Final Report

Mortality of Employees of an Ammonium Perfluorooctanoate Production Facility

Jessica I. Lundin, MPH

Bruce H Alexander, PhD
Associate Professor
Principal Investigator

Division of Environmental Health Sciences
University of Minnesota, School of Public Health

August 22, 2007

Executive Summary

Background: This report presents the results of a cohort mortality study of workers employed at the 3M Ammonium Perfluorooctanoate (APFO) production facility in Cottage Grove Minnesota. The purpose of this study was to examine possible associations between working in jobs with varying exposure to APFO and specific causes of death.

Methods: The study population included all employees of the Cottage Grove facility with a minimum of 365 days of cumulative employment prior to 1997. The population was followed from the time they entered the workforce through 2002. Underlying and contributing causes of death were obtained from the National Death Index and death certificates.

Work history records were used to determine potential APFO exposure. Each job held was assigned to one of three exposure categories; non-exposed, probable APFO exposure, and definite APFO exposure. Exposure categories were initially established based on duration of employment in each of these jobs. The cohort members were classified as ever or never having a job with probable exposure, probable or definite exposure or for a minimum period of time in these job categories. To estimate cumulative exposure a weighted cumulative exposure model was constructed by multiplying the duration of employment by an exposure weight of 1 for non exposed, 30 for probable exposure and 100 for definite exposure. The weights, though somewhat arbitrary, reflect differences in biological monitoring of the jobs and consider the long half-life of the chemical. The cumulative exposures were then categorized as estimates equivalent to less than one, one to five and more than five years of employment in high exposure jobs.

Standardized mortality ratios (SMR) were estimated for all cause and cause specific mortality using mortality rates from the general population of Minnesota as a reference. SMR estimates were made for the sub-cohorts ever exposed to APFO, by exposure category, and for a minimum of one year of exposure.

Time dependent Cox regression models were used to estimate the risk of specific causes of death using an internal referent population. Risks were estimated for working in a definite exposure job for a minimum of 6 months (high exposure) and ever in a job with probable exposure or a job with definite exposure for less than 6 months (moderate exposure) in comparison to those who never held a job with definite or probable exposure (low exposure). A similar time dependent analysis for cumulative exposure used weighted estimates equivalent to less than one, one to five and more than five years in a job with definite exposure. All models were adjusted for sex, birth year, year of eligibility, wage type (salary, hourly or both), and an estimate of smoking habit.

Causes of death of *a priori* interest were liver, pancreatic and testicular cancer and cirrhosis of the liver based on animal toxicological data, and prostate cancer and cerebrovascular disease from prior analyses of this cohort.

Results: There were 3993 eligible workers, and 807 deaths, in the cohort. The SMR for all causes of death was 0.8 (95% CI 0.7-0.9) and 0.9 (95% CI=0.8-1.0) for malignant causes of death. No malignant or non-malignant causes of death had significantly elevated for any exposure classification, however the members of the non-exposed cohort had significantly reduced mortality due to prostate cancer (SMR=0.4, 95% CI=0.1-0.9), cerebrovascular disease (SMR=0.5, 95% CI=0.3-0.8), and ischemic heart disease (SMR=0.7, 95% CI=0.3-0.8). The

members of the cohort with definite exposure did have lower than expected rate of death from ischemic heart disease, but not prostate cancer (SMR=2.1, 95% CI=0.4-6.1), or cerebrovascular disease (SMR=1.6, 95% CI=0.5-3.7)

The time dependent analysis using the internal referent population produced hazard ratios indicating an association with APFO exposure and prostate cancer and cerebrovascular disease. Those with high or moderate exposure had an elevated risk of dying from cerebrovascular disease (HR=5.1, 95% CI = 1.4-18.6 and HR= 2.1, 95% CI = 1.0-4.6, respectively) and prostate cancer (HR=7.0, 95% CI = 1.2-42.2 and HR=3.0, 95% CI = 0.8-11.0, respectively). The highest cumulative exposure score was associated with an elevated risk of dying from cerebrovascular disease (HR=2.4, 95% CI=1.1-5.5) and prostate cancer (HR=3.8, 95% CI=1.2-13.2). When stratified by wage type similar associations were observed for prostate cancer and cerebrovascular disease. Lagging exposures by 10 years made little or no difference in the hazard ratio estimates.

Conclusion: APFO exposed workers did not have an elevated risk of death when compared to the population of the state of Minnesota, however within the cohort risk of death from prostate cancer and cerebrovascular disease was elevated for workers with higher estimated exposure. Interpreting the somewhat contradictory results requires caution and consideration of several assumptions. *A priori* causes of death selected based on animal toxicology studies, liver, pancreatic and testicular cancer and cirrhosis of the liver, were not observed to be associated with APFO exposure.

Introduction

Ammonium Perfluorooctanoate (APFO, $CF_3(CF_2)_6CO_2^-NH_4^+$) is a thermally stable synthetic surfactant which is resistant to a large variety of chemicals, and resistant to degradation. These unique properties led to its use in industrial applications, as well as ist use as an ingredient in consumer products such as non-stick coatings for cookware, clothing, automotive products, and paper coatings (sandwich wrappers, popcorn bags, etc) for oil and moisture resistance (1). In the presence of biologic media, APFO dissociates into perfluorooctanoic acid (PFOA, $CF_3(CF_2)_6COOH$;), an anion of APFO. APFO was produced at the 3M facility in Cottage Grove, Minnesota from 1947 until the year 2000.

Laboratory studies have shown PFOA to be absorbed through inhalation, ingestion, and dermal contact and is distributed in the liver and in the blood with notable gender differences varying by species (2). PFOA is metabolically inert; it is not biotransformed or conjugated and is eliminated primarily through urine and feces (2).

Biological monitoring data indicate that occupational exposures to APFO in manufacturing workers result in median serum PFOA levels in the range of 0.3 to 5.2 parts per million (ppm), depending on the work area (3). The general population has been shown to have average sera PFOA concentrations of 5 parts per billion (ppb) (4, 5). A comparisons of banked serum from community base samples showed an increase in serum concentrations between 1974 and 1989, but no significant change between 1989 and 2001(6). Preliminary data suggest that the population exposure has decreased following the phase out of the production of these materials (7).

PFOA is a peroxisome proliferator with demonstrated effects in laboratory animals. Animal studies have shown effects on the liver, atrophy of lymphoid tissues (spleen and lymph nodes), benign hepatocellular tumors, , pancreatic acinar cell tumors, and testicular leydig cell

tumors (2) A previous mortality study of this cohort have shown an association with working in the chemical division of the APFO manufacturing facility and dying from prostate cancer(8), and a updated analysis identified a potential association with high APFO exposure and death from cerebrovascular disease (9). The purpose of this study with an updated mortality follow-up was to further evaluate potential associations between occupational APFO exposure and specific causes of death in this cohort.

Methods

Study Population

The protocol for this study was reviewed and approved by the University of Minnesota Institutional Review Board. This occupational cohort of workers at the APFO production plant in Cottage Grove, Minnesota included all workers with one year (365 days) of cumulative employment between the dates of January 1, 1943 and December 31, 1997. Cohort members meeting eligibility criteria were followed until either December 31, 2002 or their date of death. The human resource records of all eligible employees were abstracted for demographic information, including the worker's name, social security number, employee identification number, date of birth, and details of work history. The latter included job specific start and end dates, department codes, and job classifications. Demographic information and vital status was verified using TRW/Experian (a credit reporting agency) and the Social Security Administration service for epidemiologic research studies.

Determination of Vital Status

Vital record searches were performed for all cohort members not employed by the company on December 31, 2002 and who had not been identified as deceased in previous studies (8, 9). Vital status of these cohort members was determined through the National Death Index (NDI). All potential matches from the NDI search were reviewed by hand to ensure a valid match. The underlying and contributing cause of death was obtained from NDI Plus for deaths after 1979. Death certificates were obtained for decedents who died prior to 1979 and were coded by a certified nosologist for causes of death in the International Classification of Disease (ICD) revision in effect at the time of death. If a death certificate could not be found for an NDI

identified decedent, the individual cause of death was classified in the 'other' cause of death category.

Exposure Assessment

The goal of this study was to describe mortality experience in relation to fluorochemical exposure with particular interest in PFOA. Some biological monitoring data are available for more recent years, however they are insufficient to fully characterize exposure to workers over the life of the plant. Therefore, the exposure assessment relied on work history records and expert knowledge of the history of the APFO manufacturing process to first develop a qualitative exposure assessment for each job held by the cohort members. All perfluorochemical development and production occurred in departments affiliated with the chemical division of the plant. The specific areas where APFO and other perfluorochemicals were produced changed over the years, as did the work area department codes, thus exposure levels could not be assigned to workers based on work history alone. To remedy this, the department codes were reviewed by year to determine the building and division assigned to each code. The resulting lists were reviewed independently by a panel of veteran workers and plant industrial hygienists to determine where the perfluorochemical production, or the development of the perfluorochemical products, took place over the history of the facility. The individual responses were summarized and the panel met as a group to discuss any discrepancies and confirm the exposure assignments. The available information permitted the panel to classify the jobs in the work histories into three general classifications of exposure.

- Definite occupational APFO exposure: These jobs were in areas where electrochemical fluorination, drying, shipping, and packaging of APFO occurred and the worker would be

exposed to APFO on a regular basis. These jobs also had the potential for higher exposures.

- Probable occupational APFO exposure: These jobs were in other chemical division areas where exposure to APFO was possible, but the exposures were considered lower or transient.
- No or minimal occupational APFO exposure: These jobs were primarily in the non-chemical division of the plant. These workers may have had the opportunity for some exposure if they passed through an exposed area, but were not exposed specifically as part of their job. They likely had higher exposures than the general population due to contamination at the work site.

Hereafter these job exposure subgroups will be referred to as definite APFO exposure, probable APFO exposure, and non-exposed.

Exposure Classification for Analysis

The employees of this plant changed job classifications frequently, thus they could not be classified into discrete, mutually exclusive exposure groups that mirrored the job exposure subgroups. To accommodate the migration between exposure subgroups we incorporated two approaches for characterizing APFO exposure in the analysis. The primary analysis is based on ever attaining a minimum tenure in jobs with probable or definite exposure. A secondary analysis used a cumulative exposure model developed to explore a weighted exposure distribution based on duration of employment and an assumed exposure intensity.

Exposure by Job Classification. The initial analyses explored the mortality experience of workers compared to that of the general population of Minnesota with respect to their entire

work history of ever working in jobs with definite or probable exposure, a minimum of one year in definite or probable exposure jobs, or only working in the non-exposed jobs. Subsequently a more restrictive classification was developed for an analysis using an internal referent population which classified the cohort members as; 1)those working only in jobs not exposed to fluorochemicals (low exposure), 2) ever working in a probable APFO exposure job or working a definite APFO exposure job for less than 6 months (moderate exposure), or 3) employment in a definite exposure job for 6 months or more (high exposure). Entry into the latter two categories could occur at varying points in the individual's work history. This model assumes that once a person is employed in a high exposure job for a minimum period of time or a moderate exposure job they reach a threshold where their risk is different from individuals working in jobs without direct occupational APFO exposure.

Cumulative Exposure. A model estimating cumulative APFO exposure requires that both time and intensity be considered. Biological monitoring data indicate a demarcation of exposure by job. Employees in the type of jobs classified with definite exposure had median serum PFOA levels ranging from 2.6-5.2 ppm, while employees in jobs classified with probable exposure had levels ranging from 0.3-1.5 ppm (3). The biological half-life of PFOA is believed to be 3.8 years (10), thus short-term peak exposures may equate to longer term lower exposures over time. Considering these facts, the initial cumulative exposure assigned exposure weights of 1, 30, and 100 to the time in jobs with no exposure, probable exposure, and definite exposure. These unit-less weighting factors, while somewhat arbitrary, were chosen to reflect the relative exposure intensity of jobs and long biological half-life of PFOA. For each worker the weighted exposure level was multiplied by the total days of employment at each level (weighted exposure level*days exposed), which provides a time-dependent exposure metric. The cumulative

exposure was categorized at levels representing the equivalent of up to one year (36,499 exposure-days), one to five years (36,500-182-499 exposure-days) and five or more years (182,500 exposure-days) of employment in a job with definite exposure. Because these weights are arbitrary we conducted a sensitivity analysis to explore how alternative weighting schemes may affect the results. The alternate weighting schemes were 1,10, 50 and 1, 10, 100, which would minimize migration of workers in jobs with probable exposure being classified with the higher exposed individuals.

Determination of Smoking Status

Smoking was a potentially confounding variable for some diseases of interest. To characterize the smoking habit of the cohort, the occupational medical records of the cohort members were abstracted for information on smoking status; ever smoked regularly, year started smoking, years they smoked, and cigarettes smoked per day. Cohort members were classified by the smoking history and the availability of the records; smoking history available, medical record available but no information about smoking, and medical record not available.

Determination of Salary versus Hourly Wage Type

Baseline socio-economic status is a likely determinant of mortality from several diseases. As a proxy measure of socio-economic status, the cohort members were classified by wage type based on the work history records. Workers were classified as hourly, salary, or both. The latter was designated if the job history included earning each type of wage for at least 365 days. A dichotomous version of this covariate was also established in which workers with both hourly and salary experience were classified as hourly or salary based on the predominant wage type.

Cause-Specific Mortalities of Interest

A priori causes of death of interest were selected from toxicological literature and prior studies of workers exposed to fluorochemicals. Cancer of the liver, pancreas, and testicles and cirrhosis of the liver were selected based on results from toxicological studies (2). Deaths from prostate cancer and cerebrovascular disease (CVD) were previously reported to be associated with potential flurorochemical exposure in this cohort (8, 9, 11) and bladder cancer was associated with fluorochemical perflurooctanesulfonate (PFOS) exposure in another occupational cohort (11). Ischemic heart disease was included as an a priori disease of interest due to the effect of PFOA on lipid metabolism. ICD 9th revision codes used to classify the underlying causes of death: prostate cancer, 185; pancreatic cancer, 157; liver cancer, 155; bladder cancer, 188, 189.3-189.9; CVD, 430-438; ischemic heart disease, 410-414; and cirrhosis of the liver, 571. Congenital cerebral aneurysm (ICD9 747.81) were not identified in this cohort.

Analysis

The mortality experience of the cohort was initially compared to the mortality rates for the corresponding population of the state of Minnesota. Reference data were obtained from the Mortality Population Data System (MPDS) center at the University of Pittsburgh, which were derived from National Center for Health Statistics data. The all-cause mortality and malignant neoplasm rates were available from 1940, and the non-malignant cause-specific death rates from 1962. The referent data were available in age (5 year), sex, race, and calendar period (5 year) and were coded using the rules for the ICD revision in effect for the relevant calendar period. The Standardized Mortality Ratios (SMRs) and 95% confidence intervals were computed using the PC Life Table Analysis System (PCLTAS) software developed by the National Institute of Occupational Safety and Health (NIOSH) (12). State specific referent data were only available

through 1999 so the referent rates for 1999 were applied for the years 2000-2002. The all-cause and cause-specific SMRs were first computed for the full cohort. SMRs were then computed separately for the cohort member ever employed in a job with definite APFO exposure, those who worked jobs with definite or probable exposure for at least one year, and for the cohort members who worked primarily in the non-chemical division. SMRs were also computed for workers by hourly and salary wage type. For this analysis, workers with both hourly and salary jobs were classified by the predominant wage type.

To model the risk of the cause-specific mortalities of interest as a function of PFOA exposure using an internal referent population, hazard ratios and 95% confidence intervals were estimated using in multivariable time-dependent Cox regression models (13). Exposure was characterized by job classification and then cumulative exposure. The time variable was the number of days from the first day of employment at the production facility to an event (death) or the end of the study. In the cause-specific mortality models, all other causes of death were censored at the time of death. The models were adjusted for sex, age eligible to be in the study, year of birth, and wage type. To explore potential effects of latency the exposure models were lagged by 10 years prior to end of study or the date of death. The Cox regression analysis was conducted using SAS 9.1(14).

Smoking is an important potential confounding variable in this study, but smoking habit data were unavailable for many of the cohort members. An initial Cox regression model was fit with smoking coded as ever smoked, never smoked, no information about smoking on medical record, and no medical record available. In a second approach a multiple imputation model was constructed using individuals with smoking data to predict the smoking status of those without

smoking data (15). The predictors used for the imputation process were sex, year of birth, year of first employment at the facility, age eligible to be in the study, and wage type. Eighteen independent, completed data sets were generated and a Cox regression procedure, as described above, was performed on each data set. The results were pooled to give single parameter estimates and 95% confidence intervals. The hazard ratios from the final models are presented to describe the potential effects of confounding by smoking. All imputation procedures were conducted using SAS 9.1(14).

Results

Of the 6678 individual workers identified at the facility, 3993 employees met the inclusion criteria. Of these, 513 workers (12.8%) were ever employed in a job with definite PFOA exposure, 1688 workers (42.3%) were ever employed in a job with probable exposure (and never worked a job with definite exposure), and 1792 workers (44.9%) were employed in jobs where they were never exposed to fluorochemicals (Table 1). The majority of the study cohort was male (80%), particularly for the definite exposure subgroup (92%). The average age at the end of follow-up was slightly younger in the definite exposure subgroup, but the average number of years of employment was longer. The total number of deaths in the cohort was 807, with 68 deaths in the definite, 368 in the probable, and 371 in the non-exposed exposure subgroups.

Smoking data was found for 1430 (36%) cohort members, of these, 783 (55%) were found to have ever smoked (Table 2). There was a higher prevalence of smoking in those who ever worked a job with definite APFO exposure compared to the non-exposed workers, 65% and 47% respectively. However, smoking data was available for 66% of the definite exposure subgroup (338/513), whereas it was only available for a 20% of the non-exposed subgroup (355/1792).

The all-cause and cause-specific mortality ratios for the entire cohort, and exposure subgroups, were generally lower than expected compared to the Minnesota referent population (Table 3-6). The all-cause standardized mortality ratio (SMR) for the entire cohort was 0.8 (95% CI = 0.7-0.9) (Table 3). The results were similar for all deaths from cancer (SMR = 0.9, 95% CI = 0.8-1.0). The cause-specific mortality ratios for one or more years of definite or probable PFOA exposure were lower than expected for cerebrovascular disease (SMR=0.8, 95% CI=0.5-1.3) and ischemic heart disease (SMR=0.7, 95% CI=0.6-0.9). The SMRs for prostate cancer

(SMR = 1.4, 95% CI = 0.7-2.4), pancreatic cancer (SMR = 1.2, 95% CI = 0.5-2.4), bladder cancer (SMR = 1.3, 95% CI = 0.3-3.9), and diabetes mellitus (SMR=1.7, 95% CI = 0.9-2.8) were modestly, albeit imprecisely, above unity (Table 4). The cause-specific mortality ratios for cohort members ever employed in jobs with definite PFOA exposure were greater than expected for prostate cancer (SMR = 2.1, 95% CI = 0.4-6.1) and cerebrovascular disease (SMR = 1.6, 95% CI = 0.5-3.7), although the confidence intervals are quite wide and include the null (Table 5). Similar patterns are present when the analysis is restricted to one year of definite exposure (Table 6) though the number of deaths is small. The cause specific SMRs for all definite exposure strata all have confidence intervals indicating these elevations are not beyond chance. Cohort members who worked in jobs with probable exposure, but never held a job with definite exposure had an elevated risk of death from diabetes mellitus (SMR=2.0, 95% CI =1.2-3.2), but low risk of death from ischemic heart disease (SMR=0.8, 95% CI=0.7-1.0) and cerebrovascular disease (SMR=0.7, 95% CI=0.4-1.1) (Table 7). In contrast, the number of deaths from prostate cancer and cerebrovascular disease were significantly lower among the never exposed members of the cohort; 0.4 (95% CI 0.1-0.9) and SMR 0.5 (95% CI 0.3-0.8)respectively (Table 8).

No deaths from testicular cancer were observed and only 3 cases of liver cancer (SMR=0.5, 95% CI=0.1-1.4), of which two held jobs with probable exposure. These small numbers precluded further analysis for these causes of death. Thirteen deaths from cirrhosis of the liver were identified (SMR= 0.7, 95% CI=0.4-1.2) with only 4 occurring in workers with at least one year of definite or probable exposure (SMR=0.5, 95% CI=0.2-1.4).

The SMRs for salaried workers showed a decreased risk of death for all cancers (SMR 0.7, 95% CI 0.6-0.8), respiratory cancers (SMR 0.6, 95% CI 0.4-0.9), prostate cancer (SMR=0.5, 95% CI 0.2-1.2), diabetes (SMR= 0.2, 95% CI = 0.02-0.74,), cerebrovascular disease (SMR=0.6, 95% CI=0.4-1.0) and heart disease (SMR=0.6, 95% CI=0,5-0.7) (Table 9). The results were somewhat different for hourly employees; all cancers (SMR 1.0, 95% CI 0.9-1.2), respiratory cancers (SMR 1.2, 95% CI 0.9-1.6), prostate cancer (SMR=0.9, 95% CI 0.4-1.6), cerebrovascular disease (SMR=0.7, 95% CI=0.4-1.0) and heart disease (SMR=0.9, 95% CI=0.8, 1.1) (Table 10). The SMR for diabetes (2.1, 95% CI = 1.3-3.1) was elevated for the hourly workers.

Comparing the mortality experience within the cohort in the time-dependent Cox regression models revealed differences for some of the outcomes of interest. A high or moderate exposure work history, compared to only working in low exposure jobs, was associated with an increased risk for cerebrovascular disease (HR=5.3, 95% CI = 1.5- 19.6 and HR= 2.1, 95% CI = 1.0-4.5, respectively) and prostate cancer (HR=6.9, 95% CI = 1.2-41.8 and HR=3.0, 95% CI = 0.8-11.0, respectively) (Table 11). A moderate exposure work history was also associated, imprecisely, with an elevated risk of dying from diabetes mellitus; HR=1.9, 95% CI = 0.7-5.4, however no deaths from diabetes were reported in cohort members in the high exposure category. Diabetes mellitus was included in these analyses because of modestly elevated SMRs; specifically in the hourly workers. The inclusion of the imputed values for smoking status derived from the multiple imputation procedure, nor the inclusion of the actual smoking data, made little or no difference in the risks estimates (Table 11). The results for prostate cancer, cerebrovascular disease, ischemic heart disease and diabetes were further explored by stratifying by wage type (Table 12). These analyses suffered from small numbers for prostate cancer,

cerebrovascular disease, and diabetes. The risk associated with the high exposure category persisted for cerebrovascular disease. The high exposure prostate cancer deaths were salary workers while most of the moderate exposure prostate cancers were hourly employees. Overall, there was not strong evidence that the effects in the models adjusted for wage type were limited to either hourly or salary workers. Lagging exposures by 10 years also made little or no difference in the hazard ratio estimates (Table 13).

Estimated hazard ratios (HR) comparing the highest to lowest weighted exposure category for cerebrovascular disease and prostate cancer were HR=2.4, 95% CI = 1.1-5.4 and HR=3.6, 95% CI = 1.2-10.6, respectively (Table 14). There was no association between the metrics of weighted exposure and risk of pancreatic or bladder cancer, cirrhosis of the liver, disease and diabetes. The risk of dying from ischemic heart disease was, if anything, lower among those with increased exposure. As with the results for exposure by job classification, there was little evidence that the risks were different between hourly and salary workers (Table 15). The sensitivity analysis using alternate weighting schemes did not change the overall conclusions the analysis of cumulative exposure (Table 16).

Discussion

This study evaluated the mortality experience of a population of workers at an ammonium perfluorooctanoate production facility, with specific attention to exposure to PFOA. No excess mortality was observed for malignant or non-malignant causes of death when compared to the corresponding Minnesota mortality rates. The SMRs for prostate cancer and cerebrovascular disease were slightly elevated for those with a history of working in jobs with definite PFOA exposure, while the SMRs for the members of the cohort never working in a PFOA exposed job were significantly below unity. Analyses using an internal referent category found increased risk of death from prostate cancer and cerebrovascular disease among workers with a history of greater PFOA exposure when compared to those working in jobs with no or minimal exposure. A priori causes of death selected based on animal toxicology studies, liver, pancreatic and testicular cancer and cirrhosis of the liver, were not observed to be associated with PFOA exposure. Interpreting these somewhat contradictory results requires caution and consideration of several assumptions.

Some elements of the study design for this study differs from the earlier mortality analyses of this cohort (8, 9). Gilliland and Mandel (8) required six months of cumulative employment for inclusion, while the current study required one year of employment to exclude short-term workers, often summer interns, who might have different underlying risk factors than the long-term workers. In that analysis, job exposures were assigned as working for at least one month in the chemical division compared to working in the non-chemical division (or chemical division for less than one month). To minimize exposure misclassification the current study focused on PFOA and classified jobs in the chemical division as definite or probable, as only certain areas and tasks within the chemical division likely led to high APFO exposure. Lastly,

169 additional cohort members were included in the current study that, according to available employment data, were eligible for both studies. This study also differs from the more recent mortality analysis of this cohort (9). The population for the current study was followed through 2002, four years longer than the previous study, increasing the number of deaths from 607 to 807, and included analyses using an internal referent group.

The association between prostate cancer and work in a APFO exposed job is similar to the results of Gilliland and Mandel (8) who reported a 3.3-fold increase (95% CI = 1.0-10.6) in prostate cancer mortality associated with working ten years in the chemical division compared to non-chemical division workers; based on 6 cases. In the current study an association was observed between both metrics of PFOA exposure and prostate cancer when compared to the internal referent category. The biological mechanism for an association between PFOA and prostate cancer is not clear. An effect of PFOA on the endocrine system has been described in the rat which involves regulation of estradiol, testosterone, follicle stimulating hormone, luteinizing hormone and thyroid stimulating hormone through action in the liver (16-18). In this occupationally exposed population PFOA exposure was not clearly associated with changes in circulating levels of reproductive hormones (19), but this cross-sectional assessment was based on single blood samples.

The association between APFO exposure and prostate cancer and cerebrovascular disease was most apparent when the internal referent population was used. An internal referent population from within a cohort may provide a more valid comparison, assuming similar social and demographic characteristics; however the interpretation of these results should also consider how the strata specific prostate cancer deaths compare to the expected deaths based on

Minnesota general population. The SMR for the exposed categories were only modestly above unity, while the non-exposed members of the cohort were significantly below. The latter suggests that 3M employees who are not regularly exposed to APFO at work are different from other men in Minnesota with respect to baseline prostate cancer risk; some of which may be related to socioeconomic status (SES). The extent to which this difference may have influenced the internal analysis is unknown. Our analyses adjusted for wage status as a proxy for socioeconomic status, which may influence several factors associated with prostate cancer death. The proportional hazards analysis stratified by wage type revealed similar patterns of risk with exposure in the hourly and salary workers, though the numbers were very small.

Deaths from heart disease and cerebrovascular disease are almost always below unity in epidemiologic studies of chemical workers (20) , for this reason the increased risk of cerebrovascular disease death associated with higher exposure was unexpected. It is possible that the coding of cerebrovascular disease deaths vary by region, however using mortality from local counties rather than the state made no differences in the earlier analysis (9). The risk of stroke is related to hypertension, diabetes, and life style factors including diet and smoking (21-23). The SMRs for diabetes mellitus and hypertension in the non-exposed subgroup were 0.52 and 0.98, respectively and 1.73 and 1.84, respectively, in the exposed subgroup. The SMR for lung cancer, a potential indicator of smoking in the cohort was 1.01 in the exposed compared to 0.76 in the non-exposed sub-cohort. Though not directly comparable, these patterns may be related to the cerbreovascular disease finding in that the lifestyle characteristics of the cohort members with high PFOA exposure were different than the lower exposed persons. Nevertheless, adjusting for smoking habit and wage type did not alter the association, and similar to prostate cancer, the analysis stratified by wage type indicated higher risk of death from cerebral vascular

disease associated with exposure in both hourly and salary workers. Diet is a potential factor in the risk of stroke, though it was not measured in this study. In the same working population, however, body mass index (BMI) of almost 50% of the workers ranged from 25-30 (24) , which is considered overweight (25). However, it has also been shown that worker BMIs were similar among varying serum PFOA levels (26).

Any findings in a mortality study related to diabetes should be interpreted with caution as the use of mortality data to evaluate diabetes risk is problematic. In a study of 2,766 decedents with a known history of diabetes it was shown that diabetes was recorded as the underlying cause of death on approximately 10% of the death certificates, and those recorded were related by age, duration of diabetes, and co-morbidities (27). The excess in the hourly workers could indicate lifestyle differences, but future research would require a more comprehensive assessment of diabetes morbidity to fully describe any potential relationship with PFOA exposure.

When interpreting this mortality analysis several limitations should be considered. Some exposure misclassification is likely. For example, maintenance and other mobile workers that routinely entered the definite PFOA exposure departments and work areas, but may have not been classified in the definite exposure subgroup. On the other hand, a few workers assigned to the definite exposure subgroup may not have spent much time in those departments or work areas. The extent of exposure misclassification and the effects on the study results remains unknown, as no additional data are available to verify these assumptions. Although several methods of approach were used to find all deaths in this cohort, it is possible that some deaths were not accounted for, which can occur when an individual leaves the country, changes their identity, or due to errors in surveillance systems. Race data were not available for the cohort.

The impact of this is likely to be limited as the population of Minnesota has been predominately Caucasian over the decades (97% in the 1980 census, 94% in the 1990 census, and 89% in the 2000 census) (28). The analysis was able to account for potential confounding by age, sex, wage status, and, to some extent, smoking habit. Unfortunately the smoking data were sparse, and though sophisticated methods to impute the missing data were applied, it is debatable whether the assumptions pertaining to this imputation were upheld. Another noteworthy limitation is the power of the study. The mean age at follow-up was 60 years, thus the relatively small number of deaths from the causes of interest limits the ability of the study to examine exposure responses, particularly using an internal reference category.

By definition, mortality studies, although cost effective and convenient, miss the cases that do not result in death. Prostate cancer and cerebrovascular disease, the two findings of potential importance, do not always result in death and may not be listed as contributing causes of death on a death certificate unless they had recently been diagnosed or the person was undergoing treatment. While the mortality study does capture the worse case scenario for the diagnosis of these conditions, death from these conditions may be associated with other factors, including access to health care and availability of screening. The potential contribution of these factors are difficult to quantify, however all members of the cohort were, at least for 1 year, employed by 3M, and would have had access to similar health benefits.

There are also notable strengths of this study. The cohort was constructed from the production facility employment records, thus allowing for complete enumeration of the cohort. The availability of the work history information in conjunction with detailed review of the

production history of PFOA at this plant with veteran workers and industrial hygienists helped reduce exposure uncertainty related to exposure misclassification. A final noteworthy strength to this study is the comprehensive follow-up of the cohort. An underlying cause of death was found for 99.6% of the known deaths (804/807), all unavailable or unfound death certificates were from cohort members who worked in the non-chemical division of the plant.

The low SMRs in the non-exposed subgroup are suggestive of a bias contributing to the associations found in the internal analyses. There is also potential bias in the regression models with an internal referent group in that they were used under the assumption that all individuals in the model were the same by all risk factors except exposure. An attempt was made to account for the differences in lifestyle by the inclusion of wage type and smoking status in the models; however we were not able to fully account for the bias from smoking because the amount of available data was so small and the ability of the wage type to fully account for socio-economic differences is unknown. Interestingly, the ischemic heart disease mortality risk did not vary by exposure strata, as would be expected if significant differences in risk factors for heart disease existed between the exposure categories. To the extent that the underlying (unmeasured) risk factors for ischemic heart disease are similar to those for CVD and prostate cancer, potential confounding from these factors is of less concern.

In summary, this study evaluated the mortality experience of an occupational cohort exposed to APFO and showed an association within the cohort between both death from cerebrovascular disease and prostate cancer and working in jobs with higher APFO exposure and an estimate of cumulative APFO exposure. No association was observed between APFO exposure and a priori diseases of interest based on toxicology studies. While findings have been

suggested in previous cohort studies; the current study had a longer follow-up period, therefore more deaths, increasing the power of the study. Additional follow-up of this cohort is recommended to clarify these associations, and if possible, should account for confounding factors such as BMI, smoking, access to health care, and other lifestyle factors. Studies of disease incidence that capture the cases that do not result in death would be informative, though these types of studies can be difficult to implement. Assessing the incidence of prostate cancer through cancer registries would be helpful in clarifying the association with prostate cancer. Future studies should also consider more sophisticated exposure models to properly assign etiologically relevant estimates of exposure.

References

1. Begley TH, White K, Honigfort P, Twaroski ML, Neches R, Walker RA. Perfluorochemicals: potential sources of and migration from food packaging. *Food Additives & Contaminants* 2005;22(10):1023-31.

2. Kennedy GL, Jr., Butenhoff JL, Olsen GW, O'Connor JC, Seacat AM, Perkins RG, Biegel LB, Murphy SR, Farrar DG. The toxicology of perfluorooctanoate. *Critical Reviews in Toxicology* 2004;34(4):351-84.

3. Olsen GW, Butenhoff JL, Mandel JH. Assessment of lipid, hepatic, and thyroid function in relation to an occupational biologic limit value for perfluorooctanoate. Saint Paul: 3M Company; 2003. Report No.: USEPA Public Docket AR-226-1351.

4. Olsen GW, Church TR, Miller JP, Burris JM, Hansen KJ, Lundberg JK, Armitage JB, Herron RM, Medhdizadehkashi Z, Nobiletti JB, O'Neill EM, Mandel JH, Zobel LR. Perfluorooctanesulfonate and other fluorochemicals in the serum of American Red Cross adult blood donors. *Environmental Health Perspectives* 2003;111(16):1892-901.

5. Olsen GW, Church TR, Larson EB, van Belle G, Lundberg JK, Hansen KJ, Burris JM, Mandel JH, Zobel LR. Serum concentrations of perfluorooctanesulfonate and other fluorochemicals in an elderly population from Seattle, Washington. *Chemosphere* 2004;54(11):1599-611.

6. Olsen GW, Huang HY, Helzlsouer KJ, Hansen KJ, Butenhoff JL, Mandel JH. Historical comparison of perfluorooctanesulfonate, perfluorooctanoate, and other fluorochemicals in human blood. *Environmental Health Perspectives* 2005;113(5):539-45.

7. Olsen GW, Mair DC, Reagen WK, Ellefson ME, Ehresman DJ, Butenhoff JL, Zobel LR. Preliminary evidence of a decline in perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations in American Red Cross blood donors. *Chemosphere* 2007;68(1):105-11.

8. Gilliland FD, Mandel JS. Mortality among employees of a perfluorooctanoic acid production plant. *J Occup Med.* 1993;35(9):950-4.

9. Alexander BH. Mortality study of workers employed at the 3M Cottage Grove Facility. Minneapolis: University of Minnesota; 2001. Report No.: U.S. EPA Docket AR-226-1030a018.

10. Olsen G, Ehresman D, Froehlich J, Burris J, Butenhoff J. Evaluation of the half-life of elimination of perfluorooctanesulfonate (PFOS), perfluorohexanesulfonate (PFHS) and perfluorooctnaoate (PFOA) from human serum. FLUOROS 2005 [cited 2006 August 3]; Available from: http://chem.utoronto.ca/symposium/fluoros/pdfs/TOX017Olsen.pdf

11. Alexander BH, Olsen GW, Burris JM, Mandel JH, Mandel JS. Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility. *Occupational & Environmental Medicine* 2003;60(10):722-9.

12. National Institute for Occupational Safety and Health. PC LTAS: Life table analysis system for use on the PC. In. Cincinnati: U.S. Department of Health and Human Services; 1998.

13. Breslow NE, Day NE. Statistical Methods in Cancer Research. Lyon: International Agency for Research on Cancer; 1987.

14. SAS Institute Inc. SAS 9.1 for Windows. In. Cary, NC USA; 2003.

15. Allison PD. Missing Data. Thousand Oaks: Sage Publications; 2001.

16. Biegel L, Liu R, Hurtt M, Cook J. Effects of ammonium perfluorooctanoate on Leydig cell function: in vitro, in vivo, and ex vivo studies. *Toxicol Appl Pharm* 1995;134:18-25.

17. Liu RC, Hurtt ME, Cook JC, Biegel LB. Effect of the peroxisome proliferator, ammonium perfluorooctanoate (C8), on hepatic aromatase activity in adult male Crl:CD BR (CD) rats. *Fund Appl Toxicol.* 1996;30(2):220-8.

18. Biegel LB, Hurtt ME, Frame SR, O'Connor JC, Cook JC. Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. *Toxicol Sci* 2001;60:40-55.

19. Olsen GW, Gilliland FD, Burlew MM, Burris JM, Mandel JS, Mandel JH. An epidemiologic investigation of reproductive hormones in men with occupational exposure to perfluorooctanoic acid. *J Occup Environ Med* 1998;40(7):614-22.

20. Greenberg RS, Mandel JS, Pastides H, Britton NL, Rudenko L, Starr TB. Chemical workers in the U.S. and Western Europe: a meta-analysis of cohort studies describing mortality and cancer incidence. *Epidemiology* 2001;12:727-740.

21. Gorelick PB, Sacco RL, Smith DB, Alberts M, Mustone-Alexander L, Rader D, Ross JL, Raps E, Ozer MN, Brass LM, Malone ME, Goldberg S, Booss J, Hanley DF, Toole JF, Greengold NL, Rhew DC. Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *Jama.* 1999;281(12):1112-20.

22. Kuller LH. Epidemiology and prevention of stroke, now and in the future. *Epidemiol Rev.* 2000;22(1):14-7.

23. Desai J, Devlin H. Diabetes in Minnesota. St Paul: Minnesota Department of Health; 2002.

24. Gilliland FD, Mandel JS. Serum perfluorooctanoic acid and hepatic enzymes, lipoproteins and cholesterol: a study of occupationally exposed men. *Am J Ind Med* 1996;29:560-568.

25. CDC. BMI: Body Mass Index. Atlanta: Centers for Disease Control and Prevention; 2006.

26. Olsen GW, Burris JM, Burlew MM, Mandel JH. Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. *Drug & Chemical Toxicology* 2000;23(4):603-20.

27. Bild DE, Stevenson JM. Frequency of recording of diabetes on U.S. death certificates: analysis of the 1986 National Mortality Followback Survey. *Journal of Clinical Epidemiology* 1992;45(3):275-81.

28. US Census Bureau. State and County Quick Facts; 2006.

Table 1. Characteristics of APFO Manufacturing Cohort by Job Exposure Subgroups

	Definite APFO exposure[a]	Probable APFO exposure[b]	Non-exposed[c]	Total
Total	513	1688	1792	3993
Gender				
Male	473 (92%)	1389 (82%)	1323 (74%)	3184 (80%)
Female	40 (8%)	298 (18%)	470 (26%)	809 (20%)
Age at follow-up (Mean)	55.6	60.0	60.6	59.6
Person years (Mean)	29.3	31.6	31.6	31.3
Year of birth (Mean)	1945	1938	1938	1939
Years of employment (Mean)	17.8	16.4	9.7	13.8
Age at death (Mean)	60.1	65.6	64.9	64.8
Deaths	68	368	371	807

a: Ever employed in job with definite APFO exposure
b: Ever employment in a job with probable APFO exposure, but never in a job with definite exposure
c: Never held job with definite or probable exposure; primarily non-chemical division

Table 2. Characteristics of APFO Manufacturing Cohort Smoking Status by Job Exposure Subgroups

	Definite APFO exposure[a] (n=513)		Probable APFO exposure[b] (n=1688)		Non-exposed[c] (n=1792)		Total (n=3993)	
	N	%	N	%	N	%	N	%
Ever smoke cigarettes								
Yes	220	42.7%	396	23.5%	167	9.3%	783	19.6%
No	118	23.0%	341	20.2%	188	10.5%	647	16.2%
MR[d] reviewed, no data found	92	17.8%	414	24.6%	368	20.5%	874	21.9%
No MR found	83	16.4%	537	31.7%	1069	59.6%	1689	42.3%
Number of packs smoked per day								
<1 pack per day	68	17.7%	127	32.0%	49	28.7%	244	31.2%
1 pack per day	84	21.3%	125	31.5%	54	32.9%	263	33.6%
>=2 packs per day	23	5.9%	34	8.6%	12	7.2%	69	8.8%
MR[d] reviewed, no data found	45	55.1%	110	28.0%	52	31.1%	207	26.4%
Year began smoking								
1928-39	2	0.9%	10	2.5%	4	2.4%	16	2.0%
1940-49	14	6.4%	45	11.3%	5	3.0%	64	8.2%
1950-59	35	16.4%	59	14.6%	15	9.0%	109	13.9%
1960-69	40	17.8%	48	12.1%	14	9.0%	102	13.0%
1970-79	22	10.0%	27	6.8%	9	5.4%	58	7.4%
1980-89	8	3.7%	9	2.3%	7	4.2%	24	3.1%
1990-99	1	0.5%	0	0.0%	3	1.8%	4	0.5%
MR[d] reviewed, no data found	98	44.3%	198	50.4%	110	65.3%	406	51.9%

Table 2. (Continued)

	Definite APFO exposure[a] (n=513)		Probable APFO exposure[b] (n=1688)		Non-exposed[c] (n=1792)		Total (n=3993)	
	N	%	N	%	N	%	N	%
Number of years smoked								
1-5	13	5.9%	30	7.6%	11	6.6%	54	6.9%
6-10	24	11.0%	29	7.3%	15	9.0%	68	8.7%
11-20	82	37.0%	115	29.0%	15	9.6%	212	27.1%
21-30	32	14.6%	56	14.1%	18	10.8%	106	13.5%
31-40	19	9.1%	49	12.1%	10	6.0%	78	10.0%
41-50	3	1.4%	12	3.0%	3	1.8%	18	2.3%
51+	0	0.0%	1	0.3%	0	0.0%	1	0.1%
MR[d] reviewed, no data found	47	21.0%	104	26.7%	95	56.3%	246	31.4%

a: Ever employed in job with definite APFO exposure
b: Ever employment in a job with probable APFO exposure, but never in a job with definite exposure
c: Never held job with definite or probable exposure; primarily non-chemical division
d: MR = Medical record

Table 3. Standardized Mortality Ratios (SMRs) for Selected Cause-Specific Mortalities for the Entire APFO Manufacturing Cohort

Cause[a]	Observed	Expected	SMR[b]	95% CI
All deaths	807	1000.18	0.81	0.75-0.86
Cancers				
All cancers	246	286.28	0.86	0.76-0.97
Buccal cavity and pharynx	2	5.54	0.36	0.04-1.30
Digestive organs and peritoneum	61	69.94	0.86	0.67-1.12
Esophagus	4	7.30	0.55	0.15-1.40
Stomach	7	8.49	0.82	0.33-1.70
Large Intestine	28	25.48	1.10	0.73-1.59
Rectum	4	5.23	0.76	0.21-1.96
Biliary passages and liver primary	3	6.36	0.47	0.10-1.38
Pancreas	13	15.08	0.86	0.46-1.47
Other	2	1.99	1.00	0.12-3.63
Respiratory System	79	86.42	0.91	0.72-1.14
Larynx	3	2.48	1.21	0.25-3.54
Trachea, bronchus, and lung	75	83.02	0.90	0.71-1.13
Other	1	0.92	1.08	0.03-6.01
Breast[c]	6	11.28	0.53	0.19-1.16
Female genital organs	5	6.74	0.74	0.24-1.73
Cervix	2	0.90	2.21	0.27-7.99
Other	3	3.70	0.81	0.17-2.37
Male genital organs	17	23.16	0.73	0.43-1.18
Prostate	16	22.20	0.72	0.41-1.17
Other	1	0.96	1.04	0.03-5.77
Urinary Organs	11	14.20	0.77	0.39-1.39
Kidney	4	8.53	0.47	0.13-1.20
Bladder and other urinary organs	7	5.67	1.23	0.49-2.54
Other and unspecified sites	12	15.94	0.75	0.39-1.31
Skin	4	4.18	0.96	0.26-2.45
Central nervous system	7	9.84	0.71	0.29-1.47
Thyroid gland	1	0.99	1.01	0.03-5.64
Lymphatic and hematopoietic tissue	29	32.75	0.89	0.59-1.27
Lymphosarcoma and reticulosarcoma	3	2.50	1.20	0.25-3.52
Hodgkin’s disease	1	2.00	0.50	0.01-2.78
Leukemia and aleukemia	12	12.46	0.96	0.50-1.68
Other	13	15.80	0.82	0.44-1.41
All other cancers	24	20.30	1.18	0.76-1.76
Benign neoplasms	3	3.11	0.96	0.20-2.82

Table 3. (Continued)

Cause[a]	Observed	Expected	SMR[b]	95% CI
Non-malignant causes				
Tuberculosis	1	0.49	2.05	0.05-11.40
Diabetes mellitus	23	19.97	1.15	0.73-1.73
Cerebrovascular disease	35	54.39	0.64	0.45-0.90
All heart disease	256	329.61	0.78	0.68-0.88
Rheumatic heart disease	6	4.39	1.37	0.50-2.97
Ischemic heart disease	201	259.23	0.78	0.67-0.89
Chronic disease of endocardium	11	15.63	0.70	0.35-1.26
Hypertension with heart disease	5	4.58	1.09	0.35-2.55
Other	33	45.78	0.72	0.50-1.01
Hypertension without heart disease	6	4.20	1.43	0.52-3.11
Diseases of respiratory system	50	73.91	0.68	0.50-0.89
Influenza and pneumonia	12	22.53	0.53	0.28-0.89
Bronchitis	1	1.49	0.67	0.02-3.74
Emphysema	3	8.18	0.37	0.08-1.07
Asthma	3	2.11	1.42	0.29-4.15
Other	31	39.61	0.78	0.53-1.11
Ulcer of stomach	1	3.02	0.33	0.01-1.84
Cirrhosis of the liver	13	17.87	0.73	0.39-1.24
Nephritis and nephrosis	7	6.39	1.10	0.44-2.26
Accidents	49	55.84	0.88	0.65-1.16
Motor vehicle accidents	27	25.74	1.05	0.69-1.53
Other	22	30.10	0.73	0.46-1.11
Violence	22	26.75	0.82	0.52-1.25
Suicides	17	22.02	0.77	0.45-1.24
Homicides and other	5	4.74	1.06	0.34-2.47
All other causes	95	114.61	0.83	0.67-1.01

a: Cause not listed if not observed
b: Reference rates from state of Minnesota
c: All breast cancers observed in female employees

Table 4. Standardized Mortality Ratios for Selected Cause-Specific Mortalities for APFO Manufacturing Cohort Members with a Minimum of One Year of Employment in Jobs with Definite or Probable APFO Exposure[a]

Cause[b]	Observed	Expected	SMR[c]	95% CI
All deaths	309	398.02	0.78	0.69-0.87
Cancers				
All cancers	109	112.58	0.97	0.80-1.17
Digestive organs and peritoneum	30	27.81	1.08	0.73-1.54
Esophagus	2	3.05	0.66	0.08-2.37
Stomach	4	3.39	1.18	0.32-3.02
Large Intestine	12	10.00	1.20	0.62-2.10
Rectum	3	2.09	1.43	0.30-4.19
Biliary passages and liver	2	2.51	0.80	0.10-2.88
Pancreas	7	5.99	1.17	0.47-2.41
Respiratory System	34	35.00	0.97	0.67-1.36
Larynx	2	1.02	1.95	0.24-7.06
Trachea, bronchus, and lung	32	33.60	0.95	0.65-1.34
Female genital organs	3	1.72	1.75	0.36-5.10
Male genital organs	13	9.33	1.39	0.74-2.38
Prostate	12	8.90	1.35	0.70-2.35
Urinary Organs	4	5.75	0.70	0.19-1.78
Kidney	1	3.50	0.29	0.01-1.59
Bladder and other urinary organs	3	2.25	1.33	0.28-3.90
Other and unspecified sites	7	6.56	1.07	0.43-2.20
Skin	2	1.75	1.15	0.14-4.14
Central nervous system	5	4.04	1.24	0.40-2.90
Lymphatic and hematopoietic tissue	11	13.12	0.84	0.42-1.50
Lymphosarcoma and reticulosarcoma	1	0.97	1.03	0.03-5.71
Leukemia and aleukemia	6	5.02	1.19	0.44-2.60
All other cancers	7	8.08	0.87	0.35-1.78
Benign neoplasms	2	1.22	1.64	0.20-5.91
Non-malignant causes				
Diabetes mellitus	13	7.87	1.65	0.88-2.82
Cerebrovascular disease	17	20.62	0.82	0.48-1.32

Table 4. (Continued)

Cause[b]	Observed	Expected	SMR[c]	95% CI
All heart disease	87	131.57	0.66	0.63-0.82
Rheumatic heart disease	1	1.64	0.61	0.02-3.38
Ischemic heart disease	74	103.94	0.71	0.56-0.89
Chronic disease of endocardium	3	5.95	0.50	0.10-1.47
Hypertension with heart disease	3	1.79	1.67	0.34-4.89
Hypertension without heart disease	3	1.63	1.84	0.38-5.38
Diseases of respiratory system	13	28.49	0.46	0.24-0.78
Influenza and pneumonia	4	8.49	0.47	0.13-1.21
Emphysema	1	3.19	0.31	0.01-1.74
Asthma	1	0.80	1.25	0.03-6.94
Ulcer of stomach	1	1.17	0.85	0.02-4.73
Cirrhosis of the liver	4	7.35	0.54	0.15-1.39
Nephritis and nephrosis	4	2.44	1.64	0.45-4.19
Accidents	19	24.20	0.79	0.47-1.23
Motor vehicle accidents	11	11.37	0.97	0.48-1.73
All other accidents	8	12.83	0.62	0.27-1.23
Violence	8	11.86	0.67	0.29-1.33
Suicides	8	9.76	0.82	0.35-1.61
All other causes	29	44.91	0.65	0.43-0.93

a: Includes workers who accrued one year of exposure with definite and probable jobs combined
b: Cause not listed if not observed
c: Reference rates from state of Minnesota

Table 5. Standardized Mortality Ratios for Selected Cause-Specific Mortalities for APFO Manufacturing Cohort Members Ever Employed In Jobs with Definite APFO Exposure

Cause[a]	Observed	Expected	SMR[b]	95% CI
All deaths	68	77.31	0.88	0.68-1.12
Cancers				
All cancers	19	21.95	0.87	0.52-1.35
Digestive organs and peritoneum	4	5.36	0.75	0.20-1.91
Esophagus	1	0.65	1.54	0.04-8.57
Large Intestine	2	1.87	1.07	0.13-3.86
Pancreas	1	1.17	0.85	0.02-4.74
Respiratory System	9	7.11	1.27	0.58-2.40
Larynx	1	0.21	4.72	0.12-26.23
Trachea, bronchus, and lung	8	6.81	1.17	0.51-2.31
Male genital organs	3	1.55	1.93	0.40-5.65
Prostate	3	1.43	2.10	0.43-6.13
Lymphatic and hematopoietic tissue	1	2.68	0.37	0.01-2.08
Leukemia and aleukemia	1	1.04	0.96	0.02-5.34
All other cancers	2	1.62	1.23	0.15-4.45
Non-malignant causes				
Cerebrovascular disease	5	3.14	1.59	0.52-3.72
All heart disease	21	24.01	0.87	0.54-1.34
Ischemic heart disease	16	19.13	0.84	0.48-1.36
Hypertension with heart disease	1	0.31	3.27	0.08-18.17
Other	4	3.48	1.15	0.31-2.94
Hypertension without heart disease	1	0.27	3.73	0.09-20.71
Diseases of respiratory system	3	4.50	0.67	0.14-1.95
Asthma	1	0.14	7.32	0.19-40.68
Other	2	2.54	0.79	0.10-2.84
Nephritis and nephrosis	2	0.38	5.22	0.63-18.85
Accidents	8	6.91	1.16	0.50-2.28
Motor vehicle accidents	4	3.57	1.12	0.31-2.87
Other	4	3.34	1.2	0.33-3.06
Violence	6	3.64	1.65	0.60-3.59
Suicides	5	2.96	1.69	0.55-3.94
Homicides and other	1	0.67	1.49	0.04-8.26
All other causes	3	8.07	0.37	0.08-1.09

a: Cause not listed if not observed
b: Reference rates from state of Minnesota

Table 6. Standardized Mortality Ratios for Selected Cause-Specific Mortalities for APFO Manufacturing Cohort Members with a Minimum of One Year of Employment in a Job with Definite APFO Exposure

Cause[a]	Observed	Expected	SMR[b]	95% CI
All deaths	25	35.95	0.70	0.45-1.03
Cancers				
All cancers	7	10.29	0.68	0.27-1.40
Digestive organs and peritoneum	2	2.54	0.79	0.10-2.85
Esophagus	1	0.31	3.28	0.08-18.21
Large Intestine	1	0.89	1.12	0.03-6.24
Respiratory System	2	3.36	0.59	0.07-2.15
Trachea, bronchus, and lung	2	3.23	0.62	0.08-2.24
Male genital organs	2	0.80	2.51	0.30-9.04
Prostate	2	0.75	2.67	0.32-9.65
All other cancers	1	0.76	1.32	0.03-7.32
Non-malignant causes				
Cerebrovascular disease	3	1.55	1.94	0.40-5.66
All heart disease	8	11.51	0.70	0.30-1.37
Ischemic heart disease	6	9.16	0.66	0.24-1.43
Other	2	1.64	1.22	0.15-4.40
Diseases of respiratory system	2	2.27	0.88	0.11-3.18
Other	2	1.29	1.55	0.19-5.61
Nephritis and nephrosis	1	0.19	5.23	0.13-29.08
Accidents	1	2.77	0.36	0.01-2.01
Other	1	1.39	0.72	0.02-3.99
Violence	2	1.43	1.39	0.17-5.03
Suicides	2	1.18	1.70	0.21-6.13
All other causes	1	3.83	0.26	0.01-1.45

a: Cause not listed if not observed
b: Reference rates from state of Minnesota

Table 7. Standardized Mortality Ratios for Selected Cause-Specific Mortalities for APFO Manufacturing Cohort Members Ever Employed In Jobs with Probable APFO Exposure, but Did Not Hold Jobs with Definite APFO Exposure

Cause[a]	Observed	Expected	SMR[b]	95% CI
All deaths	368	443.52	0.83	0.75-0.92
Cancers				
All cancers	119	126.63	0.94	0.78-1.12
Buccal cavity and pharynx	1	2.47	0.40	0.01-2.25
Digestive organs and peritoneum	27	31.19	0.87	0.57-1.26
Esophagus	1	3.26	0.31	0.01-1.70
Stomach	4	3.78	1.06	0.29-2.71
Large Intestine	10	11.35	0.88	0.42-1.62
Rectum	3	2.33	1.28	0.26-3.76
Biliary passages and liver primary	2	2.84	0.71	0.09-2.55
Pancreas	7	6.74	1.04	0.42-2.14
Respiratory System	38	38.37	0.99	0.70-1.36
Larynx	1	1.10	0.91	0.02-5.03
Trachea, bronchus, and lung	37	36.86	1.00	0.71-1.38
Breast[c]	2	4.72	0.42	0.05-1.53
Female genital organs	4	2.89	1.38	0.38-3.54
Other	3	1.59	1.89	0.39-5.52
Male genital organs	10	10.12	0.99	0.47-1.82
Prostate	9	9.69	0.93	0.42-1.76
Other	1	0.43	2.33	0.06-12.96
Urinary Organs	5	6.30	0.79	0.26-1.85
Kidney	2	3.80	0.53	0.06-1.90
Bladder and other urinary organs	3	2.50	1.20	0.25-3.50
Other and unspecified sites	7	7.01	1.00	0.40-2.06
Skin	2	1.83	1.09	0.13-3.95
Central nervous system	5	4.32	1.16	0.37-2.70
Lymphatic and hematopoietic tissue	14	14.55	0.96	0.53-1.61
Lymphosarcoma and reticulosarcoma	2	1.11	1.80	0.22-6.51
Leukemia and aleukemia	7	5.52	1.27	0.51-2.61
Other	5	7.04	0.71	0.23-1.66
All other cancers	11	9.01	1.22	0.61-2.18
Benign neoplasms	2	1.39	1.44	0.17-5.19

Table 7. (Continued)

Cause[a]	Observed	Expected	SMR[b]	95% CI
Non-malignant causes				
Diabetes mellitus	18	8.87	2.03	1.20-3.21
Cerebrovascular disease	17	24.15	0.70	0.41-1.13
All heart disease	110	146.86	0.75	0.62-0.90
Rheumatic heart disease	2	1.96	1.02	0.12-3.68
Ischemic heart disease	93	115.52	0.81	0.65-0.99
Chronic disease of endocardium	7	7.00	1.00	0.40-2.06
Hypertension with heart disease	2	2.07	0.97	0.12-3.49
Other	6	20.31	0.30	0.11-0.64
Hypertension without heart disease	3	1.90	1.58	0.33-4.62
Diseases of respiratory system	19	32.70	0.58	0.35-0.91
Influenza and pneumonia	7	9.82	0.71	0.29-1.47
Bronchitis	1	0.66	1.53	0.04-8.47
Emphysema	2	3.64	0.55	0.07-1.99
Other	9	17.65	0.51	0.23-0.97
Ulcer of stomach	1	1.35	0.74	0.02-4.13
Cirrhosis of the liver	6	7.94	0.76	0.28-1.65
Nephritis and nephrosis	2	2.82	0.71	0.09-2.56
Accidents	23	24.56	0.94	0.59-1.41
Motor vehicle accidents	12	11.29	1.06	0.55-1.86
Other	11	13.27	0.83	0.41-1.48
Violence	8	11.60	0.69	0.30-1.36
Suicides	8	9.56	0.84	0.36-1.65

a: Cause not listed if not observed
b: Reference rates from state of Minnesota
c: All breast cancers observed in female employees

Table 8. Standardized Mortality Ratios for Selected Cause-Specific Mortalities for APFO Manufacturing Cohort Members Never Employed in Jobs with APFO Exposure

Cause[a]	Observed	Expected	SMR[b]	95% CI
All deaths	371	479.34	0.77	0.70-0.86
Cancers				
All cancers	108	137.70	0.78	0.64-0.95
Buccal cavity and pharynx	1	2.59	0.39	0.01-2.14
Digestive organs and peritoneum	30	33.39	0.90	0.61-1.28
Esophagus	2	3.39	0.59	0.07-2.13
Stomach	3	4.08	0.74	0.15-2.15
Large Intestine	16	12.26	1.30	0.75-2.12
Rectum	1	2.50	0.40	0.01-2.22
Biliary passages and liver	1	3.04	0.33	0.01-1.83
Pancreas	5	7.17	0.70	0.23-1.63
Respiratory System	32	40.94	0.78	0.53-1.10
Larynx	1	1.16	0.86	0.02-4.79
Trachea, bronchus, and lung	30	39.35	0.76	0.51-1.09
Other	1	0.44	2.30	0.06-12.76
Breast[c]	4	6.27	0.64	0.17-1.63
Female genital organs	1	3.70	0.27	0.01-1.50
Cervix	1	0.51	1.96	0.05-10.92
Male genital organs	4	11.49	0.35	0.09-0.89
Prostate	4	11.08	0.36	0.10-0.92
Urinary Organs	6	6.77	0.89	0.32-1.93
Kidney	2	3.98	0.50	0.06-1.81
Bladder and other urinary organs	4	2.78	1.44	0.39-3.67
Skin	2	1.91	1.05	0.13-3.79
Central nervous system	2	4.55	0.44	0.05-1.59
Thyroid gland	1	0.46	2.16	0.05-12.00
Lymphatic and hematopoietic tissue	14	15.52	0.90	0.49-1.51
Lymphosarcoma and reticulosarcoma	1	1.20	0.84	0.02-4.65
Hodgkin’s disease	1	0.92	1.09	0.03-6.04
Leukemia and aleukemia	4	5.90	0.68	0.18-1.73
All other cancers	11	9.67	1.14	0.57-2.04
Benign neoplasms	1	1.49	0.67	0.02-3.73

Table 8. (Continued)

Cause[a]	Observed	Expected	SMR[b]	95% CI
Non-malignant causes				
Tuberculosis	1	0.23	4.28	0.11-23.80
Diabetes mellitus	5	9.55	0.52	0.17-1.22
Cerebrovascular disease	13	27.10	0.48	0.26-0.82
All heart disease	125	158.74	0.79	0.66-0.94
Rheumatic heart disease	4	2.14	1.86	0.51-4.77
Ischemic heart disease	92	124.58	0.74	0.60-0.91
Chronic disease of endocardium	4	7.82	0.51	0.14-1.31
Hypertension with heart disease	2	2.21	0.90	0.11-3.27
Hypertension without heart disease	2	2.03	0.98	0.12-3.55
Diseases of respiratory system	28	36.71	0.76	0.51-1.10
Influenza and pneumonia	5	11.50	0.43	0.14-1.02
Emphysema	1	4.01	0.25	0.01-1.38
Asthma	2	1.04	1.93	0.23-6.97
Cirrhosis of the liver	7	8.27	0.85	0.34-1.75
Nephritis and nephrosis	3	3.19	0.94	0.19-2.75
Accidents	18	24.38	0.74	0.44-1.17
Motor vehicle accidents	11	10.89	1.01	0.50-1.81
All other accidents	7	13.49	0.52	0.21-1.07
Violence	8	11.52	0.69	0.30-1.37
Suicides	4	9.49	0.42	0.11-1.08
Homicides and other	4	2.02	1.98	0.54-5.05
All other causes	52	55.57	0.94	0.70-1.23

a: Cause not listed if not observed
b: Reference rates from state of Minnesota
c: All breast cancers observed in female employees

Table 9. Standardized Mortality Ratios for Selected Cause-Specific Mortalities for Salaried Workers of the APFO Manufacturing Cohort

Cause	Deaths	Expected	SMR	95% CI
All deaths	307	484.92	0.63	0.56-0.71
Cancers				
All Cancers	97	140.47	0.69	0.56-0.84
Buccal cavity and pharynx	0	2.68	0.00	0.00-1.38
Digestive organs and peritoneum	27	33.77	0.80	0.53-1.16
Esophagus	2	3.56	0.56	0.07-2.03
Stomach	2	4.06	0.49	0.06-1.78
Large intestine	17	12.33	1.38	0.80-2.21
Rectum	2	2.50	0.80	0.10-2.89
Biliary passages and liver	0	3.09	0.00	0.00-1.19
Pancreas	4	7.29	0.55	0.15-1.40
All other digestive	0	0.95	0.00	0.00-3.87
Respiratory system	27	42.53	0.63	0.42-0.92
Larynx	1	1.20	0.83	0.02-4.62
Bronchus, trachea, and lung	25	40.87	0.61	0.40-0.90
All other respiratory	1	0.45	2.20	0.06-12.22
Breast	2	5.90	0.34	0.04-1.22
Female genital organs	3	3.33	0.90	0.19-2.64
All uterine (non-cervix)	0	1.03	0.00	0.00-3.59
Cervix	2	0.47	4.29	0.52-15.49
Other female genital organs	1	1.84	0.54	0.01-3.03
Male genital organs	6	11.47	0.52	0.19-1.14
Prostate	6	11.01	0.54	0.20-1.19
Testis and other male genital	0	0.46	0.00	0.00-8.04
Urinary organs	5	6.94	0.72	0.23-1.68
Kidney	2	4.18	0.48	0.06-1.73
Bladder and other urinary organs	3	2.76	1.09	0.22-3.18
Other and unspecified sites	6	7.92	0.76	0.28-1.65
Skin	2	2.10	0.95	0.12-3.43
Eye	0	0.09	0.00	0.00-42.92
Central nervous system	3	4.88	0.61	0.13-1.80
Thyroid gland/other endocrine	1	0.48	2.07	0.05-11.50
Bone	0	0.37	0.00	0.00-9.98

Table 9. (Continued)

Cause	Deaths	Expected	SMR	95% CI
Lymphatic and hematopoietic	13	15.97	0.81	0.43-1.39
Lymphosarcoma and reticulosarcoma	2	1.16	1.72	0.21-6.21
Hodgkin's disease	1	0.97	1.04	0.03-5.75
Leukemia and aleukemia	2	6.10	0.33	0.04-1.18
Other lymphatic hematologic	8	7.74	1.03	0.45-2.04
All other malignant neoplasms	8	9.96	0.80	0.35-1.58
Benign neoplasm	2	1.51	1.33	0.16-4.79
Non-Malignant Causes				
Diabetes mellitus	2	9.75	0.21	0.02-0.74
Cerebrovascular disease	16	25.95	0.62	0.35-1.00
All heart disease	96	157.89	0.61	0.49-0.74
Rheumatic heart disease	2	2.03	0.99	0.12-3.56
Ischemic heart disease	73	123.83	0.59	0.46-0.74
Chronic disease of endocardium	4	7.52	0.53	0.14-1.36
Hypertension with heart disease	0	2.16	0.00	0.00-1.71
All other heart disease	17	22.35	0.76	0.44-1.22
Hypertension without heart disease	2	2.00	1.00	0.12-3.61
Nonmalignant respiratory disease	22	35.92	0.61	0.38-0.93
Influenza and pneumonia	5	11.00	0.45	0.15-1.06
Bronchitis	0	0.71	0.00	0.00-5.21
Emphysema	1	3.91	0.26	0.01-1.42
Asthma	2	1.03	1.94	0.23-7.00
Other nonmalignant respiratory	14	19.27	0.73	0.40-1.22
Cirrhosis of liver	5	8.68	0.58	0.19-1.35
Nephritis and nephrosis	2	3.11	0.64	0.08-2.32
Nephritis and nephrosis	2	3.11	0.64	0.08-2.32
Accidents	14	27.20	0.51*	0.28-0.86
Motor vehicle accidents	8	12.59	0.64	0.27-1.25
All other accidents	6	14.61	0.41	0.15-0.89
Violence	7	13.32	0.53	0.21-1.08
Suicides	5	10.93	0.46	0.15-1.07
Homicides	2	2.39	0.84	0.10-3.02
All other causes	42	55.60	0.76	0.54-1.02

a: Cause not listed if not observed
b: Reference rates from state of Minnesota
c: All breast cancers observed in female employees

Table 10. Standardized Mortality Ratios for Selected Cause-Specific Mortalities for Hourly Workers of the APFO Manufacturing Cohort

Cause	Observed	Expected	SMR	95% CI
All Deaths	500	515.26	0.97	0.89-1.06
Cancers				
All Cancers	149	145.81	1.02	0.86-1.20
Buccal cavity and pharynx	2	2.86	0.70	0.08-2.53
Digestive organs and peritoneum	34	36.17	0.94	0.65-1.31
Esophagus	2	3.74	0.53	0.06-1.93
Stomach	5	4.43	1.13	0.37-2.64
Large intestine	11	13.15	0.84	0.42-1.50
Rectum	2	2.74	0.73	0.09-2.64
Biliary passages and liver	3	3.27	0.92	0.19-2.68
Pancreas	9	7.79	1.16	0.53-2.19
All other digestive	2	1.04	1.93	0.23-6.95
Respiratory system	52	43.89	1.18	0.88-1.55
Larynx	2	1.27	1.57	0.19-5.66
Bronchus, trachea, and lung	50	42.15	1.19	0.88-1.56
All other respiratory	0	0.47	0.00	0.00-7.87
Breast	4	5.38	0.74	0.20-1.90
Female genital organs	2	3.41	0.59	0.07-2.12
All uterine (non-cervix)	0	1.10	0.00	0.00-3.35
Cervix	0	0.44	0.00	0.00-8.43
Other female genital organs	2	1.87	1.07	0.13-3.87
Male genital organs	11	11.69	0.94	0.47-1.68
Prostate	10	11.18	0.89	0.43-1.64
Testis and other male genital organs	1	0.50	1.99	0.05-11.03
Urinary organs	6	7.27	0.83	0.30-1.80
Kidney	2	4.35	0.46	0.06-1.66
Bladder and other urinary organs	4	2.91	1.37	0.37-3.51
Other and unspecified sites	6	8.02	0.75	0.27-1.63
Skin	2	2.07	0.97	0.12-3.48
Eye	0	0.10	0.00	0.00-37.85
Central nervous system	4	4.96	0.81	0.22-2.06
Thyroid/other endocrine gland	0	0.50	0.00	0.00-7.34
Bone	0	0.39	0.00	0.00-9.48
Lymphatic and hematopoietic	16	16.78	0.95	0.54-1.55
Lymphosarcoma and reticulosarcoma	1	1.33	0.75	0.02-4.17
Hodgkin's disease	0	1.03	0.00	0.00-3.59
Leukemia and aleukemia	10	6.37	1.57	0.75-2.89
Other lymphatic hematologic	5	8.05	0.62	0.20-1.45

Table 10. (Continued)

Cause	Observed	Expected	SMR	95% CI
All other malignant neoplasms	16	10.34	1.55	0.88-2.51
Benign neoplasm	1	1.60	0.62	0.02-3.46
Non-Malignant Causes				
Diabetes mellitus	21	10.22	2.06	1.27-3.14
Cerebrovascular disease	19	28.43	0.67	0.40-1.04
All heart disease	160	171.72	0.93	0.79-1.09
Rheumatic heart disease	4	2.36	1.69	0.46-4.33
Ischemic heart disease	128	135.40	0.95	0.79-1.12
Chronic disease of endocardium	7	8.11	0.86	0.35-1.78
Hypertension with heart disease	5	2.42	2.06	0.67-4.82
All other heart disease	16	23.43	0.68	0.39-1.11
Hypertension without heart disease	4	2.20	1.82	0.50-4.65
Nonmalignant respiratory disease	28	38.00	0.74	0.49-1.07
Influenza and pneumonia	7	11.53	0.61	0.24-1.25
Bronchitis	1	0.78	1.28	0.03-7.13
Emphysema	2	4.26	0.47	0.06-1.69
Asthma	1	1.08	0.92	0.02-5.14
Other nonmalignant respiratory	17	20.34	0.84	0.49-1.34
Ulcer of stomach and dueodenum	1	1.59	0.63	0.02-3.49
Cirrhosis of liver	8	9.19	0.87	0.37-1.72
Nephritis and nephrosis	5	3.28	1.52	0.49-3.56
Accidents	35	28.64	1.22	0.85-1.70
Motor vehicle accidents	19	13.15	1.45	0.87-2.26
All other accidents	16	15.49	1.03	0.59-1.68
Violence	15	13.43	1.12	0.62-1.84
Suicides	12	11.09	1.08	0.56-1.89
Homicides	3	2.34	1.28	0.26-3.74
All other causes	53	59.01	0.90	0.67-1.17

a: Cause not listed if not observed
b: Reference rates from state of Minnesota
c: All breast cancers observed in female employees

Table 11. Hazard Ratio Estimates and 95% Confidence Intervals from Time-Dependent Cox Regression Analysis to Model the Risk of Cause-Specific Mortalities as a Function of APFO Exposure Characterized by Job Classification

Cause of Death Job Exposure Classification[a]	No.of deaths	Crude HR	95% CI	Adjusted[b] HR	95% CI	Adjusted[b] model + actual smoking data HR	95% CI	Adjusted[b] model + imputed smoking data HR	95% CI
Prostate cancer[c]	16								
High	2	3.9	0.7-21.1	6.9	1.2-41.8	5.6	0.9-35.9	7.0	1.2-42.2
Moderate	10	2.3	0.7-7.5	3.0	0.8-11.0	2.8	0.8-10.2	3.0	0.8-11.0
Low	4	1		1		1		1	
Pancreatic cancer	13								
High	0	.		.		.		.	
Moderate	8	1.5	0.5-4.5	1.5	0.4-5.3	1.2	0.3-4.2	1.5	0.4-5.2
Low	5	1		1		1		1	
Bladder cancer	7								
High	0	.		.		.		.	
Moderate	3	0.7	0.2-3.3	0.4	0.1-1.8	0.3	0.1-1.7	0.4	0.1-1.8
Low	4	1		1		1		1	
Cerebrovascular disease	35								
High	3	2.3	0.7-8.2	5.3	1.5-19.6	6.6	1.7-24.5	5.1	1.4-18.6
Moderate	19	1.5	0.8-3.1	2.1	1.0-4.5	2.2	1.0-4.8	2.1	1.0-4.6
Low	13	1		1		1		1	
Ischemic heart disease	201								
High	6	0.6	0.3-1.4	0.8	0.3-1.8	0.9	0.4-2.1	0.8	0.3-1.8
Moderate	103	1.1	0.8-1.5	1.0	0.7-1.3	1.0	0.7-1.4	1.0	0.7-1.3
Low	92	1		1		1		1	
Cirrhosis of the liver	13								
High	0	.		.				.	
Moderate	6	0.8	0.3-2.6	1.1	0.3-3.7	1.1	0.3-3.6	1.1	0.3-3.7
Low	7	1		1		1		1	
Diabetes mellitus	23								
High	0	.		.		.		.	
Moderate	18	3.7	1.4-9.9	1.9	0.7-5.4	2.0	0.7-5.6	1.9	0.7-5.3
Low	5	1		1		1		1	

a: Job Classification. High=Worked a job with definite exposure for 6 months or greater; Moderate=Ever worked a job with probable exposure or worked a job with definite exposure for less than 6 months; Low=Ever worked a job primarily in the non-chemical division of the plant

b: Hazard ratio adjusted for sex, age eligible to be in the study, birth year, and wage type

c: Men only, n=3184

Table 12. Hazard Ratio Estimates and 95% Confidence Intervals to Model the Risk of Prostate Cancer and Cerebrovascular Disease, Ischemic Heart Disease and Diabetes by APFO Job Exposure Classification and Wage Type

	Wage Type[a]					
	Hourly			*Salary*		
Cause of death Job exposure classification[b]	No.of deaths	HR[c]	95% CI	No.of deaths	HR[c]	95% CI
Prostate cancer[d]						
High	0	-		2	9.7	1.3-72.4
Moderate	9	4.3	0.5-35.7	1	1.0	0.1-9.9
Low	1	1		3	1	
Cerebrovascular disease						
High	2	8.9	1.4-54.6	1	4.1	0.5-33. 9
Moderate	12	1.6	0.6-4.9	7	2.8	1.0-8.0
Low	5	1		8	1	
Ischemic heart disease						
High	5	1.1	0.4-3.0	1	0.42	0.1-3.1
Moderate	83	1.1	0.7-1.6	20	0.8	0.5-1.5
Low	40	1		52	1	
Diabetes mellitus						
High	0	-		0	-	
Moderate	17	1.9	0.6-5.9	1	1.7	0.8-33.9
Low	4	1		1	1	

a: Wage type for persons who worked both hourly and salary jobs is classified by the predominant wage type.
b: Job Classification. High=Worked a job with definite exposure for 6 months or greater; Moderate=Ever worked a job with probable exposure or worked a job with definite exposure for less than 6 months; Low=Ever worked a job primarily in the non-chemical division of the plant
c: Hazard ratio adjusted for sex, age eligible to be in the study, birth year, and if both wage type jobs were held
d: Men only, n=3184

Table 13. Hazard Ratio Estimates and 95% Confidence Intervals to Model the Risk of Prostate Cancer and Cerebrovascular Disease Mortalities as a Function of APFO Exposure, by Exposure Lag (0 and 10 years)

	Zero exposure lag					*10 year exposure lag*				
Cause of Death										
Job Exposure Classification[a]	No.of deaths	Crude HR	95% CI	Adjusted[b] HR	95% CI	No.of deaths	Crude HR	95% CI	Adjusted[b] HR	95% CI
Prostate cancer[c]										
High	2	3.9	0.7-21.1	6.9	1.2-41.8	2	5.4	1.1-28.0	8.2	1.5-44.6
Moderate	10	2.3	0.7-7.5	3.0	0.8-11.0	9	3.3	1.1-9.9	3.4	1.1-10.7
Low	4	1		1		5	1		1	
Pancreatic cancer[c]										
High	0	.		.		0	.	.	.	.
Moderate	8	1.5	0.5-4.5	1.5	0.4-5.3	7	2.0	0.7-5.9	2.0	0.6-6.2
Low	5	1		1		6	1		1	
Bladder cancer[c]										
High	0	.		.		0	.	.	.	.
Moderate	3	0.7	0.2-3.3	0.4	0.1-1.8	3	1.3	0.3-5.8	0.8	0.2-4.0
Low	4	1		1		4	1		1	
Cerebrovascular disease[c]										
High	3	2.3	0.7-8.2	5.3	1.5-19.6	3	2.2	0.7-7.6	4.4	1.2-15.5
Moderate	19	1.5	0.8-3.1	2.1	1.0-4.5	14	1.4	0.7-2.9	1.8	0.9-3.7
Low	13	1		1		18	1		1	
Ischemic heart disease[c]										
High	6	0.6	0.3-1.4	0.8	0.3-1.8	6	0.6	0.3-1.3	0.7	0.3-1.6
Moderate	103	1.1	0.8-1.5	1.0	0.7-1.3	59	0.8	0.6-1.0	0.7	0.5-0.9
Low	92	1		1		136	1		1	
Cirrhosis of the liver[c]										
High	0	.		.		0	.	.	.	.
Moderate	6	0.8	0.3-2.6	1.1	0.3-3.7	4	0.8	0.3-2.6	1.0	0.3-3.4
Low	7	1		1		9	1		1	
Diabetes mellitus										
High	0	.		.		0	.	.	.	.
Moderate	18	3.7	1.4-9.9	1.9	0.7-5.4	12	1.9	0.9-4.4	1.3	0.6-3.1
Low	5	1		1		11	1		1	

a: Job Classification. High=Worked a job with definite exposure for 6 months or greater; Moderate=Ever worked a job with probable exposure or worked a job with definite exposure for less than 6 months; Low=Ever worked a job primarily in the non-chemical division of the plant

b: Hazard ratio adjusted for sex, age eligible to be in the study, birth year, and wage type

c: Men only, n=3184

Table 14. Hazard Ratio Estimates and 95% Confidence Intervals from Time-Dependent Cox Regression Analysis to Model the Risk of Cause-Specific Mortalities as a Function of Cumulative APFO Exposure

Cause of Death Equivalent years of exposure[a]	No.of deaths	Crude HR	95% CI	Adjusted[b] HR	95% CI	Adjusted[b] model + actual smoking data HR	95% CI	Adjusted[b] model + imputed smoking data HR	95% CI
Prostate cancer[c]	16								
≥5	7	3.8	1.4-13.5	3.6	1.2-10.6	3.6	1.0-12.7	3.8	1.2-13.2
1 - <5	1	0.3	0.1-2.9	0.5	0.1-3.6	0.5	0.1-3.9	0.4	0.1-3.6
<1	8	1		1		1		1	
Pancreatic cancer	13								
≥5	2	1.7	0.3-8.0	1.5	0.3-7.5	1.1	0.2-6.2	1.6	0.3-7.8
1 - <5	4	2.1	0.6-7.2	2.2	0.6-8.1	1.9	0.5-6.9	2.3	0.6-8.2
<1	7	1		1		1		1	
Bladder cancer	7								
≥5	1	1.3	0.1-11.9	0.7	0.1-7.2	0.6	0.1-7.1	0.7	0.1-7.3
1 - <5	2	1.9	0.3-10.3	1.4	0.2-8.6	1.4	0.2-8.3	1.5	0.3-8.9
<1	4	1		1		1		1	
Cerebrovascular disease	35								
≥5	9	2.3	1.1-4.9	2.4	1.1-5.4	3.1	1.3-7.3	2.4	1.1-5.5
1 - <5	3	0.5	0.1-1.6	0.7	0.2-2.3	0.7	0.2-2.5	0.7	0.2-2.4
<1	23	1		1		1		1	
Ischemic heart disease	201								
≥5	21	1.0	0.6-1.5	0.7	0.4-1.1	0.8	0.5-1.4	0.7	0.4-1.1
1 - <5	42	1.1	0.8-1.6	1.1	0.8-1.5	1.1	0.8-1.6	1.1	0.8-1.6
<1	138	1		1		1		1	
Cirrhosis of the liver	13								
≥5	1	0.7	0.1-5.6	0.7	0.1-5.8	0.7	0.1-5.9	0.7	0.1-5.7
1 - <5	3	1.4	0.4-5.3	1.9	0.5-7.3	1.8	0.5-7.1	1.8	0.5-7.3
<1	9	1		1		1		1	
Diabetes mellitus	23								
≥5	4	1.6	0.5-4.8	1.1	0.3-3.4	1.4	0.4-4.8	1.1	0.4-3.5
1 - <5	5	1.3	0.5-3.7	1.0	0.3-2.7	1.0	0.4-2.9	1.0	0.3-2.8
<1	14	1		1		1		1	

a: Weighted exposure days equivalent to 5 years (182,500 weighted exposure days), 1-<5 years (36,500-182,499 weighted exposure days), and less than 1 year (<36,500 weighted exposure days) of working in a job with definite exposure.
b: Hazard ratio adjusted for sex, age eligible to be in the study, birth year, and wage type
c: Men only, n=3184

Table 15. Hazard Ratio Estimates and 95% Confidence Intervals to Model the Risk of Prostate Cancer and Cerebrovascular Disease, Ischemic Heart Disease and Diabetes by Weighted Cumulative APFO Exposure and Wage Type

	Wage Type[a]					
	Hourly			*Salary*		
Cause of death Weighted exposure Days[b]	No.of deaths	HR[c]	95% CI	No.of deaths	HR[c]	95% CI
Prostate cancer[d]						
≥5	5	3.9	1.0-15.4	2	3.0	0.5-18.6
1 - <5	1	0.6	0. 7-5.9	0	0.0	
<1	4	1		4	1	
Cerebrovascular disease						
≥5	5	1.7	0.6-5.0	4	3.5	1.0-11.5
1 - <5	1	0.3	0.0-2.4	2	1.6	0.3-7.4
<1	13	1		10	1	
Ischemic heart disease						
≥5	17	0. 9	0.51.5	4	0.4	0.1-1.1
1 - <5	31	1.2	0.8-1.8	11	1.0	0.5-1.9
<1	80	1		58	1	
Diabetes mellitus						
≥5	3	0.9	0.3-3.3	1	3.3	0.2-71.7
1 - <5	5	1.0	0.3-2.8	0	-	
<1	13	1		1	1	

a: Wage type for persons who worked both hourly and salary jobs is classified by the predominant wage type.
b: Weighted exposure days equivalent to 5 years (182,500 weighted exposure days), 1-<5 years (36,500-182,499 weighted exposure days), and less than 1 year (<36,500 weighted exposure days) of working in a job with definite exposure.
c: Hazard ratio adjusted for sex, age eligible to be in the study, birth year, and if both wage type jobs were held
d: Men only, n=3184

Table 16. Sensitivity Analysis of Hazard Ratio Estimates and 95% Confidence Intervals for Prostate Cancer, Cerebrovascular Disease, Ischemic Heart Disease and Diabetes by Weighted Cumulative APFO Exposure Using Three Exposure Weighting Schemes.

	Weighting Scheme[a]: Exposure weights for Non-exposed, probable exposure and definite exposure jobs								
	1, 30, 100			1, 10, 50			1, 10, 100		
Equivalent years of exposure[b]	N	HR[c]	CI	N	HR[c]	CI	N	HR[c]	CI
Prostate cancer[d]	16								
≥5	7	4.0	1.1-14.0	5	4.5	1.3-15.1	2	8.8	1.8-42.9
1-4	1	0.5	0.1-4.2	3	1.1	0.3-4.3	6	2.5	0.8-7.6
<1	8	1.0		8	1.0		8	1.0	
Cerebrovascular disease	35								
≥5	9	3.3	1.4-7.9	6	3.4	1.3-8.7	3	7.1	2.1-24.3
1-4	3	0.7	0.2-2.5	6	1.1	0.4-2.7	8	1.7	0.7-3.8
<1	23	1.0		23			24	1.0	
Ischemic heart disease	201								
≥5	21	0.8	0.5-1.4	13	1.0	0.5-1.8	6	1.5	0.6-3.3
1-4	42	1.1	0.8-1.6	44	1.0	0.7-1.4	30	0.8	0.5-1.1
<1	138	1.0		144			165	1.0	
Diabetes	23								
≥5	4	1.4	0.4-4.8	2	1.2	0.3-5.7	0		
1-4	5	1.0	0.4-2.9	7	1.7	0.7-4.2	7	1.3	0.4-4.9
<1	14	1.0		14			16	1.0	

a: Exposure weights for Non-exposed, probable exposure and definite exposure jobs. Time in each job type multiplied by these weights.
b: Exposure equivalents: weighted exposure days working < 1, 1-4, and 5 or more years of in a job with definite exposure.
c: Hazard ratio adjusted for sex, age eligible to be in the study, birth year, and if both wage type jobs were held
d: Men only, n=3184