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Original Contribution

Cohort Mortality Study of Workers Exposed to Perfluorooctanoic Acid

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Perfluorooctanoic acid (PFOA) is persistent in the human body; the general population has serum levels of approximately 4 ng/mL. It causes tumors of the liver, pancreas, and testicles in rodents. The authors studied the mortality of 5,791 workers exposed to PFOA at a DuPont chemical plant in West Virginia, using a newly developed job exposure matrix based on serum data for 1,308 workers from 1979–2004. The estimated average serum PFOA level was 350 ng/mL. The authors used 2 referent groups: other DuPont workers in the region and the US population. In comparison with other DuPont workers, cause-specific mortality was elevated for mesothelioma (standardized mortality ratio (SMR) = 2.85, 95% confidence interval (CI): 1.05, 6.20), diabetes mellitus (SMR = 1.90, 95% CI: 1.35, 2.61), and chronic renal disease (SMR = 3.11, 95% CI: 1.66, 5.32). Significant positive exposure-response trends occurred for both malignant and nonmalignant renal disease (12 and 13 deaths, respectively). PFOA is concentrated in the kidneys of rodents, and there are prior findings of elevated kidney cancer in this cohort. Multiple-cause mortality analyses tended to support the results of underlying-cause analyses. No exposure-response trend was seen for diabetes or heart disease mortality. In conclusion, the authors found evidence of positive exposure-response trends for malignant and nonmalignant renal disease. These results were limited by small numbers and restriction to mortality data, which are of limited relevance for several nonfatal outcomes of a priori interest.

fluorocarbons; mortality; occupational exposure; octanoic acids; perfluorooctanoic acid

Abbreviations: CI, confidence interval; JEM, job exposure matrix; PFOA, perfluorooctanoic acid; SMR, standardized mortality ratio.

Until recently, perfluorooctanoic acid (PFOA) was used extensively in the production of a number of consumer products (Teflon, Gore-Tex, etc.). Most uses of PFOA are gradually being phased out because of suspected toxicity. PFOA does not break down in the environment, and it is currently present in the blood of virtually all Americans at levels of about 4 ng/mL (0.04 parts per million (ppm)) (1). It has a half-life of approximately 2.3–3.5 years (2, 3), with some evidence of a biphasic excretion pattern, with more rapid excretion early, followed by slower excretion later. PFOA is not metabolized in the body, is not lipophilic, and is found primarily in the liver, kidney, and serum (4).

PFOA is a suspected human carcinogen and causes neonatal loss in mice (Environmental Protection Agency draft risk assessment, 2005 (http://www.epa.gov/oppt/pfoa/pubs/pfoarisk.pdf)). It causes tumors of the pancreas, liver, and testes in rodents. It also causes liver enlargement in rodents and nonhuman primates. There are also human data, primarily from cross-sectional studies, indicating that higher levels of PFOA are associated with higher cholesterol levels; this relation appears to be nonlinear, attenuating with higher exposures (4).

Most epidemiologic data on chronic disease associated with PFOA come from 2 occupational cohorts studied for mortality. Findings have not been conclusive or consistent across these two cohorts (4). In a previous study of the same occupational cohort as that studied here—workers at a DuPont chemical plant (E. I. du Pont de Nemours and Company)—Leonard et al. (5) found 2-fold elevated standardized mortality ratios (SMRs) for diabetes mellitus (SMR = 1.96, 95% confidence interval (CI): 1.23, 2.98) and kidney cancer (SMR = 1.81, 95% CI: 0.94, 3.16) when

the referent group was workers at other DuPont plants. Furthermore, Sakr et al. (6) found a positive exposure-response trend for heart disease ($P = 0.06$) in the same cohort in internal analyses stratified by quartile of estimated cumulative serum PFOA level, when cutpoints were chosen from all exposed workers and a 10-year lag was used; other lags did not show any clear positive trends. In the second occupational cohort, Lundin et al. (7) found suggestive positive trends in internal exposure-response analyses for diabetes, stroke, prostate cancer, and pancreatic cancer, but analyses were limited by small numbers for most outcomes.

Diabetes is best studied in terms of incidence rather than mortality, because diabetes incidence rates are 30–40 times higher than mortality rates (8, 9), and mortality data reflect treatment and survival patterns and therefore may not be a good surrogate for underlying incidence data. There has been one large community case-control study for diabetes incidence in a highly exposed residential population; it showed no positive trend with serum PFOA levels (10).

Here we update prior mortality analyses of a cohort of workers at a DuPont chemical plant studied previously by Leonard et al. (5) with follow-up through 2002. Our study had follow-up through 2008, increasing the number of deaths from 806 to 1,084. The DuPont plant studied here produces polymers in Parkersburg, West Virginia. The plant began operations in 1948 and has produced fluoropolymers, nylon filaments, and acrylic polymers, as well as other complex polymers that are used in many commercial products.

Previous exposure-response analyses of the cohort studied here (6) were based on a job exposure matrix (JEM) developed by Kreckmann et al. (11). This JEM estimated the serum levels of workers by grouping all job/department combinations into 4 categories (nonexposed, low exposure, medium exposure, and high exposure), based on a large cross-sectional study of serum levels among 1,000 workers in 2004 (12). In that JEM, no attempt was made to consider changes in exposure over time. Instead, median levels observed in the 4 job categories in 2004 were assumed to apply backward in time. However, approximately 1,000 additional PFOA blood samples were available from 1979 to 2004, with higher serum levels recorded in the earlier years. Here we used 2,125 blood samples taken from 1979 to 2004, covering 1,308 workers (median PFOA concentration, 580 ng/mL (0.58 ppm); range, 160 ng/mL for nonexposed workers to 2,880 ng/mL for directly exposed workers). We developed regression models to estimate serum PFOA levels over time for 8 job category/job group combinations (13).

MATERIALS AND METHODS

The cohort was originally assembled by DuPont and included all workers with at least 1 day of work at the plant between 1948 and 2002 (5). Analyses were conducted with the National Institute for Occupational Safety and Health Life Table Analysis System (version 3.0), using 92 causes of death (14). We obtained referent rates from DuPont (Morel Symons, DuPont, personal communication, 2010), covering the period 1955–2009, based on 67,294 male and 19,404 female workers in plants in the Appalachian region; these were considered to be the DuPont workers most similar to the West Virginia workers. Rates in the DuPont workers are a slightly updated version of the referent rates used previously for analyzing this cohort by Leonard et al. (5). DuPont workers included in the rates came from the states of West Virginia and 7 neighboring states: Ohio, Virginia, Kentucky, Indiana, Pennsylvania, Tennessee, and North Carolina. The rates excluded workers at the plant currently under study.

We used the DuPont rates for our principal comparison with the exposed workers, in order to avoid the healthy worker effect, which occurs when comparing workers with a US referent population. However, we also present some results for underlying cause of death based on US referent rates for the period 1940–2007, with extrapolation to 2009. US rates were also used in some analyses based on multiple-cause-of-death (underlying cause plus contributing cause(s)) rates, which were available for the United States but not available using the DuPont reference population. Multiple-cause-of-death rates are most useful for diseases which are not often fatal but are likely to be listed as contributory causes on the death certificate (15).

Deaths were ascertained though 2008 via the National Death Index or from death certificate data prior to the start of the National Death Index in 1979. Deaths occurring prior to 1979 had been previously identified by DuPont, using the Social Security Administration and state death certificates. Exposure-response analyses were conducted via life-table analyses, using cumulative serum levels derived from the JEM described below (13). The study was approved by the Emory University Institutional Review Board.

Exposure-response analyses using SMRs were conducted with cumulative serum levels, in terms of ppm-years (e.g., 100 ppm over 5 years would be 500 ppm-years). Quartiles for analyses were derived from the cumulative serum levels of decedents, with separate cutpoints developed for no-lag, 10-year-lag, and 20-year-lag analyses. Tests for trend in SMRs in the quartile analyses were based on the trend test described by Breslow et al. (16), which results in a chi-square statistic with 1 degree of freedom. Midpoints of quartiles for trend tests were the mean cumulative serum level of decedents within each quartile. In analyses using lags, the "lagged-out" person-years were assigned to the lowest exposure category, a procedure which has been shown to lead to unbiased estimation of rate ratios in analogous nested case-control studies (17).

There were 6,027 workers in the cohort, but only 5,801 had work histories with sufficient detail to allow estimation of PFOA serum levels over time. All workers with less than 50% of their work time in known jobs and departments were eliminated from the analysis ($n = 226$) (4%). Ten other workers were deleted due to missing dates of birth. A total of 5,791 workers were available for analysis.

PFOA was used at the plant from 1950 onward, with peak usage occurring in the 1990s and sharply decreased usage and emissions after 2001 (Figure 1). Serum levels were estimated annually for each worker, with workers grouped into 8 job category/job group combinations, as described in detail by Woskie et al. (13). There were 5 job

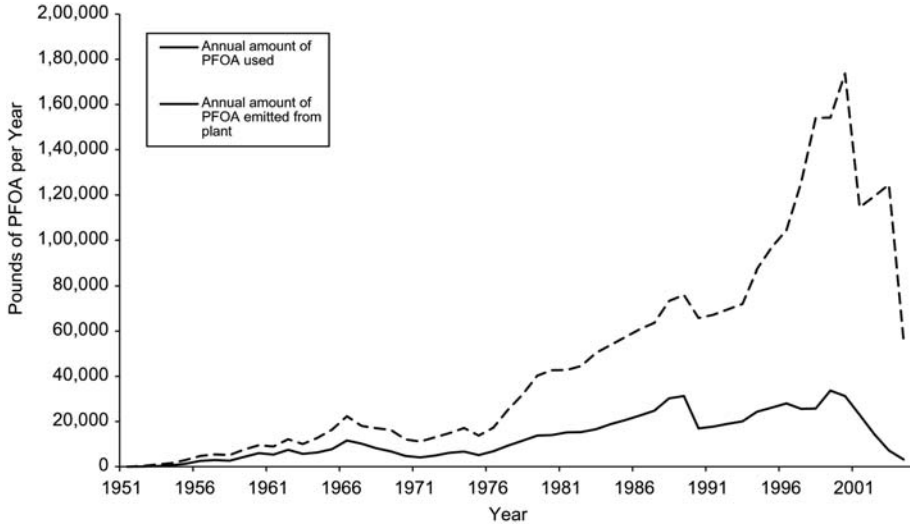

Figure 1. Annual amount (pounds; 1 pound = 0.45 kg) of perfluorooctanoic acid (PFOA) used at a DuPont chemical plant and the estimated annual amount of PFOA emitted from the plant, West Virginia, 1952–2008. (Adapted from Woskie et al. (13)).

category/job group combinations, 3 of which had subgroups: 1) direct PFOA exposure in the Teflon production area (fine powder/granular polytetrafluoroethylene chemical department, with a dichotomous variable for working in the chemical operator job group); 2) direct PFOA exposure among workers in the other copolymer production areas that used PFOA, including fluorinated ethylene propylene and perfluoroalkoxy fluoropolymer operations; 3) intermittent direct non-PFOA-use jobs such as the tetrafluoroethylene monomer production operation and Teflon and copolymer jobs, including laboratory workers, engineers, upper-level supervisors, and clerks, with a dichotomous variable for working in a tetrafluoroethylene monomer job group; 4) maintenance jobs with intermittent direct or plant

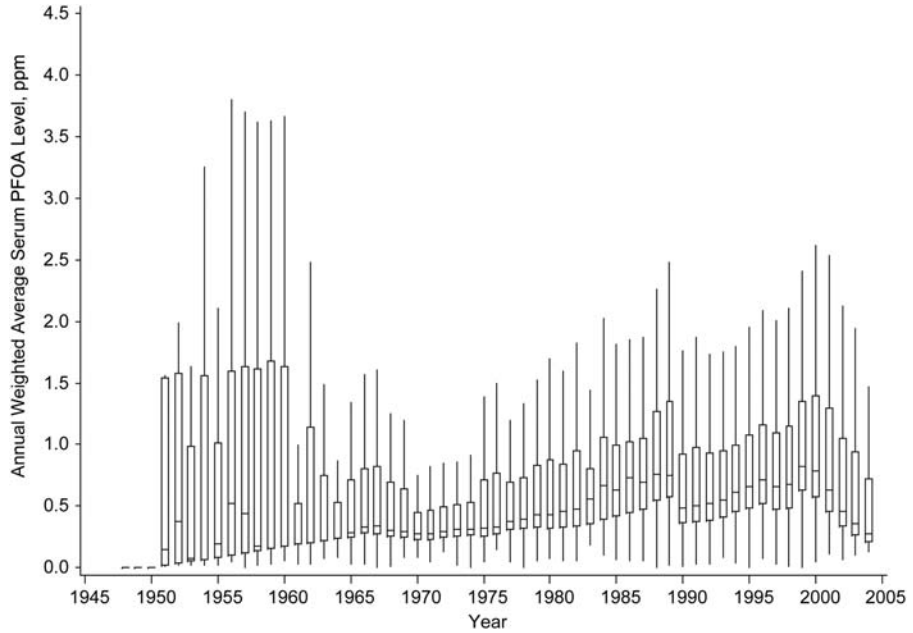

Figure 2. Model-estimated weighted annual average serum perfluorooctanoic acid (PFOA) levels (ppm) among workers in job groups with potential PFOA exposure at a DuPont chemical plant, West Virginia, 1952–2008. (Adapted from Woskie et al. (13)). Vertical lines represent ranges; vertical bars represent interquartile ranges (25th percentile–75th percentile); and horizontal lines represent median values.

Table 1. Standardized Mortality Ratios for Selected Causes of Death in Analyses With No Lag Among Workers at a DuPont Chemical Plant, West Virginia, 1952–2008[a]

Cause of Death (ICD-9 Code)[b]	Quartile of PFOA Exposure															US Referent Group	
	Quartile 1 (0–<904 ppm-years)			Quartile 2 (904–<1,520 ppm-years)			Quartile 3 (1,520–<2,700 ppm-years)			Quartile 4 (≥2,700 ppm-years)			All Quartiles Combined				
	No. of Deaths	SMR	95% CI	No. of Deaths	SMR	95% CI	No. of Deaths	SMR	95% CI	No. of Deaths	SMR	95% CI	No. of Deaths	SMR	95% CI	SMR	95% CI
All deaths	270	1.02	0.90, 1.15	262	1.00	0.89, 1.13	279	0.97	0.86, 1.09	273	0.94	0.84, 1.06	1,084	0.98	0.92, 1.04	0.70	0.66, 0.74
All cancers (140–199)	62	0.93	0.72, 1.20	68	0.90	0.70, 1.14	83	0.95	0.75, 1.76	91	0.94	0.76, 1.16	304	0.93	0.83, 1.04	0.74	0.66, 0.83
Liver cancer (155–156)	4	2.39	0.65, 6.13	0	0.00	0.00, 1.81	5	2.01	0.65, 4.68	1	0.32	0.01, 1.76	10	1.07	0.51, 1.96	0.77	0.35, 1.47
Pancreatic cancer (157)	4	1.18	0.32, 3.03	4	1.02	0.28, 2.61	5	1.09	0.35, 2.54	5	0.92	0.30, 2.16	18	1.04	0.62, 1.64	0.85	0.51, 1.35
Lung cancer (162)	12	0.58	0.30, 1.02	16	0.63	0.36, 1.02	32	1.09	0.35, 2.54	24	0.75	0.48, 1.11	84	0.78	0.62, 1.64	0.60	0.48, 0.74
Breast cancer (174–175)	2	1.49	0.18, 5.39	0	0.00	0.00, 3.56	1	0.87	0.02, 4.83	0	0.00	0.00, 3.42	4	0.65	0.13, 1.90	0.79	0.21, 2.02
Prostate cancer (185)	6	1.07	0.39, 2.34	6	0.82	0.30, 1.78	5	0.65	0.21, 1.51	4	0.57	0.16, 1.46	21	0.76	0.47, 1.16	0.72	0.45, 1.10
Testicular cancer (186)	N/A[c]			N/A			N/A			N/A			1	1.80	0.05, 10.03	0.74	0.02, 4.12
Kidney cancer (189.0–189.2)[d]	1	1.07*	0.02, 3.62	3	1.37*	0.28, 3.99	0	0.00*	0.00, 1.42	8	2.66*	1.15, 5.24	12	1.28	0.66, 2.24	1.09	0.56, 1.90
Bladder cancer (188, 189.3–189.9)	2	1.24	0.15, 4.47	6	2.49	0.97, 5.78	1	0.39	0.01, 2.17	1	0.36	0.10, 2.01	10	1.08	0.52, 1.99	0.95	0.46, 1.75
Mesothelioma[e]	0	0.00*	0.00, 15.40	0	0.00*	0.00, 7.51	1	1.73*	0.04, 9.65	5	6.27*	2.04, 14.63	6	2.85*	1.05, 6.20	4.83*	1.77, 10.52
Non-Hodgkin's lymphoma (200, 202, 273.3)	4	1.54	0.42, 3.95	3	0.99	0.20, 2.88	3	0.85	0.17, 2.48	4	0.96	0.26, 2.46	14	1.05	0.57, 1.76	0.79	0.42, 1.35
Leukemia (204–208)	1	0.28	0.01, 1.59	7	2.34	0.94, 4.81	2	0.57	0.07, 2.05	4	1.03	0.28, 2.63	14	1.05	0.57, 1.76	0.88	0.48, 0.47
Diabetes (250)	6	1.85	0.68, 4.03	7	1.47	0.59, 3.02	13	2.30	1.22, 3.93	12	1.90	0.98, 3.32	38	1.90*	1.35, 2.61	1.06	0.75, 1.46
Ischemic heart disease (410–414)	84	1.07	0.85, 1.32	72	1.02	0.80, 1.28	66	0.87	0.67, 1.11	65	0.93	0.72, 1.19	287	0.97	0.86, 1.09	0.68	0.60, 0.77
Stroke (430–438)	10	0.63	0.85, 1.32	11	0.78	0.39, 1.39	20	1.34	0.82, 2.07	9	0.69	0.32, 1.31	50	0.86	0.64, 1.14	0.70	0.52, 0.92
Chronic obstructive pulmonary disease (490–492, 496)	7	0.93	0.37, 1.91	11	1.00	0.48, 1.83	14	1.30	0.71, 2.18	10	0.93	0.45, 1.71	41	1.05	0.75, 1.42	0.60	0.43, 0.82

Table continues

Table 1. Continued

Cause of Death (ICD-9 Code)[b]	Quartile of PFOA Exposure												US Referent Group	
	Quartile 1 (0–<904 ppm-years)			Quartile 2 (904–<1,520 ppm-years)			Quartile 3 (1,520–<2,700 ppm-years)			Quartile 4 (≥2,700 ppm-years)			All Quartiles Combined				
	No. of Deaths	SMR	95% CI	No. of Deaths	SMR	95% CI	No. of Deaths	SMR	95% CI	No. of Deaths	SMR	95% CI	No. of Deaths	SMR	95% CI	SMR	95% CI
Chronic liver disease (571)	3	1.32	0.27, 3.86	5	2.10	0.68, 4.89	1	0.37	0.01, 2.08	2	0.72	0.09, 2.61	13	1.09	0.54, 1.95	0.28	0.14, 0.52
Chronic renal disease[f] (582–583, 585–587)	0	0.00*	0.00, 3.03	4	3.79*	1.03, 9.71	2	1.83*	0.22, 6.62	7	8.60*	3.46, 17.72	13	3.11*	1.66, 5.32	0.96	0.51, 1.64

Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases*, Ninth Revision; N/A, not applicable; ppm, parts per million; SMR, standardized mortality ratio.

* $P < 0.05$.

[a] The referent group was comprised of other DuPont workers in the Appalachian region, unless otherwise specified.

[b] For more detail on ICD-9 codes, see Robinson et al. (21).

[c] There were too few cases for quartile analyses.

[d] Test for trend: $P = 0.02$.

[e] No ICD-9 code; *International Classification of Diseases*, Tenth Revision, code C45. No rates were available before 1999; SMRs were calculated using observed and expected numbers of deaths from 1999–2008. Test for trend: $P = 0.02$.

[f] Test for trend: $P = 0.001$.

background PFOA exposures, with a dichotomous variable for having been assigned to the Teflon/copolymer maintenance job group; and 5) non-Teflon/copolymer production division jobs with no PFOA use (plant background PFOA exposures), including acrylics, Butacite, Delrin, engineering polymers, compounding, nylon filaments, specialty compounding, power services, utility pool, and non-Teflon polymer/copolymer-associated administrative jobs in engineering, business services, and other plant services.

Briefly, we created models in which the outcome measure was the natural log of the measured serum PFOA levels in samples collected from 1979 to 2004 from workers with at least 1 year of residence in the job category at the time of sampling. A SAS mixed model procedure with a repeated-measures covariance structure (SAS Institute Inc., Cary, North Carolina) was used to account for the presence of multiple samples on some of the same subjects within a job category/job group combination. Five separate models were fitted, one for each job category, along with a dichotomous variable for specific job groups within the larger job categories, resulting in a total of 8 job category/job group combinations. Other covariates in the models varied but included 1) the cumulative number of prior years spent in potentially PFOA-exposed jobs and 2) the annual amount of PFOA product used at the plant or, alternatively, the estimated annual amount of PFOA emitted from the plant (18, 19). In addition, for models for the 3 job categories with direct exposure, a 4-knot restricted cubic spline function was used to address process changes over calendar time that could affect these jobs. For each model, covariates that most improved model fit and therefore predictive power were chosen, at the cost of some cross-model consistency.

To estimate the cumulative exposure of each worker in the cohort, a job category/job group assignment was made to each work history entry, and then the retrospective serum concentration predictions for each year were made using the regression models described above. For years in which multiple jobs were held, an annual weighted average serum level was calculated as the time-weighted combination of the serum level in each job times the amount of time spent in that job for the year. For people who were missing job information within a given year and were presumably unemployed at that time, we used a background serum level of 0.03 ppm, based approximately on the median value for community residents living near the plant in 2005 (0.28 ppm), who were drinking water contaminated with PFOA (20). When a worker was missing an entire year of work history or left employment, his or her serum levels were assigned as 82% of the previous year's level (based on an assumed half-life of 3.5 years) or 0.03 ppm, whichever was higher (3). If the person returned to work, then estimates were made from the model as before. Over 56,000 individual jobs for the 6,027 cohort members were reviewed and classified into the 8 job category/job group combinations described above, allowing assignment of annual serum levels for each worker for each year.

Note that our serum estimates crudely incorporated any residential exposure incurred, since they were based on observed serum levels, which reflected the workers'

Table 2. Standardized Mortality Ratios for Selected Causes of Death in Analyses With a 10-Year Lag Among Workers at a DuPont Chemical Plant, West Virginia, 1952–2008[a]

Cause of Death (ICD-9 Code)[b]	Quartile of PFOA Exposure											
	Quartile 1 (0–<798 ppm-years)			Quartile 2 (798–<1,379 ppm-years)			Quartile 3 (1,379–<2,384 ppm-years)			Quartile 4 (≥2,384 ppm-years)		
	No. of Deaths	SMR	95% CI	No. of Deaths	SMR	5% CI	No. of Deaths	SMR	95% CI	No. of Deaths	SMR	95% CI
All deaths	254	0.97	0.86, 1.10	261	0.99	0.87, 1.12	259	1.00	0.89, 1.13	255	0.96	0.84, 1.08
All cancers (140–199)	69	0.97	0.75, 1.22	69	0.91	0.71, 1.15	76	0.95	0.75, 1.19	79	0.92	0.73, 1.15
Kidney cancer (189.0–189.2)[c]	2	1.05*	0.13, 3.79	2	0.87*	0.11, 3.15	1	0.44*	0.01, 2.44	7	2.82[c]*	1.13, 5.81
Mesothelioma[d]	0	0.00	0.00-17.8	0	0.00	0.00, 9.55	2	3.08	0.37, 11.12	4	4.66	1.27, 11.93
Diabetes (250)	6	2.02	0.74, 4.40	9	1.87	0.85, 3.54	2.0011		1.00, 3.58	12	1.90	0.98, 3.33
Ischemic heart disease (410–414)	83	0.95	0.76, 1.18	71	1.01	0.79, 1.27	60	0.93	0.71, 1.20	59	0.93	0.71, 1.20
Chronic renal disease[e] (582–583, 585–587)	0	0.00*	0.00, 3.53	2	1.63*	0.20, 5.91	4	3.85*	1.05, 9.85	7	9.12*	3.67, 18.80

Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases*, Ninth Revision; ppm, parts per million; SMR, standardized mortality ratio.

* $P < 0.05$.

[a] The referent group was comprised of other DuPont workers in the Appalachian region, unless otherwise specified.

[b] For more detail on ICD-9 codes, see Robinson et al. (21).

[c] Test for trend: $P = 0.02$. Trend test included lagged-out group (not shown in table).

[d] No ICD-9 code; *International Classification of Diseases*, Tenth Revision, code C45. No rates were available before 1999; SMRs were calculated using observed and expected numbers of deaths from 1999–2008. Test for trend: $P = 0.15$.

[e] Test for trend: $P = 0.0003$. Trend test included lagged-out group (not shown in table).

residential exposure in addition to their occupational exposure. Residential exposure could at times be high for workers living in residential areas with drinking water that was highly contaminated with PFOA (20). As we noted above, the median 2005 serum level for residents of 6 water districts surrounding the plant was 28 ng/mL, but the level was sometimes much higher for water districts closest to the plant.

RESULTS

The mean years of first and last employment for the cohort were 1976 and 1995, respectively (the mean duration of employment was 19 years). The mean year of birth was 1948, and the mean length of follow-up was 30 years. Women made up 19% of the cohort, while nonwhites made up 5%. The mean cumulative exposure was 7.8 ppm-years (median, 4.3), and the estimated average annual serum concentration was 0.35 ppm or 350 ng/mL (median, 0.23 ppm). The corresponding figures for the earlier JEM from Kreckman et al. (11) were a mean cumulative exposure of 5.6 ppm-years (median, 4.4) and an estimated average annual serum concentration of 0.30 ppm or 300 ng/mL (median, 0.21 ppm). The higher mean values in our JEM most likely resulted from our higher estimates of exposure in earlier years as compared with the earlier JEM, but medians between the JEMs did not differ much because most jobs in the plant were nonexposed jobs, which were not affected by changes in exposure over time. The relative proportions of jobs with direct PFOA exposure, indirect PFOA exposure, Teflon maintenance, non-Teflon maintenance, and no exposure were approximately 8%, 10%, 1%, 15%, and 66%, respectively. Figure 2 (adapted from Woskie et al. (13)) shows the estimated cumulative serum levels for workers with direct and indirect exposure over time (omitting the nonexposed).

Table 1 presents life-table results for overall mortality and exposure-response analyses with no lag, for causes of a priori interest and a range of selected other causes, using DuPont referent rates. Overall mortality rates using the US population as the referent group are also presented for comparison. There is a notable healthy worker effect affecting most causes when using US referent rates, as expected; this is a relatively young cohort (19% mortality), without sufficient follow-up time for the healthy worker effect to decline appreciably.

There were too few deaths for analysis for several endpoints of interest, particularly testicular cancer and breast cancer (analyses restricted to women also showed no exposure-response trends). Most cancers and other health outcomes showed no elevation for overall mortality. However, using referent rates from other DuPont workers in the region, cause-specific mortality rates were elevated for mesothelioma (SMR = 2.85, 95% CI: 1.05, 6.20), diabetes (SMR = 1.90,

Table 3. Standardized Mortality Ratios for Selected Causes of Death in Analyses With a 20-Year Lag Among Workers at a DuPont Chemical Plant, West Virginia, 1952–2008[a]

Cause of Death (ICD-9 Code)[b]	Quartile of PFOA Exposure											
	Quartile 1 (0–<515 ppm-years)			Quartile 2 (515–<1,057 ppm-years)			Quartile 3 (1,057–<1,819 ppm-years)			Quartile 4 (≥1,819 ppm-years)		
	No. of Deaths	SMR	95% CI	No. of Deaths	SMR	95% CI	No. of Deaths	SMR	95% CI	No. of Deaths	MR	95% CI
All deaths	243	1.02	0.90, 1.16	228	0.91	0.80, 1.04	233	1.07	0.94, 1.22	226	0.97	0.85, 1.10
All cancers (140–199)	78	1.08	0.85, 1.34	63	0.83	0.64, 1.06	60	0.92	0.71, 1.19	65	0.94	0.72, 1.20
Kidney cancer (189.0–189.2)[c]	3	1.34*	0.28, 3.91	1	0.46*	0.01, 2.55	0	0.00*	0.00, 2.03	7	3.67*	1.48, 7.57
Mesothelioma[d]	1	9.09	0.23, 50.6	0	0.00	0.00, 15.24	2	2.60	0.31, 9.39	3	3.44	0.71, 10.05
Diabetes (250)	5	1.87	0.61, 4.36	9	1.94	0.88, 3.67	13	2.50	1.33, 4.27	10	1.73	0.83, 3.18
Ischemic heart disease (410–414)	80	1.00	0.79, 1.24	60	0.92	0.70, 1.18	54	1.05	0.79, 1.37	49	0.89	0.65, 1.18
Chronic renal disease[e] (582–583, 585–587)	1	1.08*	0.03, 5.99	2	1.47*	0.18, 5.31	4	5.37*	1.46, 13.75	6	9.04*	3.32, 19.67

Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases*, Ninth Revision; ppm, parts per million; SMR, standardized mortality ratio.

* $P < 0.05$.

[a] The referent group was comprised of other DuPont workers in the Appalachian region, unless otherwise specified.

[b] For more detail on ICD-9 codes, see Robinson et al. (21).

[c] No ICD-9 code; *International Classification of Diseases*, Tenth Revision, code C45. No rates were available before 1999; SMRs were calculated using observed and expected numbers of deaths from 1999–2008. Test for trend: $P = 0.53$.

[d] Test for trend: $P = 0.003$.

[e] Test for trend: $P = 0.0009$.

95% CI: 1.35, 2.61), and chronic renal disease (SMR = 3.11, 95% CI: 1.66, 5.32). The elevation in mesothelioma was likely to have been caused by asbestos exposure.

Exposure-response analyses by quartile of cumulative exposure with no lag showed significant positive trends for kidney cancer, mesothelioma, and nonmalignant kidney disease, although all trends were based on small numbers (Table 1). The uppermost quartiles of malignant and nonmalignant kidney disease, as well as mesothelioma, were all significantly elevated at the $P < 0.05$ level. The positive trend with mesothelioma is likely to have been due to a correlation between cumulative PFOA serum level and duration of work (which in turn is correlated with cumulative asbestos exposure). No positive trend was seen for diabetes (Table 1).

Some additional analyses were conducted using deciles of cumulative exposure for ischemic heart disease (again using DuPont regional rates as the comparison), for which there was a large number of deaths ($n = 287$). No positive trends were detected. Rate ratios for ischemic heart disease using a 10-year lag (for which a positive trend was found by Sakr et al. (6)) were 0.86, 1.06, 1.11, 1.02, 0.85, 0.75, 0.81, 1.30, 1.15, and 0.77 from the lowest decile to the highest, respectively.

Tables 2 and 3 show SMR results from 10-year- and 20-year-lag analyses, respectively, for selected a priori causes of interest as well as all causes and all cancers. The only significant positive trends, generally consistent across both lags, were for kidney cancer and nonmalignant kidney disease. Diabetes did not show a positive trend regardless of the lag used.

Multiple-cause-of-death analyses were possible only with US referent rates, because no multiple-cause rates were available for the DuPont worker referent population. For kidney cancer, which is rapidly fatal, we found 3 more cases (a total of 15) using multiple-cause analyses. Positive dose-response trends continued to be apparent regardless of lag; the strongest trend ($P = 0.003$) was apparent using a 20-year lag, with SMRs of 1.08, 0.73, 0.41, and 3.54 across cumulative exposure quartiles, respectively. For chronic kidney disease, the multiple-cause analysis found 73 deaths. The most pronounced trend was for a 20-year lag, and the SMRs by cumulative exposure quartile were 0.67, 1.14, 1.00, and 1.36, respectively (test for trend: $P = 0.03$).

DISCUSSION

We extended follow-up of this cohort for an additional 6 years compared with the study by Leonard et al. (5) and conducted new exposure-response analyses. The only prior published exposure-response analyses in this cohort were limited to heart disease (6), using the JEM developed by Kreckmann et al. (11).

Using referent rates from other DuPont workers in the region, cause-specific mortality rates were elevated for mesothelioma (SMR = 2.85, 95% CI: 1.05, 6.20 ($n = 6$)), diabetes (SMR = 1.90, 95% CI: 1.35, 2.61 ($n = 38$)), and chronic renal disease (SMR = 3.11, 95% CI: 1.66, 5.32 ($n = 13$)). Significant positive exposure-response trends were seen for both malignant and nonmalignant renal disease but not for diabetes.

With mortality follow-up through 2002, kidney cancer and diabetes were found to be in overall excess in this cohort by Leonard et al. (5), using DuPont regional referent rates. Leonard et al. found the same 12 kidney cancer deaths as we observed here (no new deaths occurred during the period 2003–2008) (5). The diabetes excess found by Leonard et al. (SMR = 1.97, 95% CI: 1.23, 12.98) (5) was similar to our own but based on fewer deaths ($n = 22$). Leonard et al. found only a nonsignificant excess of renal disease (SMR = 1.29) using DuPont referent rates, based on 8 cases (5).

The kidney cancer result should be considered in relation to the fact that tetrafluoroethylene, used in the manufacture of a variety of fluoropolymers, has been identified as a rodent kidney carcinogen (22). PFOA and tetrafluoroethylene are highly correlated potential exposures in this worker population (23). However, tetrafluoroethylene is highly volatile and explosive and for that reason is well controlled, such that appreciable exposures during normal operations would have been unlikely.

Although no animal studies have found kidney disease or cancer from PFOA exposures, tissue measurements have found PFOA primarily in the liver, kidney, and serum in rodents, and presumably these same tissues would contain higher PFOA levels in humans. Thus, the kidney is a site of interest a priori. There are no prior findings in the literature for nonmalignant renal disease in humans from this cohort or elsewhere.

We found an excess of mesothelioma, which is caused by asbestos exposure, not PFOA. Mesothelioma showed a significant positive exposure-response relation with PFOA in unlagged analyses, possibly driven by duration of employment, which is correlated with cumulative PFOA exposure. Asbestos was once a widely used insulator for piping, furnaces, and other hot processes, as well as for fire-resistant clothing, until its use was restricted in the 1980s. In addition to the operators of equipment insulated with asbestos, maintenance mechanics could also have been exposed to this material during standard maintenance operations and repairs.

There was no indication in these analyses of a positive trend in heart disease mortality, regardless of the lag period used. In prior analyses of this cohort with mortality data through 2002, Sakr et al. (6) found a borderline-significant positive trend for heart disease mortality using a 10-year lag, but only when quartile cutpoints were based on the whole cohort rather than on heart disease deaths, and only using a 10-year lag. In this study, we chose cutpoints a priori based on quartiles of cumulative exposure for all decedents. This procedure tends to result in similar numbers of deaths across quartiles for most outcomes, which is desirable so that the variances of the rate ratios are similar across quartiles. We will be investigating heart disease further in this cohort using incidence data, which should provide additional information.

Workers in this cohort were exposed to levels of PFOA much higher than those in the general US population, by 2 orders of magnitude (median of 403 ng/mL vs. 4 ng/mL). Their exposures were also 1 order of magnitude higher than that in the community surrounding the plant, which had a median PFOA level of 28 ng/mL in 2005 (20). However, there was some overlap in exposures between less exposed workers and highly exposed community members. The community residents were exposed primarily via drinking water contaminated with PFOA, while the workers had exposure via dermal, inhalation, and ingestion pathways.

Our findings for renal disease were based on small numbers. Small numbers are a limitation for any rare disease, especially in mortality studies for diseases which may not be fatal, such as testicular cancer and nonmalignant liver disease, both of which were of a priori interest based on animal studies or prior human studies. Furthermore, numbers were limited for all outcomes among women, who made up a minority of the cohort. Research on disease incidence in this cohort and in a larger community cohort is in progress.

Future work should make up for some of these limitations. We interviewed approximately 70% of these workers and will be conducting an incidence analysis which will enable us to focus better on nonfatal diseases. We are also conducting an incidence study of a large cohort ($n = 30{,}000$) of community residents exposed to PFOA via drinking water, where women make up half of the population.

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