Mortality Among Employees of a Perfluorooctanoic Acid Production Plant

Frank D. Gilliland, MD, PhD
Jack S. Mandel, PhD, MPH

Perfluorooctanoic acid (PFOA) has been found at low levels (10 to 100 parts per billion) in sera of the general population and at higher levels in occupationally exposed workers. Although PFOA has been reported to be a promoter of rodent hepatocarcinogenesis and to alter reproductive hormones in humans and rodents, there is little information on human health effects associated with PFOA exposure. The present study examined the relationship between PFOA and mortality using a retrospective cohort mortality design. The cohort consisted of 2788 male and 749 female workers employed between 1947 and 1983 at a plant that produced PFOA. The all-causes standardized mortality ratio was .75 (95% confidence interval [CI], .56 to .99) for women and .77 (95% CI, .69 to .86) for men. Among men the cardiovascular standardized mortality rate was .68 (95% CI, .58 to .80) and the all-gastrointestinal diseases was .57 (95% CI, .29 to .99). There was no significantly increased cause-specific standardized mortality ratio for either men or women. Ten years of employment in exposed jobs was associated with a 3.3-fold increase (95% CI, 1.02 to 10.6) in prostate cancer mortality compared to no employment in PFOA production. There were only six prostate cancer deaths overall and four among the exposed workers; thus, the results must be interpreted cautiously. If prostate cancer mortality is related to PFOA, PFOA may increase prostate cancer mortality by altering reproductive hormones in male workers.

Perfluorooctanoic acid (PFOA) and its salt, ammonium perfluorooctanoate, are perfluorinated surfactants. Because of their unique surface active properties they are used in a large number of industrial applications and consumer products including plasticizers, lubricants, wetting agents, and emulsifiers.[1-3] Despite their widespread use, little is known about potential adverse health effects.

PFOA induced marked hepatomegaly and peroxisome proliferation in rodent livers.[3-8] The chemically diverse group of xenobiotics that induce peroxisomes is of concern because of its association with nongenotoxic hepatocarcinogenesis.[3-10] PFOA did not produce an increased number of hepatocellular carcinomas in a 2-year rat feeding study.[8] However, biphasic (initiation and promotion) and triphasic (initiation, selection, and promotion) hepatic carcinogenesis studies in rodents have shown significantly increased numbers of carcinomas in the PFOA-treated rats.[11,12] It has been suggested that the marked rodent hepatomegaly produced by PFOA is a marker for carcinogenic potential.[13] The observations of increased Leydig cell tumors in a 2-year rat PFOA feeding study and of disruption of the hypothalamic-pituitary-gonad axis in PFOA-treated rats[8] are consistent with the hypothesis that PFOA-associated tumors are mediated by a hormonal nongenotoxic mechanism.

PFOA has a long half-life in humans. A study of occupationally exposed workers showed that the half-life in men is greater than 1.5 years.[14] Hence, accumulation of PFOA may occur from small, frequent PFOA doses. PFOA in the serum of the gen-

From the Division of Environmental and Occupational Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota (Dr Gilliland, Dr Mandel); and Department of Internal Medicine, Occupational and Environmental Medicine Section, St Paul Ramsey Medical Center, St Paul, Minnesota (Dr Gilliland).

Address correspondence to: Frank D. Gilliland, MD, University of New Mexico School of Medicine, New Mexico Tumor Registry, 900 Camino de Salud NE, Albuquerque, NM 87131.

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eral populations of industrialized countries[15–19] is likely to be the result of an accumulation of small PFOA doses.

No health problems related to PFOA exposure were observed in a cross-sectional study among workers employed at the PFOA production plant.[14] Cross-sectional studies of PFOA-exposed workers at this plant have shown that PFOA was associated with decreased free testosterone and increased estradiol.[20]

To determine whether mortality from any cause was associated with occupational exposure to PFOA, a retrospective cohort mortality study was conducted at a plant that has produced PFOA since 1947.

Methods

The plant consists of several divisions, with PFOA production restricted to the Chemical Division. A number of other specialty chemicals have been produced in this division. The study cohort consisted of workers who were employed at the plant for at least 6 months between Jan 1, 1947, and Dec 31, 1983. Data were abstracted from plant personnel records, which were maintained on all workers ever employed at the plant. Vital status was ascertained from the Social Security Administration for the period 1947 to 1982 and from the National Death Index for the period 1979 to 1989. All workers with unknown vital status were traced using a variety of tracing strategies such as directory assistance, Metronet and TRW searches, reverse directories, motor vehicle registration lists, contacting neighbors and relatives, and the post offices. Death certificates were obtained from the appropriate state health departments for those identified as, or presumed to be, deceased. Information concerning the data and cause of two deaths which occurred outside the United States was obtained from family members. A nosologist coded the death certificates for underlying cause of death according to the International Classification of Diseases, 8th revision. The reliability of the coding was evaluated by resubmitting a random sample of death certificates for coding by the same nosologist. In the 25 death certificates from 1970 to 1989 resubmitted to the nosologist for ICD coding, there were no changes in the major categories of cause of death.

Workers were categorized as exposed or unexposed to PFOA based on their job histories. Exposed workers were defined as all workers employed for 1 month or more in the Chemical Division. Unexposed workers were employees who either never worked in the Chemical Division or worked in the Chemical Division for less than 1 month. Cumulative exposure to PFOA was estimated using the surrogate measure of months of Chemical Division employment.

The observed numbers of cause-specific deaths were compared to the expected numbers of deaths obtained by applying sex- and race-specific quinquennial age, calendar period, and cause-specific mortality rates for the United States and Minnesota populations to the distribution of observed person-time.[21,22] Because less than 1% of plant employees were nonwhite, white male and white female rates were used for comparison. For women, only United States rates were used because cause- and calendar period-specific Minnesota rates for women were not available. The effects of latency, duration of employment, and work in the Chemical Division were examined using stratified standardized mortality ratio (SMR) analyses. Cause-specific mortality rates were compared between exposed and unexposed workers using stratified SMRs.[23] SMRs were calculated for men based on US and Minnesota white male mortality rates for three latency intervals (10, 15, and 20 years) and three categories of duration of employment (5, 10, and 20 years). The SMRs were calculated using the program developed by Monson.[22]

The relative risk (RR) and 95% confidence interval (CI) for deaths from all causes, cancer, cardiovascular diseases, and other selected causes were estimated using proportional hazard models.[24,25] The time to event or censoring was defined as time from first employment to event or to December 31, 1989. In models for specific causes of death, deaths from other causes were censored at the time of death. Age at first employment, year of first employment, and duration of employment were included as covariates in the model. The analyses were stratified by gender. The appropriateness of the proportional hazard assumptions was tested using stratified models with graphical analysis of log (−log[survival]) versus follow-up time relationships and models that tested the significance of a product term between exposure and log follow-up time.[25,26] Proportional hazard calculations were conducted using SAS.[25]

Results

A total of 3537 workers employed at the plant between Jan 1, 1947 and Dec 31, 1983 were identified from company records. Six workers who had incomplete employment records were excluded from the study. The cohort consisted of 2788 (79%) men and 749 (21%) women (Table 1). Men

TABLE 1
Characteristics of Female and Male Employees, 1947–1989

	Chemical Division		Non-Chemical Division		Total	
	Female	Male	Female	Male	Female	Male
Number of workers	245	1339	504	1449	749	2788
Person-years of observation	6029.0	33385.3	13280.4	37732.4	19309.4	71117.7
Mean follow-up (y)	24.6	24.8	26.4	26.0	25.8	25.5
Mean age at employment (y)	28.8	25.6	26.9	28.9	27.6	27.3
Mean year of death	1965.0	1963.8	1962.8	1962.3	1963.5	1963.0
Mean year of death	1981.3	1978.3	1979.2	1978.1	1979.6	1978.2
Mean age at death (y)	58.7	54.2	54.4	58.1	55.4	56.4

contributed 71,117.7 person-years of observation, which were equally divided between the Chemical Division and non-Chemical Division. Women contributed 19,309.4 person-years, two-thirds of which were in the non-Chemical Division.

Vital status was obtained for 100% of the cohort (Table 2). There were 50 deaths among the women (11 in the Chemical Division cohort and 39 in the non-Chemical Division cohort) and 348 deaths among the men (148 deaths in the Chemical Division group and 200 in the non-Chemical Division group). Death certificates were obtained for 99.5% of deaths.

For women, the SMR for all causes of death (SMR = .75; 95% CI, .56 to .99) was significantly lower than expected (Table 3). There was no association with duration of employment or latency for deaths from all causes, cancer, and cardiovascular diseases (data not shown). Mortality among Chemical Division women was less than expected. In Chemical Division women, the all-causes SMR was .46 (95% CI, .23 to .86) and the cancer SMR was .36 (95% CI, .07 to 1.05). The all-causes SMR for the non-Chemical Division women was .91 (95% CI, .64 to 1.24) and the cancer SMR was .91 (95% CI, .49 to 1.52) (data not shown).

Using Minnesota rates for comparison, the SMR for men for all causes, for cardiovascular diseases, and for all gastrointestinal diseases was significantly less than 1 (Table 4). None of the cause-specific SMRs was large nor was any significantly different from 1. The results were similar when the expected numbers of male deaths were based on US mortality rates. For the three latency intervals, the SMRs for deaths from all causes ranged from .75 to .77. For all cancers, the SMRs ranged from 1.06 to 1.12 and were nonsignificant.

Among men, there was no association between any cause of death and duration of plant employment. The all-causes SMRs were .86 (95% CI, .72 to 1.01) for the Chemical Division group and .69 (95% CI, .59 to .79) for the non-Chemical Division group (data not shown). The SMRs for prostate cancer were 2.03 (95% CI, .55 to 4.59) in the Chemical Division group and .58 (95% CI, .07 to 2.09) in the non-Chemical Division cohort. In the Chemical Division group, there were 4 observed and 2 expected deaths from prostate cancer. There was no significant association between any cause of death and latency in either exposure group. For the Chemical Division cohort, the prostate cancer SMR was 1.61 (95% CI, .32 to 4.70) in the greater than 15-year latency group.

Table 5 presents the final proportional hazard model for all-causes, all-cancer, and prostate-cancer mortality among the 2788 male workers employed for more than 6 months. The estimated relative risk for all-cause mortality for a 1-year increase in age at first employment was 1.08 (95% CI, 1.07 to 1.09). Year of first employment and duration of employment were negatively associated with deaths from all causes. The risk associated with months employed in the Chemical Division was small and nonsignificant.

In the final prostate cancer mortality model, length of employment in the Chemical Division was positively and significantly associated with prostate cancer risk. The relative risk for a 1-year increase in Chemical Division employment time was 1.13 (95% CI, 1.01 to 1.27) For 10 years' employment in the Chemical Division, the relative risk was estimated to be 3.3 (95% CI, 1.02 to 10.6) compared with workers never employed in the Chemical Division. Age at first employment was positively associated with prostate cancer mortality. Length of time employed in the Chemical Division was not significantly related to mortality from lung cancer, gastrointestinal cancer, pancreatic cancer, or diabetes mellitus.

TABLE 2
Vital Status and Cause of Death Ascertainment among Female and Male Employees, 1947–1989

Vital Status	Chemical Division				Non-Chemical Division				Total			
	Female		Male		Female		Male		Female		Male	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Alive	234	95.3	1191	88.9	465	91.6	1249	86.2	699	93.3	2440	87.5
Dead	11	4.7	148	11.1	39	8.4	200	13.8	50	6.7	348	12.5
Total	245	100.0	1339	100.0	504	100.0	1449	100.0	749	100.0	2788	100.0

TABLE 3
Observed (Obs) and Expected (Exp) Deaths, Standardized Mortality Ratios (SMR) and 95% Confidence Intervals (CI) for 749 Female Employees

Cause of Death	Obs	Exp	SMR	95% CI
All causes	50	66.74	0.75	0.56–.99
Cancer	17	23.04	0.71	0.42–1.14
Gastrointestinal	2	4.54	0.44	0.05–1.59
Respiratory	4	4.72	0.95	0.26–2.43
Breast	3	5.87	0.51	0.10–1.49
Genital	2	3.37	0.59	0.07–2.14
Lymphopoietic	3	2.04	1.47	0.30–4.29
Cardiovascular	10	12.39	0.81	0.49–1.29
Cerebrovascular	3	3.51	0.86	0.01–4.80
Gastrointestinal	3	3.41	0.88	0.18–2.57
Injuries	4	6.23	0.64	0.17–1.64
Suicide	1	1.78	0.56	0.01–3.13

Discussion

This was the first retrospective cohort mortality study of workers employed in a PFOA production plant. Mortality from all causes in both men and women was significantly less than expected. Because of the healthy worker effect, internal comparisons

TABLE 4
Deaths and Standardized Mortality Ratios (SMR) Based on Minnesota White Male Rates, Among 2788 Male Employees, 1947–1989, and 1339 Men Ever Employed in the Chemical Division, 1947–1989

Causes of Death	All Male Employees				Men Employed in Chemical Division			
	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All causes	347	450.79	0.77	0.69–0.86	148	172.96	0.86	0.72–1.01
Cancer	103	97.29	1.05	0.86–1.27	40	36.31	1.10	0.79–1.50
Gastrointestinal	24	26.78	0.90	0.57–1.33	9	9.77	0.92	0.42–1.75
Colon	9	9.42	0.96	0.44–1.81	4	3.46	1.15	0.31–4.01
Pancreas	8	5.58	1.43	0.62–2.83	4	2.04	1.96	0.53–5.01
Respiratory	31	30.42	1.02	0.69–1.45	12	11.26	1.07	0.55–1.86
Lung	29	28.94	1.00	0.67–1.44	11	10.70	1.03	0.51–1.84
Prostate	6	6.07	0.99	0.36–2.15	4	1.97	2.03	0.55–4.59
Testis	1	0.92	1.09	0.01–6.05	1	0.44	2.28	0.03–12.66
Bladder	3	2.18	1.37	0.28–4.01	1	0.75	1.33	0.02–7.40
Lymphopoietic	13	12.07	1.09	0.57–1.84	5	4.76	1.05	0.34–2.45
Cardiovascular	145	212.19	0.68	0.58–0.80	54	76.65	0.70	0.53–0.92
CHD*	110	159.09	0.69	0.57–0.83	43	57.74	0.74	0.54–1.00
Cerebrovascular	10	24.66	0.60	0.32–1.02	4	8.53	0.47	0.13–1.20
All gastrointestinal	12	21.13	0.57	0.29–0.99	8	8.27	0.97	0.42–1.91
All respiratory	13	21.75	0.60	0.32–1.06	7	7.77	0.91	0.36–1.87
Diabetes	8	6.52	1.23	0.53–2.42	3	2.55	1.18	0.24–3.44
Injuries	38	47.74	0.80	0.56–1.08	31	31.72	0.98	0.66–1.39
Suicide	12	15.09	0.79	0.41–1.39	10	6.99	1.43	0.68–2.63

*CHD, coronary and atherosclerotic heart disease.

were made between Chemical Division and non-Chemical Division employees. There were no significantly elevated SMRs in Chemical Division or non-Chemical Division employees. However, prostate cancer mortality was associated with length of employment in the Chemical Division in proportional hazard analysis. Ten years of employment in the Chemical Division was associated with an estimated 3.3-fold increase (95% CI, 1.02 to 10.60) in prostate cancer mortality.

The use of prostate cancer mortality to assess the association between PFOA and prostate cancer occurrence is problematic. Age-adjusted prostate cancer mortality rates from 1983 to 1989 (949 per 100,000) were only 25% of the incidence rates (99.4).[27] This low proportion of deaths among cases attributed to prostate cancer reflects the high risk of death for competing causes for this disease of elderly men. Given the small number of observed deaths from prostate cancer in the study, and the observed difference in incidence and mortality rates, the suggested association between PFOA exposure and prostate cancer must be viewed as hypothesis generating and should not be overinterpreted. The association may be real, may have been a chance finding, or may be the result of an unrecognized environmental factor. However, the biologic plausibility for any association between PFOA employment and prostate cancer is provided by animal toxicologic and human epidemiologic data that show an association between PFOA and reproductive hormone changes.[20]

The all-causes, all-cancer, and all-cardiovascular mortality among women was less than expected in the overall cohort. The low SMRs are most likely to be a result of the healthy worker effect. Latency and duration of plant employment did not have a strong relationship with the healthy worker effect.

The interpretation of this study requires consideration of methodological issues. SMRs for the subgroups of workers are not strictly comparable. We attempted to calculate standardized rate ratios; however, the rates were based on small numbers and produced unstable ratios. Estimates of PFOA exposure were based on job history, and categorization of workers into ever versus never employed in the Chemical Division may not reflect the biologic effective dose of PFOA. PFOA exposure was apparently widespread among employees not directly exposed to PFOA,[14] and the exposure categorization may misclassify workers as unexposed when they were ex-

TABLE 5
Proportional Hazard Regression Model of Factors Predicting Mortality among All Male Employees*

Variable	All Causes of Death				Cancer Deaths				Prostate Cancer Deaths			
	β	SE(β)	P	RR†	β	SE(β)	P	RR†	β	SE(β)	P	RR†
Year of first employment	−0.55	0.009	0.0001	0.946	−0.031	0.019	0.11	0.969	0.010	0.081	0.9	1.011
Age at first employment (y)	0.079	0.006	0.0001	1.08	0.078	0.011	0.0001	1.081	0.082	0.045	0.06	1.085
Duration of employment (y)	−0.34	0.001	0.0001	0.967	−0.028	0.009	0.002	0.972	−0.07	0.052	0.18	0.932
Months in chemical division	0.001	0.001	0.24	1.001	0.002	0.001	0.2	1.002	0.01	0.005	0.03	1.01

* Abbreviations used are: β, regression parameter; SE(β), standard error of the slope parameter; RR, relative risk.
† Relative risk for one unit change in independent variable.

posed. Such misclassification would be expected to bias the effect estimates toward the null if increased exposure increases death rates. Months employed in the Chemical Division may better reflect the biologic effective dose because cumulative exposure reflects the bioaccumulation of PFOA. Workers were exposed to many other xenobiotics, such as benzene and asbestos, during their employment at the plant. However, none of these materials has been associated with prostate cancer.

Although the mean age at first employment and mean year of first employment are similar in the Chemical Division and non-Chemical Division cohorts of men and women, the comparisons of the rates of disease are confounded by differences in the distribution of age at risk. The use of an internal comparison group may reduce, but not eliminate, confounding if the internal comparison groups have different distributions of these time factors. Because the disease occurrence relationship is defined in terms of cumulative exposure, the true effect of PFOA exposure may have been biased toward or away from the null by uncontrolled confounding by time factors.[28,29]

Further research is needed to evaluate and confirm the association between PFOA and prostate cancer. The findings in this study are based on a small number of cases and could have resulted from chance or unrecognized confounding from exposure to other factors. Studies of prostate cancer incidence in this and other PFOA-exposed work forces may clarify the suggested increase in prostate cancer risk.

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