Bladder Cancer in Perfluorooctanesulfonyl Fluoride Manufacturing Workers

Final Report

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November 21, 2004

Abstract

A mortality study of employees of a perfluorooctanesulfonyl fluoride (POSF) manufacturing facility reported a significant excess risk of death from bladder cancer in workers who held jobs with exposure to high levels of to perfluorooctanesulfonate (PFOS). To further investigate this finding a study to ascertain all cases of bladder cancer was conducted.

Members of the original cohort were contacted by mail to inform them of the study and invite them to complete a brief questionnaire that ascertained any history of bladder cancer. Non-respondents were contacted by telephone to ensure receipt of the study material and offered the chance to complete the questionnaire by telephone. Validation of reported cancers was attempted through medical records for those cases consenting to release of medical records. Death certificates were obtained for all cohort members identified as deceased and coded for underlying and contributing causes of death. The rates of bladder cancer were compared to the expected population based rates from the Surveillance Epidemiology and End Results (SEER) data published by the National Cancer Institute. Analyses were conducted by estimated cumulative exposure to PFOS. The risk of bladder cancer was compared between workers with varying degrees of exposure.

The questionnaires were returned by 1,400 of the 1895 cohort members presumed alive during the study period, of which 1,137 were men and 263 were women. The questionnaire respondents contributed 36,982 person-years of follow-up to the analysis. One hundred eighty-eight cohort members were identified as deceased. The overall response rate was 74%, with 77% for women and 73% for men. There were 838 respondents and 120 deceased cohort members who held jobs in high or low PFOS exposed jobs, with 624 and 82 of these holding at least one job with high exposure.

A total of eleven cases of primary bladder cancer cases were identified from the surveys (N=6) and death certificates (N=5). The age, gender and calendar period adjusted Standardized Incidence Ratio (SIR) for the entire cohort was 1.28 (95% CI=0.64-2.29). The SIR for ever working (N=6), and working for more than a year (n=3) in a high exposed job were 1.74 (95% CI=0.64-3.79) and 1.12 (95% CI = 0.23-3.27) respectively. Compared to employees in the lowest

cumulative exposure category the relative risk of bladder cancer was 0.83, (95% CI=0.15-4.65), 1.92 (95% CI=0.30-12.06), and 1.52 (95% CI=0.21-10.99).

Overall, the results of this study do not confirm the high excess risk of bladder cancer reported in the mortality study of this population of fluorochemical manufacturing workers. However, the possibility remains for a smaller risk (approximately 1.5 to 2 fold) in the higher exposed workers, but the limited size of the population prohibits a conclusive exposure response analysis.

Background

The 3M facility in Decatur Alabama was one of two major production sites of perfluorooctanesulfonyl fluoride (POSF, $C_8F_{17}SO_2F$) based specialty chemicals. These specialty chemicals have a wide range of applications, including surface treatments, paper and packaging protectants, and performance chemicals.[1] POSF based chemicals can degrade or be metabolized to perfluorooctanesulfonate (PFOS, $C_8F_{17}SO_3^-$). PFOS is also used as a primary component of limited number of specialty chemical applications.

The presence of PFOS in non-occupationally exposed populations and wildlife, particularly marine mammals and piscivorous birds, has raised concerns about the environmental and health effects of PFOS. PFOS is now recognized as a pervasive compound that will persist in the environment and can accumulate in wildlife.[1-3] Moreover, PFOS has been detected at levels of 30 to 40 parts per billion in the general population.[4-6] These facts prompted the phase-out of the production of POSF-based chemicals by the major producer (3M Company).

Toxicological studies of rats and cynomolgus primates have shown that high doses of PFOS induced enlargement of liver and apparent alterations in metabolic processes, including reduced serum cholesterol levels.[7] PFOS was not found to be a developmental toxicant in rats or rabbits.[8] Higher maternal doses of PFOS increased neonatal mortality, absorptions, resorptions, and reduced weight gain in rat pups. There were no effects on post-natal neurological development or on fertility and estrous cycling in offspring in multigeneration studies. Multiple genotoxicity assays indicate PFOS does not present a hazard from interaction with genetic material.[1] Although the mechanism of toxicity in laboratory animals is not fully understood, it may be due to an effect on fatty acid transport and metabolism, membrane function, peroxisome proliferation, and/or mitochondrial bioenergetics.[9-11]

The potential health effects of PFOS exposure have been studied in occupationally exposed populations. PFOS has not been shown to affect clinical blood and urine chemistry analyses.[12] A study of health insurance claims filed by workers at the Decatur site 1993-1998 evaluated the relative frequency of episodes of care for specific conditions between employees of the chemical

plant (fluorochemical exposed) and the film plant (fluorochemical nonexposed).[13] Workers employed in the area of the plant where PFOS exposure may occur had more frequent claims for biliary tract disorders and cystitis recurrence, which were included in the list of a priori conditions from the 424 categories of conditions identified. Claims for benign colon polyps, malignant colorectal tumors and malignant melanoma were also more frequent in the exposed population. A cohort mortality study of current and former employees of the 3M Decatur facility was conducted to evaluate the health of workers exposed to POSF based fluorochemicals.[14] The cohort included 2083 workers who were employed for a minimum of 1 year at the Decatur facility, and the mortality experience was ascertained through December, 31, 1998. The main finding from the study was an excess of death from bladder cancer. The standardized mortality ratio (SMR) for bladder cancer for the entire workforce was 4.81 (95% CI=1.0-14.1), and the SMR for employees who held high exposure jobs was 12.8 (95% CI=2.6-37.4). However, these results were based on only three cases. The employees who died from bladder cancer all worked for several years in high exposure jobs, however jobs were primarily maintenance and waste water treatment, and not specifically related to fluorochemical production. Two of the cases were maintenance workers and the third worked a majority of his career in the wastewater treatment plant and incinerator. Subsequent to the completion of the study an additional death from bladder cancer was identified outside the study period, and another employee informed the 3M Medical Department that he had been diagnosed with bladder cancer. Neither of these cases worked in PFOS exposed jobs, but they were long time employees at the Decatur facility.

In response to the elevated risk of bladder cancer in the mortality study,[14] a review of the current and past use of known or suspected bladder carcinogens at this facility was conducted. Four materials, 4,4 methylene-dianiline, orthotoluidine, benzidine salts, and butyl benzyl phthalate, were formerly used at the plant and the use of these materials ended in the 1960's and 1970's. The chemicals were not widely used in the plant; however the available exposure monitoring and use information was very limited. Melamine has been used for the last decade in an epoxy capsule (non-fluorochemical) product line. Qualitative exposure assessments indicated exposures to melamine were low based on short exposure task durations. Chloroprene was also used in several manufacturing processes in the chemical plant in the 1960's and 1970's. Chloroprene is considered a possible human carcinogen, however the evidence for a role in

bladder cancer is equivocal.[15] This review indicated that the excess of mortality from bladder cancer in the high PFOS exposed sub-cohort could not be clearly attributed to exposure to a known bladder carcinogen.

Bladder cancer is a relatively rare malignancy that has been linked to smoking [16] and several occupational exposures. Aromatic amines encountered in the textile and other industries are classified as known human carcinogens. Other occupational exposures associated with bladder cancer and classified as possible human carcinogens by the International Agency for Research on Cancer include polycyclic aromatic hydrocarbons (PAHs), plasticizers such as acetamide and di(2-ethyl hexyl)-pthalate, flame retardants such as thiourea, tris (2,3-dibromo propyl phosphate) and antimony trioxide.[17] Several other occupational exposures are inconsistently reported to be associated with bladder cancer, including, metal cutting fluids, diesel exhaust, polybrominated biphenyls, and solvents.[18-26] Bladder cancer occurs more frequently in men than women. The Surveillance Epidemiology and End Results program of the National Cancer Insitute estimates annual age adjusted incidence rates for 1992-2001 of 36.1/100,000 and 9.2/100,000 for men and women respectively. Age adjusted mortality rates for the same period are substantially lower (men = 7.7/100,000 and women =2.3/100,000), however survival rates decrease with an increasing age at diagnosis.[27] Due to the large difference between incidence and mortality rates, a mortality study will not fully ascertain the burden of bladder cancer in a population. The goal of the present study was to determine whether the association observed in the mortality is representative of the entire bladder cancer experience of the employees at the 3M Decatur facility. This was accomplished through a case finding effort using direct contact with the population.

Methods

Study Population

The study site was the 3M facility in Decatur, Alabama. The plant is divided in two major sections, which are approximately 300 yards apart. The chemical plant produces specialty chemicals, including the POSF line of chemicals. The other section is the film plant, where a variety of films are produced, but little or no occupational fluorochemical exposures occur. The population of interest included all current, retired, and former Decatur employees who were eligible for the original cohort mortality study. All current employees who were not part of the original cohort, those hired after January 1, 1998, were also included in the case finding exercise, but not a primary focus of the analysis as their exposure had occurred so recently that its contribution to bladder cancer is unlikely. The study required direct contact with the participants. A roster of all known addresses and telephone numbers were obtained through 3M personnel or retiree records. The address information and vital status was updated through a variety of tracing resources sources available to the University of Minnesota, including TRW/Experian, Lortan Data, and National Change of Address. If a cohort member was noted to have died since the mortality study was completed a copy of the death certificate was obtained from the state of record.

Questionnaires

The primary purpose of the questionnaire was to identify cases of bladder cancer and the year of diagnosis. The questionnaire also recorded history of smoking; a known risk factor for bladder cancer. Although bladder cancer was the primary focus of this study, additional questions pertaining to diseases and other conditions were included. These diseases and conditions were selected based on the toxicology studies of PFOS and a study of episodes of care conducted in the Decatur plant workforce. The results for the non-bladder cancer endpoints will be presented elsewhere. In addition to bladder cancer, the questionnaire ascertained diagnoses of melanoma, liver, prostate (men only), breast (women only), colon or rectal cancer, non-cancer conditions including liver disease, gall stones, gall bladder infections, stomach ulcers, bladder infections, colon polyps and other diseases of the prostate (men only). A brief pregnancy outcome history was asked of the women. Several other questions were asked related to routine screening procedures that may be related to the diagnosis of prostate disease or colon polyps or cancer.

Recruitment

The University of Minnesota Institutional Review Board approved the study protocol. Prior to recruitment a series of meetings were held with current employees and retirees to inform them of the upcoming study and allow them to ask questions about the study. Recruitment of all presumed living cohort members was initiated with a letter and brochure that outlined the reasons for the study, the scope of the study, what is required of participants, and assurances of confidentiality. The study questionnaire, with cover letter and postage paid return envelope, followed the recruitment letter by approximately one week. A reminder post card was sent to all non-respondents two weeks after the questionnaire and a second was mailed an additional two weeks after that. If mailings were returned with undeliverable addresses, the address information was re-entered into the search engines to identify possible alternate addresses and the mailing was re-sent. Cohort members who did not respond to the second questionnaire mailing after one month were contacted by telephone to verify receipt of the questionnaire and inquire about intent to participate. At that time the respondent was offered the opportunity to complete the questionnaire by telephone if they preferred.

All questionnaires were reviewed upon receipt and double entered into an electronic database. Validation of the diagnosis of the self-reported cases of bladder cancer was attempted through medical records. Participants reporting these conditions were contacted by letter, with telephone follow-up, to request permission to contact their physician to verify the diagnosis. Participants who agreed provided signed consent and medical release forms, and the name and address of the physician or clinic of reference. Copies of the consent and medical release forms were sent to the physician or clinic along with a request for pathology reports, surgical notes, or any other information pertaining to the diagnosis of the reported bladder cancer. If no response was received from the clinic or physician they were contacted by telephone to assure receipt of the material and encourage appropriate response.

Exposure Assessment

The exposure assessment followed the previously described method used in the mortality study.[14] This method created job specific exposure categories based on job titles, departments,

and dates of employment identified in the participant's individual work histories, and potential for PFOS exposure. The relative differences in serum PFOS by job were determined by a comprehensive assessment, which is detailed elsewhere.[28] Briefly, serum PFOS concentrations were measured in 186 employees (n = 126 chemical plant; 60 = film plant) from a randomly selected sample of 232 employees. The geometric mean serum PFOS level (95% confidence interval) for chemical plant employees was 0.94 ppm (95% CI=0.79-1.13) and for film plant employees it was 0.14 ppm (95% CI=0.11-0.16). The exposure to film plant employees is thought to be influenced by environmental exposure from proximity to the chemical plant. Chemical plant jobs were classified into eight categories: cell operators, chemical operators, maintenance workers (primarily mechanics and electricians), mill operators, waste treatment plant operators, engineers/laboratory workers, supervisors/managers and administrative assistants. The highest geometric mean level of serum PFOS was observed in cell operators (2.0 ppm) followed by the waste operators (1.5), chemical operators (1.5 ppm), and maintenance workers (1.3 ppm). Supervisors/managers (0.9 ppm), mill operators (0.6 ppm), engineer/lab workers (0.4 ppm) and administrative assistants (0.4 ppm) had lower geometric mean serum PFOS levels.

Because production processes have remained constant over time, a simple exposure matrix was developed based on the work history records of the study cohort. The work histories used in the exposure analysis covered the period from when the plant opened, 1961, till 1997 when the work histories were collected for the mortality study. With the knowledge of the major job-specific serum PFOS levels, a company industrial hygienist and epidemiologist assigned each unique job

and department combination in the work history records to one of the following three major exposure categories:

1. No direct workplace exposure to POSF-based fluorochemicals (encompasses film plant jobs).
2. Low potential workplace exposure to POSF-based fluorochemicals (includes such jobs as engineers, quality control technicians, environmental, health and safety workers, administrative assistants and managers).
3. High potential workplace exposure to POSF-based fluorochemicals (includes cell operators, chemical operators, maintenance workers, mill operators, waste operators and crew supervisors)

Hereafter these three categories will be referred to as the non-exposed, low exposed and high exposure. An additional classification for cumulative exposure assigned the non-exposed, low exposure, and high exposure jobs relative POSF-based job exposure value of 1, 3 and 10 respectively based on biomonitoring data. The years spent in each job were multiplied by the relative weights to develop a cumulative quantitative exposure metric. This exposure metric assumes a continually increasing accumulation of PFOS exposure. However, the half-life for PFOS is prolonged, thus exposures to high concentrations can result in high body burdens for a long time after exposure ceases. To account for this possibility the study participants were also classified as being in an exposed job, high or low and high only, for at least 1 year.

Analysis

The estimated incidence of bladder cancer was compared to the expected incidence based on rates derived from the Surveillance Epidemiology and End Results (SEER) at the National Cancer Institute.[29] The cohort members contributed person-time to the analysis until the diagnosis of a bladder cancer, death, or the end of the study (December 31, 2002). All self reported cases of primary bladder cancer from the questionnaire and bladder cancers identified by death certificate were included in the analysis. If participants checked 'Unsure' instead of 'Yes' for bladder cancer the case was not included. The age, gender, calendar-year, and exposure-specific person-time of the cohort was tabulated using the Life Table Analysis System for the personal computer (PCLTAS) developed by the National Institute for Occupational Safety and Health.[30] SEER referent data were only available for this program from 1970 through

1999. Accordingly, the follow-up period for the incidence analysis began in 1970 and the referent rates for 1999 were applied for the years 2000-2002. Standardized incidence ratios (SIR) were estimated for participants by exposure group and by weighted exposure. Cut-points for the weighted exposure were selected to correspond to 1, 5, and 10 years of employment in high exposed jobs.

The expected number of bladder cancer cases was also determined for the non-respondents to the questionnaire by the above weighted exposure categories. For this analysis, the time at risk was estimated from the beginning of employment till the end of the study, which estimated the maximum number of expected cases, (based on prevailing rates). These estimates were used to evaluate potential effects of selection bias from non-participation.

Estimates of bladder cancer risk by relative cumulative exposure using the study population as an internal referent were made using Poisson and logistic regression. Standardized rate ratios, adjusting for age, gender, and calendar period were estimated with Poisson regression. This analysis accounted for the time-dependent nature of the PFOS exposure, as participants accrued PFOS exposure at different levels over the course of employment. A summary analysis was conducted using logistic regression to estimate the risk of cumulative exposure at follow-up, gender and smoking habit. The precision of the estimates for all analyses are described with 95% confidence intervals.

Results

Of the 2,083 original members of the cohort, 188 were determined to be deceased at the time the questionnaire was sent and 1,400 responded to the questionnaire. The remaining 495 did not respond either because they declined to participate or were not reachable. Overall 73.9 percent of those eligible responded. For eligible cohort members with no occupational PFOS exposure, only low exposure or high exposure for less than one year, and high exposure for one year or more the response rates were 75.8% (563 of 741), 81.4% (358 of 440) and 67.2% (480 of 714) respectively. The response rate for women was slightly higher than men and the respondents were older and less likely to have a history of working in PFOS exposed areas of the plant. (Table 1-2).

Eleven bladder cancer cases were included in the analysis. Five of the cases were identified on the death certificates and 6 were reported on the questionnaire. (Table 3) The diagnosis of the self reported bladder cancers were confirmed for two cases, but four self-reported cases declined to sign the consent forms permitting validation. One self-reported case indicated on follow-up that the bladder cancer was not a primary tumor, but declined to provide access to medical records; this case was not included in the analysis. An additional nine individuals marked the question pertaining to a history of bladder cancer diagnosis as 'unknown'. These respondents marked several types cancer as unknown, thus it was assumed that bladder cancer was not diagnosed.

Two of the bladder cancer cases were women and all were over 50 years of age at the time of diagnosis or death. (Table 4) The median age of the bladder cancer cases was 63. (Table 5) Compared to the rest of the questionnaire respondents, the bladder cancer cases were more likely to smoke, with 83 percent having ever smoked regularly, compared to 56 percent of the non-cases. Two (18%) of the bladder cancer cases never worked in PFOS exposed areas while 9 worked at some time in a low or high exposed job, and six of these worked for a year or more in these jobs. Only three bladder cancer cases worked in a high exposure job for at least one year. These three are the same cases identified in the mortality study.

For the respondents and decedents, 8.6 cases of bladder cancer were expected in the period of follow-up (SIR=1.28, 95% CI=0.64-2.29).(Table 6) The SIR for women was 6.42 (95% CI= 0.78-23.18), but this was based on only 2 cases. The women who reported bladder cancer did not work in the exposed jobs. The SIRs ranged from 1.1 to 2.3 for the various exposure groups with the highest being the participants ever employed in low exposed jobs. The highest SIRs for the exposure specific strata based on the cumulative exposure score was 2.7 (95% CI=0.55-73.95) corresponding to 5-10 years of employment in the higher exposed jobs. The SIR for the workers who held a high exposure job for at least one year was 1.12 (95% CI 0.23-3.27).

There were 495 eligible cohort members who did not complete a questionnaire. Based on the U.S. population rates from SEER and the non-respondents age, and gender, an additional 1.93 cases of bladder cancer would be expected to occur in the non-respondent group during the study period (Table 7). The breakdown of the expected number of cases by cumulative exposure category is also presented in Table 7.

The risk of bladder cancer was similar for men and women. (Table 8) Those who had ever smoked regularly had a higher risk of bladder cancer, but five of the eleven cases were identified by death certificate (smoking status coded as missing) so the overall impact of smoking is hard to characterize. There was no clear association between employment in PFOS exposed jobs and bladder cancer. Similar results were observed for the cumulative exposure estimates at the end of follow-up (table 8) and the time dependent exposure analysis (Table 9). Compared to the cohort members who never held a PFOS exposed job, those with moderate PFOS exposure had nominally higher risk of bladder cancer. It must be noted in all of these analyses that the estimates are very unstable as there were only eleven bladder cancer cases. Fluctuations in the point estimates, particularly when the data are adjusted for other covariates, such as smoking, gender, and age, may be artifacts of the analysis.

Discussion

The primary objective of this study was to evaluate whether the finding from the mortality study of a twelve-fold risk of risk of bladder cancer associated with ever working in a high PFOS exposed job was representative of the overall bladder cancer experience of the cohort. The results of this study suggest that bladder cancer incidence in this cohort is similar to the incidence of bladder cancer in the U.S. population with the same age and gender. Moreover, the risk of bladder cancer in this analysis does not appear to be significantly influenced by employment in jobs where PFOS exposure is more likely.

Clearly the greatest uncertainty in these results is the completeness of case ascertainment. This study used a postal-questionnaire with telephone follow-up to identify all additional cases of bladder cancer in the population. This approach was taken because there is no population-based cancer registry available for this geographic area or time period. While the overall participation was reasonable for a mailed survey, it is quite possible that some bladder cancer cases were missed. An additional two cases of bladder cancer were expected in the non-respondents based on SEER data. The potentially missed cases would only affect the results if the rate in the non-participants was higher than the prevailing rates in the population. A sensitivity analysis of this effect can describe the potential effect of underestimating the true number of cases. If the rate in the non-participants were twice the population expected rate, the net effect would produce an overall SIR of 1.41 (95% CI=0.79-2.33). The SIR for the weighted cumulative exposure strata (Table 6) would be 1.27, 1.11, 2.57, and 1.53; all with wide confidence intervals that include the null. To reach nominal statistical significance at the $p<0.1$, 0.05, and 0.01 levels, the rate of bladder cancer in the non-respondents would need to be 2.07, 2.60, and 3.63 times that of the rate of the reference population respectively. If the two highest cumulative exposure strata are combined an SIR of 2.00 (95% CI = 0.75-4.29) would result if the rate of bladder cancer in the non-participants was twice the general population. The rates in the non-respondents for this combined strata would need to be 1.63, 3.27, and 4.91 times the population rates to reach significance at the $p<0.1$, 0.05, and 0.01 levels. The likelihood that cohort members who experienced bladder cancer were more or less likely to respond is speculative. However, as described in the sensitivity analysis the overall effect would be marginal, unless there were

substantially higher bladder cancer rates in the nonrespondent group than the reference population.

The validity of the cases ascertained by the postal questionnaire is also a potential limitation of this study. Only two of six self-reported cases consented to release their medical records pertaining to this diagnosis to confirm this diagnosis. The reasons for declining to consent to the validation protocol, be they concerns for personal privacy or the validity of the self-reported diagnosis, could not be determined. Nevertheless, the other self-reported cases were included in the analysis. Self-report of bladder cancer has been shown to be quite valid in other populations. A recent study conducted by the University of Minnesota and the National Cancer Institute using the same approach employed for the Decatur study had one-hundred percent of the 59 bladder cancers for which medical records confirmed.[31]

A significant non-occupational cause of bladder cancer is smoking, which is believed to be due to PAH's in the cigarette smoke.[16] Ascertainment of smoking habit in the study population was problematic. The only smoking information available was reported on the questionnaire, thus no smoking information was available for deceased cohort members, which accounted for five of eleven bladder cancer cases. Five of the six cases reported on the questionnaire had a history of smoking. Adjusting for smoking and vital status in the logistic regression models did not change the overall results of the analysis; however the analysis is statistically unstable with so few subjects in each category. The prevalence of smoking in the cohort may also confound the comparison to the general population. The questionnaire asked whether the participants ever smoked regularly (more than 100 cigarettes), the number of years they smoked, and at what age they stopped if they had. Overall, the lifetime prevalence of regular smoking was 56 percent based on the questionnaire responses. The prevalence of current smoking was 17 percent (18 percent of men and 16 percent of women). Data from the Centers for Disease Control and Prevention indicate that nationally 25 percent of men and 21 percent of women were regular smokers in 2001, but the prevalence of current smoking was as high as 52 and 34 percent for men and women respectively in 1965. While it is possible that smoking was under-reported by the participants, it does not appear that smoking would account for any excess risk in this population when compared to the national data.

Toxicological studies on laboratory animals have not shown effects in the urinary bladder due to exposure to PFOS and related compounds Two year feeding bioassays in rats of N-ethylperfluorooctane sulfonamide alcohol (N-EtFOSE) and PFOS have not shown an increased risk of bladder tumors.[1,7,32-34] The former compound can metabolize to an undetermined degree to PFOS. Most bladder carcinogens are genotoxic and/or precipitate in the urine. PFOS and related chemistries are neither genotoxic nor insoluble in urine at the levels measured in employees [1]. A recently completed POSF inhalation study of rats was conducted in response to the finding of bladder cancer from the mortality study. The results of this study have been reviewed by Dr. S. Cohen [35] and indicate there is no evidence that the POSF exposure, which results in high PFOS body burdens, leads to treatment related changes in the urinary bladder histology.

Overall, the results of this study do not confirm the twelve-fold excess risk of bladder cancer that was reported in the mortality study of this population of fluorochemical manufacturing workers.[14] However, the possibility remains for a smaller risk (approximately 1.5 to 2 fold) in the higher exposed workers. Bladder cancer is a relatively rare disease and the population occupationally exposed to these compounds is limited, thus the power to detect excess risks in this study is inherently low and prohibited a convincing exposure response analysis. Future follow-up of this cohort may be limited to mortality studies, which will need to consider these results when interpreting any findings on bladder cancer.

References

1. 3M Company. SIDS initial assessment report: perfluorooctane sulfonic acid and its salts: USEPA Public Docket AR-226. Saint Paul: 3M Company, 2000.

2. Hansen KJ, Clemen LA, Ellefson ME, Johnson HO. Compound-specific, quantitative characterization of organic fluorochemicals in biological matrices. Environmental Science and Technology 2001;35:766-770.

3. Giesy JP, Kannan K. Global distribution of perfluoroctane sulfonate and related perfluorinated compounds in wildlife. Environmental Science and Technology 2001;35:1339-1342.

4. 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.

5. 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 2004;111(16):1892-901.

6. Olsen GW, Church TR, Hansen KJ, Burris JM, Butenhoff JL, Mandel JH, Zobel LR. Quantitative evaluation of perfluorooctanesulfonate (PFOS) and other fluorochemicals in the serum of children. J Children's Health 2004;2(1):53-76.

7. Seacat AM, Thomford PJ, Hansen KJ, Clemen LA, Eldridge SR, Elcombe CR, Butenhoff JL. Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats. Toxicology. 2003;183(1-3):117-31.

8. Case MT, York FG, Christian MS. Rat and rabbit oral developmental toxicology studies with two perfluorinated compounds. International Journal of Toxicology 2001;20:101-109.

9. Luebker DJ, Hansen KJ, Bass N, Butenhoff JL, Seacat AM. Interactions of fluorochemicals with rat liver fatty acid-binding protein. Toxicology 2002;176:175-185.

10. Starkov A, Butenhoff JL, Seacat AM, Wallace KB. Structural determinants of mitochondrial dysfunction caused by in vitro exposure to selected perfluorootanyl compounds. Toxicologist 2001;60:1658.

11. Wallace KB, Luebker DJ, Butenhoff JL, Seacat AM. Perfluorooctanesulfonate and 2-(n-ethylperfluorooctanesulfonaminde)-ethyl alcohol are peroxisome proliferators in rats, but not guinea pigs. Toxicologist 2001;60:348.

12. Olsen GW, Burris JM, Burlew MM, Mandel JH. Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations and medical surveillance examinations. Journal of Occupational & Environmental Medicine. 2003;45(3):260-70.

13. Olsen GW, Burlew MM, Marshall JC, Burris JM, Mandel JH. Analysis of episodes of care in a perfluorooctanesulfonyl fluoride production facility. Journal of Occupational & Environmental Medicine 2004;46(8):837-846.

14. 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.

15. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans:Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (Part One). Vol. 48. Lyon: IARC, 1999.

16. Silverman DT, Morrison AS, Devesa SS. Bladder Cancer. In: Schottenfeld D, Fraumeni JF, eds. Cancer Epidemiology and Prevention. Second ed. New York: Oxford University Press, 1996;1156-1179.

17. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans: Some flame retardants and textile chemicals and exposures in the textile manufacturing industry. Vol. 48. Lyon: IARC, 1990.

18. Vineis P, Pirastu R. Aromatic amines and cancer. Cancer Causes & Control 1997;8(3):346-55.

19. Boffetta P, Jourenkova N, Gustavsson P. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Causes & Control 1997;8(3):444-72.

20. Bonassi S, Merlo F, Pearce N, Puntoni R. Bladder cancer and occupational exposure to polycyclic aromatic hydrocarbons. International Journal of Cancer 1989;44(4):648-51.

21. Hours M, Dananche B, Fevotte J, Bergeret A, Ayzac L, Cardis E, Etard JF, Pallen C, Roy P, Fabry J. Bladder cancer and occupational exposures. Scandinavian Journal of Work, Environment & Health 1994;20(5):322-30.

22. Steineck G, Plato N, Norell SE, Hogstedt C. Urothelial cancer and some industry-related chemicals: an evaluation of the epidemiologic literature. American Journal of Industrial Medicine 1990;17(3):371-91.

23. Weiss NS. Cancer in relation to occupational exposure to perchloroethylene. Cancer Causes & Control 1995;6(3):257-66.

24. Ward EM, Burnett CA, Ruder A, Davis-King K. Industries and cancer. Cancer Causes & Control 1997;8(3):356-70.

25. Anton-Culver H, Lee-Feldstein A, Taylor TH. Occupation and bladder cancer risk. American Journal of Epidemiology 1992;136(1):89-94.

26. Porru S, Aulenti V, Donato F, Boffetta P, Fazioli R, Cosciani Cunico S, Alessio L. Bladder cancer and occupation: a case-control study in northern Italy. Occupational & Environmental Medicine 1996;53(1):6-10.

27. National Cancer Institute. Surveillance Epidemiology and End Results: Incidence: Urinary Bladder. Vol. 2004 National Cancer Institute, 2004.

28. Olsen GW, Logan PW, Hansen KJ, Simpson CA, Burris JM, Burlew MM, Vorarath PP, Venkateswarlu P, Schumpert JC, Mandel JH. An occupational exposure assessment of a perfluorooctanesulfonyl fluoride production site: biomonitoring. AIHA Journal:. 2003;64(5):651-9.

29. National Cancer Institute. Surveillance Epidemiology and End Results. Vol. 2004 National Cancer Institute, 2004.

30. National Institutes for Occupational Safety and Health. PC LTAS: Life table analysis system for use on the PC. Cincinnati: U.S. Department of Health and Human Services, 1998.

31. Sigurdson AJ, Doody MM, Rao RR, Freedman DM, Alexander BH, Hauptmann M, Mohan AK, Yoshinaga S, Hill DA, Tarone R, Mabuchi K, Ron E, Linet MS. Cancer Incidence in the U. S. Radiologic Technologists Health Study, 1983-1998. Cancer 2003;97:3080-3089.

32. Seacat AM, Thomford PJ, Butenhoff JL. Terminal observations in Sprague-Dawley rats after lifetime dietary exposure to potassium perfluorooctane sulfonate. Toxicologist 2002;66:185.

33. Thomford PJ, Seacat AM, Butenhoff JL. Terminal observations in Sprague-Dawley rats after liftime dietary exposure to N-ethyl perfluorooctanesulfonamide ethanol. Toxicologist 2002;66:185.

34. Seacat AM, Thomford PJ, J HK, W OG, T CM, L BJ. Subchronic toxicity studies on perfluorooctanesulfate potassium salt in cynomolgus monkeys. Toxicological Science 2002;68:249-264.

35. Cohen S. Letter to Dr. John Butenhoff. St. Paul, MN, 2004.

Table 1. Gender, age, and exposure characteristics of participants and non-participants in the Decatur morbidity study

		Questionnaire Respondent						
		Yes		No		Deceased		Total
		N	%	N	%	N	%	
Total		1400		495		188		2083
Gender	M	1137	81.2	416	84.0	177	94.1	1730
	F	263	18.8	79	16.0	11	5.9	353
Age at end of study	<30	5	0.4	3	0.6	8	4.3	16
	30-39	65	4.6	41	8.3	21	11.2	127
	40-49	294	21.0	144	29.1	40	21.3	478
	50-59	604	43.1	207	41.8	55	29.3	866
	60-69	352	25.1	84	17.0	43	22.9	479
	70+	80	5.7	16	3.2	27	11.2	117
Years worked	<5	437	31.2	172	34.7	52	27.7	661
	5-9	148	10.6	67	13.5	33	17.6	248
	10-14	111	7.9	38	7.7	36	13.8	175
	15-19	120	8.6	38	7.7	18	9.6	176
	20+	584	4.7	180	36.4	59	31.4	823
PFOS Exposure Group*								
Non Exposed**		562	40.1	179	36.2	68	36.2	809
Low	Ever	413	29.5	121	24.4	67	35.6	601
	≥1 year	320	22.9	78	15.8	52	27.7	450
High	Ever	624	44.6	276	55.8	82	43.6	982
	≥1 year	480	34.3	234	47.3	69	36.7	783
Low or High	Ever	838	59.9	316	63.8	120	63.8	1274
	≥1 year	689	49.2	273	55.2	108	57.4	1070

*Categories overlap
** Non exposed includes workers from the film plant who never worked in the chemical plant.

Table 2. Mean, median, and range of ages and days in PFOS exposure groups for participants and non-participants in the Decatur morbidity study

		Questionnaire Respondent			
		Yes	No	Deceased	Total
Total		1400	495	188	
Age at end of study	Mean	55.6	52.7	53.7	54.7
	Median	52.6	55.4	53.7	54.7
	Min	28.9	28.8	18.9	18.9
	Max	86.3	83.0	85.7	86.3
Years worked	Mean	15.5	13.9	13.3	14.9
	Median	15.2	10.3	11.0	13.2
	Min	1.0	1.0	1.0	1.0
	Max	36.6	36.7	36.2	36.7
Days in PFOS Exposure groups					
Non Exposed*	Mean	3461	2818	2336	3234
	Median	1248	802	1120	1053
	Min	0	0	0	0
	Max	13051	12610	12637	13051
Low	Mean	833	454	938	774
	Median	0	0	0	0
	Min	0			
	Max	13030	11867	10428	13030
High	Mean	1383	1702	1279	1450
	Median	172	0	0	0
	Min	0	0	0	0
	Max	12276	12302	10804	12302
High or low	Mean	2216	2246	2218	2223
	Median	322	552	553	409
	Min	0	0	0	0
	Max	13352	12302	13211	13352

*Never exposed includes workers from the film plant who never worked in the chemical plant.

Table 3. Summary of bladder cancer cases by source of reporting and confirmation status

Source of reporting	N	Included in analysis
Death certificate	5	Yes
Questionnaire confirmed by medical records	2	Yes
Questionnaire: Declined consent to medical records	4	Yes
Questionnaire: Reported as secondary tumor	1	No
Questionnaire: Reported as unsure if ever had bladder cancer	9	No

Table 4. Demographic and exposure characteristics of bladder cancer cases and non-cases.

		Bladder		No		All
		N	%	N	%	N
Total		11		1577		1588
Vital status	Alive	6	54.5	1394	88.4	1400
	Deceased	5	45.5	183	11.6	188
Gender	M	9	81.8	1305	82.8	1314
	F	2	18.2	272	17.2	274
Age at end of study	<30	0	0	13	0.8	13
	30-39	0	0	86	5.5	86
	40-49	0	0	334	21.2	334
	50-59	4	36.4	655	41.5	659
	60-69	5	45.5	390	21.7	395
	70+	2	18.2	99	6.3	101
Tobacco use*	Cigarettes	5	83.3*	785	56.3*	790
	Missing	0	0	13	0.9	13
	Smokeless	0	0	206	14.8	206
	Missing	1	16.8	21	1.5	22
PFOS Exposure Never		2	18.2	628	39.8	630
Low	Ever	7	63.6	473	30.0	480
	≥1 year	5	45.5	367	23.3	372
High	Ever	6	54.5	700	44.4	706
	≥1 year	3	27.3	546	34.6	549
Low or High	Ever	9	81.8	949	60.2	958
	≥1 year	6	54.5	791	50.2	797

*Excludes decedents.

Table 5. Mean, median, and range of age and days in each exposure category for bladder cancer cases non-cases.

		Bladder	No	All
Age	Mean	62.8	55.3	55.4
	Median	63.3	55.3	55.4
	Min	50.5	18.9	18.9
	Max	77.2	86.3	86.3
Days in PFOS Exposure	groups			
Non-exposed	Mean	4387	3357	3364
	Median	4571	1215	1228
	Min	0	0	0
	Max	11286	13051	13051
Low	Mean	1371	841	845
	Median	7	0	0
	Min	0	0	0
	Max	7139	13030	13030
High	Mean	923	1374	1371
	Median	21	0	0
	Min	0	0	0
	Max	4963	12276	12276
Low or High	Mean	2293	2216	2216
	Median	606	370	372
	Min	0	0	0
	Max	7139	13352	13352

Table 6. Standardized Incidence Ratios by Exposure Category based on expected bladder cancer rates in U.S. population (SEER).

	OBS	Exp	SIR*	95% CI
All	11	8.6006	1.28	0.64-2.29
Men	9	8.2891	1.09	0.50-2.06
Women	2	0.3115	6.42	0.78-23.18
Never exposed	2	3.2995	0.61	0.07-2.19
Ever high	6	3.4421	1.74	0.64-3.79
Ever low	7	3.0918	2.26	0.91-4.67
Ever low or high	9	5.3011	1.70	0.77-3.22
High ≥1 year	3	2.6838	1.12	0.23-3.27
High or low ≥1 year	6	4.5835	1.31	0.48-2.85
Weighted Exposure**				
≤3653	2	1.8747	1.07	0.12-3.85
3654-18263	4	4.2209	0.95	0.25-2.43
18264-36525	3	1.1019	2.72	0.55-73.95
≥36526	2	1.4030	1.43	0.16-5.15

*Standardized by age, calendar year, and gender.
** Years in exposure jobs multiplied by exposure weight. Cutpoints to represent 1, 1-5, 5-10, and >10 years of employment in high PFOS exposed jobs.

Table 7. Expected bladder cancer cases among 495 eligible non-respondents to questionnaire based on bladder cancer rates in U.S. population (SEER).

	Expected Cases*
All non respondents	1.9266
Weighted exposure category*	
≤3653	0.5198
3654-18263	0.7959
18264-36525	0.2995
≥36526	0.3114

* Years in exposure jobs multiplied by exposure weight. Cutpoints to represent 1, 1-5, 5-10, and >10 years of employment in high PFOS exposed jobs.

Table 8. Risk estimates for bladder cancer by gender, smoking history, and cumulative exposure at the time of follow-up.

		Bladder	No		
		N	N	OR	95% CI
Total		11	1577		
Gender	M	9	1305	1.0	
	F	2	272	1.07	0.23-4.90
Ever smoked*	No	1	596	1.0	1.0
	Yes	5	785	3.8	0.44-32.6
	Missing	5	196	15.2	17.6-130.9
Cumulative PFOS** exposure	Never	2	628	1.0	
	Low or high <1year	6	403	3.9	0.8-20.2
	High for ≥1 year	3	546	1.8	0.3-8.4
Weighted exposure **+ Quartiles	Q1 ≤2,914	2	395	1.0	
	Q2 2915-8055	3	394	1.3	0.2-7.9
	Q3 8056-20525	2	395	1.7	0.9-5.3
	Q4 ≥20526	4	393	1.5	0.3-8.4
Weighted exposure categories**,+	≤3653	2	420	1.0	
	3654-18263	4	737	0.9	0.2-5.3
	18264-36525	3	152	2.6	0.4-10.2
	≥36526	2	268	1.4	0.2-10.2

*Deceased persons were included in the missing category for smoking
**Adjusted for age, and gender
+ Exposures are weighted days of employment.
+ Cutpoints represent 1, 1-5, 5-10, and >10 years of employment in high PFOS exposed jobs.

Table 9. Estimated bladder cancer rates and rate ratios using the cohort as an internal referent population.

	Cases	Person years	Rate	RR*	95% CI
Total	11	43739	0.2515		
Weighted Exposure**					
≤3653	2	15658	0.1277	1.0	
3654-18263	4	18955	0.2110	0.83	0.15-4.65
18264-36525	3	4077	0.7358	1.92	0.30-12.06
≥36526	2	5048	0.3962	1.52	0.21-10.99

*Adjusted for age, and gender

**Cutpoints represent 1, 1-5, 5-10, and >10 years of employment in high PFOS exposed jobs.