exposure based on either water districts or residence

	Water district individual-level (Ohio and WV)	Residential analysis, individual-level (Ohio)	Residential analysis, geographical area-level (Ohio)
Testicular	0.002	0.08	0.0003

ED_001670_00006710-00005

Kidney	0.07	0.01	0.33
Prostate	0.27	0.11	0.97

*lower p-value indicates stronger trend, P<0.05 conventionally considered unlikely to have occurred by chance. All trends represent increasing risk with increasing exposure except where indicated. Trend tests in column 1 for water district analyses are based on estimated average water district serum levels in 2005, and may change slightly in the future when the Science Panel calculates water district average serum levels from 1995-2005.

3) A third recent Science Panel study has examined associations between recently diagnosed prevalent cancers of the bladder, breast, cervix, colon, liver, kidney, melanoma, ovaries, pancreas, prostate, testes, thyroid and uterus reported by adult participants in the C8 Health project, in relation to measured PFOA serum concentrations (Fitz-Simon et al. 2012). This study was based on 49,082 adult participants, who had participated in the C8 Health Project and were aged over 25 in 2006. We determined primary cancer cases that were first diagnosed during the ten years prior to the C8 Health Project by self-report from questionnaire, and verification by checking against medical records, which were available for 61% of the cases identified by self-report. Only recent cancers were included as serum measurements are less relevant to exposures going back further in time. For three of the cancers we studied, the numbers of cases (recent and verified) were too small for analysis (pancreas, liver and testes). For the remaining cancers, there was little or no evidence of positive associations between serum PFOA measured in 2005/2006, for any of the cancers studied except for prostate cancer, where a risk increased with higher exposure was evident. By quartile of increasing serum PFOA, the relative risks for prostate cancer in groups with higher serum levels were all raised compared to the lowest quartile (RRs with 95% CIs: 1.0, 1.5().9-2.4), 1.7(1.1-2.7), 1.7 (1.1-2.7) respectively). This rose with the log of PFOA, so the risk of verified prostate cancer increased by 1.3 per ten-fold increase in measured PFOA (95% confidence interval 1.0, 1.6).

4) In the comprehensive study of cancer incidence (hereafter referred to as the **cohort study**) among participants in the C8 Health Project, a population of 32,254 described above (adults age 20 and above) was followed up for cancer occurrence. 3636 of these study subjects reported having had cancer across 21 different sites at the time of their interviews in 2009-2011. Of these, the Science Panel was able to validate 2420 (70%) diagnoses of primary cancer through medical record review and cancer registry data. Some cases were not validated because we did not obtain consent to review medical records, while others were not validated because medical records failed to confirm the self-reported diagnosis. For several sites, including lung cancer, with lower rates of validation, the reported cancer was a secondary cancer due to metastases instead of the primary cancer site. We also found non-melanoma skin cancer had been mis-reported as melanoma, or an abnormal screening test (Pap smear) had been reported as a cancer in the case of cervix. We did not consider non-melanoma skin cancer, nor several less frequent cancers sites without sufficient numbers for analysis (e.g., appendix, gall bladder, bone after excluding metastases, myeloma).

We conducted probable link evaluations for the following 21 cancer sites with the number of self-reported cancers and the number validated based on medical records indicated in that order for each site: bladder (115, 111), brain (33, 23), breast (608, 581), cervical (383, 22), colorectal (311, 276), esophagus (21, 15), kidney (124, 113), leukemia (79, 69), liver (18, 10), lung (164, 142), lymphoma (164, 142), melanoma (519, 245), oral (including larynx/pharynx) (31/18), ovarian (87, 43), pancreatic

ED_001670_00006710-00006

(35,26), prostate (515, 458), soft tissue (25,17), stomach (29, 12), testicular (32, 19), thyroid (98, 87), uterine (225, 105).

We investigated whether cumulative exposure to PFOA was associated with increased rates of cancer in our population. We added together annual estimated PFOA serum levels over time to create a variable for cumulative serum levels, and then determined the cancer incidence in groups with different cumulative serum levels of PFOA. We analyzed both all self-reported cancers and isolated the subset of cancers that we were able to confirm with medical records. We focused on validated cases, unless self-reported results differed substantially from the validated. In some cases (melanoma, uterine, ovarian, cervical, the majority of self-reports were not validated; these are sites which are known to be subject to low accuracy for self-reporting). We then did the same analyses for cumulative serum levels up to 10 years before people got cancer (a 10-year 'lag'), under the assumption that the last 10 years exposure were less likely to contribute to the cancer.

In all the above analyses, we divided the population into four groups (quartiles of each site) based on the cumulative PFOA exposure of the cancer cases. We considered whether the risk of quartiles 2, 3, and 4 were increased compared to the lowest quartile of exposure by calculating relative risks for each quartile versus the lowest quartile. We also calculated 3 statistical tests of trend, which were tests of whether risk increased with 1) greater cumulative exposure or 2) greater log of cumulative exposure, or whether 3) the risk across quartiles increased in a linear fashion.

In addition to these analyses we conducted analyses of new cancers restricted to those that occurred between 2005/2006 when the cohort was enrolled and our interviews in 2009/2011. These 'prospective analyses' largely avoid the problem in the overall analysis in that people who got cancer earlier may have died and not survived until 2005/2006 when the cohort was enrolled. In order for cancer cases that occurred before 2005/2006 to be included in the study, they had to develop the cancer at an earlier time and survive to participate in the C8 Health Project; this excludes those who developed cancer prior to that time and died. Hence in our overall analyses of the cohort we are missing cancer deaths which occurred before 2005, which could cause biased results. Prospective analyses avoid such problems but suffer from the limitation of having far fewer cancer cases than the overall analysis, making them less precise.

Finally, we also conducted a comparison of the rate of cancer occurrence in our Mid-Ohio Valley population compared to the cancer rates from 10 states or metropolitan areas chosen to represent the US population (called the Surveillance, Epidemiology, and End Results (SEER) data base, produced by the National Cancer Institute). Here we used all self-reported cancers plus any additional cancers confirmed by cancer registry but not self-reported, to attempt to capture the greatest number of cancers in our study population when comparing them to cancer rates which are likely to have captured all cases in the underlying population. Again, subjects were divided into quartiles of PFOA exposure, with cutpoints determined by the quartiles of the cases.

In summary, in the cohort study, we have assessed 21 different categories of cancer, and have sought evidence of dose-response (increased cancer risk with increasing exposure) in several different measure of exposure, with and without a lags to exclude recent exposure. Thus we may expect some apparent positive and negative associations through chance alone so it is important to examine not just isolated findings but patterns within and across the sets of results.

ED_001670_00006710-00007

Out of all the sites considered, only four showed any indications of positive trends with increasing exposure, as measured by cumulative serum levels. Those not mentioned below were not found to have a suggestion of an association with PFOA exposure.

a) Testicular cancer. Among medically confirmed cases, testicular cancer showed a positive trend of increasing RR with increasing cumulative exposure in internal analysis comparing the more highly exposed to the low-exposed. The RRs by quartile of increasing exposure are seen in Figures 1 and 2, for analyses with no lag and with a 10 year lag. For the no lag analyses, the quartile RRs were 1.0, 1.8, 2.2, 2.7 (test for trend with log cumulative exposure 0.04, linear test of quartile points, p=.12). The RRs with a 10 year lag were 1.0, 1.2, 1.7, and 3.0 (test for trend with log cumulative exposure 0.07, linear test of quartile points, p=.04). There were no confirmed testicular cancer cases since 2005/2006, so we could not conduct a prospective analysis of this cancer.

   Comparison to the US population for self-reported cases (minus four cases which were found to be invalid by medical records, leaving 28 for analysis) showed an overall deficit of testicular cancer (RR = 0.8, for both lagged and unlagged analyses), with some evidence of a trend of higher RR with higher exposure in lagged analyses (RRs 0.4, 1.0, 0.8, 1.3, test for trend p=0.07).

   There is some overlap in these findings with the findings in the geographical cancer study reported above for Vieira et al. (2012). Among 15 self-reported cases in this study from Ohio, 7 were included in Vieira et al. (2012). Among 10 medically confirmed cases from Ohio, 7 were also included in Vieira et al. (2012). Overlap cannot be determined for West Virginia due to lack of detailed identifying information in Vieira et al. (2012) for West Virginia cases.

b) Thyroid cancer. Medically confirmed thyroid cancer showed positive but inconsistent trends of increased RRs in internal analyses comparing the more highly exposed to the less exposed. These can be seen in quartile analyses in Figures 1 and 2. RRs by quartile in unlagged analyses were 1.0, 1.6, 1.5, and 1.9 (test for trend with log cumulative exposure, p=0.17, linear trend test by quartile p=0.24). RRs by quartile in lagged analyses were 1.0. 2.2 (1.0-4.8), 2.3 (1.0-5.1), and 1.7 (p value= 0.34 for trend with log cumulative exposure). In prospective analyses based on 24 cases, there was no indication of increasing risk with increasing exposure, with RRs for the upper three quartiles being all less than 1.0.

   In external comparisons with the US population, using a 10-year lag, there was no excess of thyroid cancer overall (RR 1.1, 0.9-1.4, 105 thyroid cancer cases) (restricting to workers, the RR was 1.4 (0.8-2.1, 20 cases)). RRs increased by ascending quartile of exposure (RRs 0.8, 1.1, 1.2, 1.6 (1.1-2.3) , showing a positive trend (p=0.02). Unlagged analyses were quite similar.

c) Kidney cancer. Kidney cancer results for internal analyses can be seen in Figures 1 (no lag) and 2 (10 year lag) for medically confirmed cases. For unlagged analyses, RRs by quartile were 1.0, 1.2, 1.4, and 1.6. There was a positive linear trend across quartiles (p=0.04), stronger than the trend using a log term for cumulative exposure (p=0.09). For lagged analyses, RRs by quartile were 1.0, 1.0, 1.7, 1.4 (test for trend, log cumulative exposure, p=0.18). Prospective analyses based on 32 cases did not show any clear trends (RRs for unlagged analyses 1.0, 0.8, 1.1, 0.9, RRs for lagged analyses 1.0, 0.7, 1.4, 0.9) (p-values for trend 0.64 and 0.85, respectively)

ED_001670_00006710-00008

In external analyses comparing the study population to the US population, using a 10 year lag, overall there was a slight excess compared to the US rates (RR 1.1, 0.9-1.2, 119 cases) (RR 1.2, 0.9-1.7, when restricting to workers, 40 cases). There was no consistent trend in RRs across quartiles (RRs 1.0, 1.0, 1.6 (1.1-2.3), and 1.0 by quartile in the 10 year lag analysis)(test for trend p=0.90). Unlagged analyses were similar.

d) Melanoma. Validated melanoma cases did not show any positive trends in internal analyses. With no lag, the RRs by quartile were 1.0, 1.0, 0.9, and 0.9 (test for trend, log cumulative exposure, p=.99). For analyses with a 10 year lag, RRs by quartiles were 1.0, 1.1, 1.4, and 1.1 (p value for trend, log cumulative exposure, p=.35). In prospective analyses of validated melanoma cases (n=63), with a 10 year lag, RRs by quartile of cumulative exposure were RRs 1.0, 0.9, 1.1, 1.6. There was evidence of a trend across quartiles (p<0.0001), but less of a trend by the log of cumulative exposure (p=0.12). For unlagged prospective analyses, the RRs for validated melanoma cases were 1.0, 0.9, 0.8, 1.2, and again there was a trend across quartiles (p=0.05), but no evidence of trend using the log of cumulative exposure (p=0.64).

In the external comparison using cases validated by the registry and the period 1995-2009 when cancer registry data were available, and comparing the study population to US cancer rates, the RR was 1.2 (1.2-1.4), and the RRs by quartile increasing cumulative exposure were 1.0, 1.3, 1.2, 1.1 (test for trend p-value 0.46).

e) Other cancers of a priori interest. There were other several cancer sites of a priori interest, because of animal data (liver, pancreas) or one or more studies with some positive human evidence (prostate, pancreas, breast).

For liver cancer, in internal analyses all trend tests showed no evidence of any positive trend in the cohort study, for self-reported or confirmed cases. For self-reported cases (n=18), quartile analysis with or without a lag showed no positive trend with increasing cumulative exposure (unlagged RR 1.0, 0.7, 1.0, 0.6, lagged RR 1.0, 0.8, 1.0, 0.6). Too few cases were available for analyses restricted to confirmed cases or prospective analyses.

For pancreatic cancer, focusing on confirmed cases (n=26), in internal analyses all trends were slightly negative. RRs by quartile in unlagged analyses were 1.0, 0.9, 1.1, and 0.8 by increasing exposure. RRs for the lagged analysis were 1.0, 1.4, 1.2, 1.0. Only 15 cases were available for prospective analyses, making results unstable; RRs showed no increasing trends in unlagged or lagged analyses.

For breast cancer, internal analysis of confirmed cases (n=581) showed slight negative trends in either unlagged or lagged analyses. RRs by quartile of increasing cumulative exposure were 1.0, 0.9, 0.9, 0.8 in unlagged analyses, and 1.0, 1.1, 1.2, and 0.9 in lagged analyses. In prospective analyses (137 cases), again all trend tests were slightly negative. RRs by quartile were 1.0, 1.7, 1.1, and 1.0 in unlagged analyses, and 1.0, 1.5, 1.6, and 0.9 in lagged analyses.

For prostate cancer, in internal analysis, trends were either slightly negative or flat for both unlagged and lagged analyses. RRs by increasing cumulative exposure in quartile analyses for unlagged data were 1.0, 1.0, 0.9, 0.9, and 1.0, 0.9, 1.0, and 0.9 for lagged analyses. In prospective analyses (154 cases), again trends were either slightly negative or flat. RRs by

increasing cumulative exposure were 1.0, 1.0, 0.8, 0.9 for unlagged analyses, and 1.0, 1.3, 1.1, and 1.1 for lagged analysis

Evaluation

We conclude that there is a **probable link between PFOA and both testicular and kidney cancer.**

We conclude there is **no probable link between PFOA and either thyroid cancer or melanoma**, for which limited but insufficient evidence to support an association was found. We also conclude that there are no **probable links with any of the other cancers considered**.

In our evaluation we considered evidence from all published studies done by others, and from published and unpublished work done by the Science Panel. We considered the weight of the evidence, looking for consistency across studies, taking into account the capability of different study designs to detect a cancer risk if such a risk exists. We gave the most weight to studies of the Mid-Ohio Valley community, as other studies are very small with little data of value for specific cancers, or in the case of the Danish population study, with much lower ranges of exposure than in this population.

For **testicular cancer**, there is evidence of a positive trend in risk across exposure groups, in some analyses, with the highest exposure group in both the internal analyses of the cohort study and the geographical cancer study showing estimated relative risks ranging from 3 to over 6 comparing the highest to lowest exposure groups. On the other hand there was little or no evidence of increasing risk in analyses from the same cohort compared with the US population, and in the period after 2005, there were no new cases compared to about five expected). The high exposure group, where the higher risk was observed, comprises only six cases therefore there remains some uncertainty. The Science Panel notes that there is experimental evidence of testis cancer being increased in exposed animals. The Science Panel considers observed excesses to indicate a probable link between PFOA and testicular cancer.

For **kidney cancer**, the worker mortality study conducted by the Science Panel showed a higher risk in the most highly exposed group compared to lower exposure groups among the workforce, but the risks were not elevated compared to the US population. In the cohort study, there was a gradient of increasing risk with increasing exposure but most strongly in the analyses that included exposure up to the time of diagnosis. When the 10 years of exposure prior to diagnosis was excluded, the association was less evident. No association was seen in the prospective analysis of cohort data, although the latter is limited by small numbers. In the geographic study some results suggested an increasing risk of kidney cancer with increasing exposure and others did not. The science panel considers that the excesses observed indicate a probable link between PFOA and kidney cancer.

For **thyroid cancer**, positive evidence comes from the external analysis of the cohort compared to the US population. Internal analyses of the cohort study provided some suggestive of positive trends but with limited statistical support (p-values did not indicate strong trends). Prospective analyses in the cohort were negative, although somewhat limited by small numbers. There is no animal evidence nor did the geographical study of cancer indicate positive trends linking PFOA to thyroid cancer.

For **melanoma**, positive evidence comes from prospective internal analyses of the cohort study and from an external analysis with the US population. Without other supportive evidence, we believe the

ED_001670_00006710-00010

positive evidence is likely to be a chance finding and do not conclude that there is a probable link between PFOA and melanoma.

There were no suggestions of positive trends with increasing exposure for any **other cancer sites** in our cohort study and only limited evidence from other studies, although for rare and fatal cancers the evidence remains inadequate to make well-founded determination.

Figure 1.

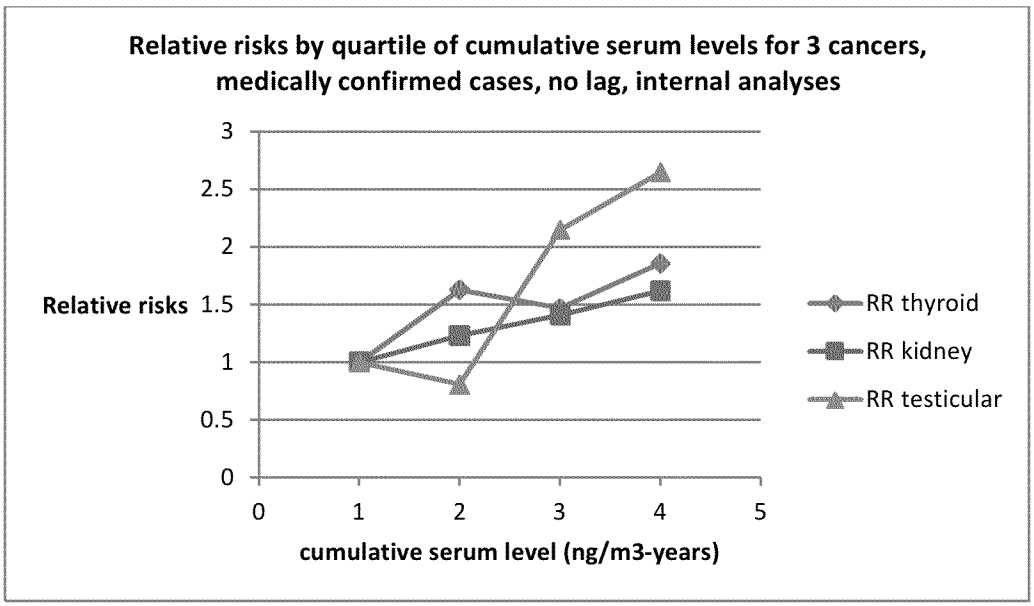
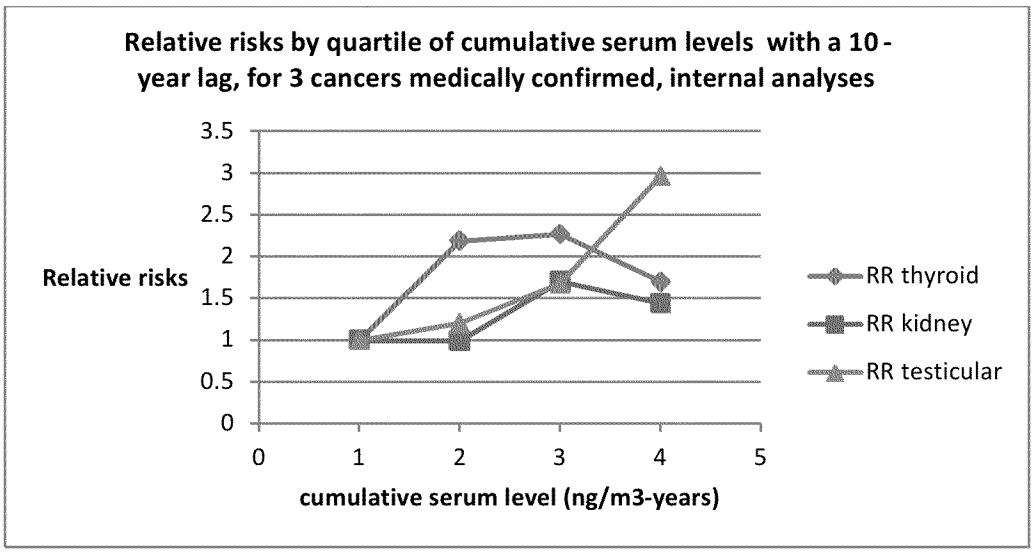


Figure 2.

ED_001670_00006710-00011



References

Bonefeld-Jorgensen EC, Long M, Bossi R, Ayotte P, Asmund G, Krüger T, Ghisari M, Mulvad G, Kern P, Nzulumiki P, Dewailly E. Perfluorinated compounds are related to breast cancer risk in Greenlandic Inuit: a case control study. Environ Health 2011;10:88

Dewitt JC, Shnyra A, Badr MZ, Loveless SE, Hoban D, Frame SR, Cunard R, Anderson SE, Meade BJ, Peden-Adams MM, Luebke RW, Luster MI. Immunotoxicity of Perfluorooctanoic Acid and Perfluorooctane Sulfonate and the Role of Peroxisome Proliferator-Activated Receptor Alpha. Crit Rev Toxicol 2009;39:76-94.

EPA, Draft Risk Assessment of the potential human health effects associated with exposure to perflouroctanoic acids and its salts, www.epa.gov/oppt/pfoa/pubs/pfoarisk.pdf, 2005

Eriksen KT, Sørensen M, McLaughlin JK, Lipworth L, Tjønneland A, Overvad K, Raaschou-Nielsen O. Perfluorooctanoate and perfluorooctanesulfonate plasma levels and risk of cancer in the general Danish population. J Natl Cancer Inst 2009;101:605-9.

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

Hardisty JF, Willson GA, Brown WR, McConnell EE, Frame SR, Gaylor DW, Kennedy GL, Butenhoff JL. Pathology Working Group review and evaluation of proliferative

lesions of mammary gland tissues in female rats fed ammonium perfluorooctanoate (APFO) in the diet for 2 years. Drug Chem Toxicol. 2010 Apr;33(2):131-7.

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.

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 2011a, 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 2011b;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

ED_001670_00006710-00013