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E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED
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EMPLOYEE RELATIONS DEPARTMENT
MEDICAL DIVISION

May 10, 1988

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Attn: 8(e) Coordinator

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Gentlemen:

Re: TSCA 8(e) Submission No. 598

Pursuant to our March 22, 1988 letter, enclosed to supplement your file is a copy of the final report "A Survey of the Prevalence of Epididymitis at the Waynesboro Plant". This survey concludes that there is no causal association between occupational exposure to dimethylformamide and epididymitis, orchitis, prostatitis, varicocele, hydrocele or testicular pain.

In addition, we are herewith submitting the final report "A Case-Control Study of Cancer Among Du Pont Employees with Potential for Exposure to Dimethylformamide". This study concludes that there is no causal association between occupational exposure to dimethylformamide and malignant melanoma, cancers of the liver, testis, prostate, and buccal cavity and pharynx.

We have communicated these study results with our employees and have submitted copies of these reports to NIOSH and OSHA. We request that the Agency provide us with any written comments it may have upon review of these studies. We would be pleased to respond to comments or questions should you decide that further exchange of scientific information is needed.

Very truly yours,

William E. Fayerweather

William E. Fayerweather, Ph.D.
Manager, Epidemiology Section

WEF/lgb
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CC: Mr. David Williams (TS-778)
Environmental Protection Agency

BETTER THINGS FOR BETTER LIVING

DUPONT

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2

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[redacted]

A SURVEY OF THE PREVALENCE OF EPIDIDYMITIS

AT THE WAYNESBORO PLANT

Judy Walrath, Ph.D.

William E. Fayerweather, Ph.D.

March, 1988

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A SURVEY OF THE PREVALENCE OF EPIDIDYMITIS AT THE WAYNESBORO PLANT

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A SURVEY OF THE PREVALENCE OF EPIDIDYMITIS AT THE WAYNESBORO PLANT

Summary of Conclusions

A survey of all male employees was conducted in response to concerns about the occurrence of epididymitis among employees at the Waynesboro plant. Analyses of the data showed no association between exposure to DMF (dimethylformamide) at the plant and epididymitis, orchitis, prostatitis, varicocele, hydrocele or testicular pain. A positive association was noted between employees who had undergone a vasectomy and epididymitis.

Summary of Survey

The objective of this survey was to determine whether the prevalence of epididymitis or other related testicular disorders is associated with exposure to DMF in the Du Pont Waynesboro Plant. Information was obtained from male employees on the rolls as of April 1987 as to whether they had suffered from epididymitis, orchitis, prostatitis, or other genitourinary conditions as well as whether they had had a vasectomy.

Complete work histories were obtained for all questionnaire respondents. To determine whether an employee could have been exposed to DMF during his career at the Waynesboro plant, all jobs with potential for exposure to DMF were identified. Each of these jobs was assigned an exposure ranking based on DMF industrial hygiene air monitoring, NMF metabolite monitoring and knowledge of the evolution of manufacturing processes and workplace exposure controls. Each employee's DMF exposure pattern during their career at the plant was then characterized in several ways: ever having been versus never having been exposed to DMF, highest DMF exposure experienced, and average DMF exposure.

A total of 1,342 (94.8% of the male employees) completed the questionnaire. The proportion of employees who reported ever having had a diagnosis of epididymitis and/or orchitis was 6.8%, 11.5% reported a history of prostatitis, and 11.1% had had testicular pain severe enough to consult a physician. Logistic regression analyses showed no association between exposure to DMF and development of epididymitis and orchitis, prostatitis, or testicular pain. Analyses of the epididymitis cases by history of vasectomy showed a statistically significant association between having had a vasectomy and the subsequent development of epididymitis. Year of birth, plant service date and history of a vasectomy were found to be statistically significant independent risk factors for subsequent development of epididymitis/orchitis. Year of birth and plant service date are highly correlated and further analyses are required to determine the relative importance of these two factors.

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A SURVEY OF THE PREVALENCE OF EPIDIDYMITIS AT THE WAYNESBORO PLANT

Objective

In mid 1986, an employee at the Waynesboro Plant was concerned that testicular pain associated with epididymitis that he had experienced over a period of 17 years may be due to workplace exposures, particularly exposure to dimethylformamide (DMF) in the "Orlon" area. The employee surveyed a number of his fellow workers and compiled a list of approximately 50 employees who allegedly had experienced testicular problems. Based on this concern, the Waynesboro site management requested that an epidemiologic survey be initiated by Du Pont's Corporate Epidemiology Section.

The objective of this survey was to determine whether the prevalence of epididymitis or other related testicular disorders is associated with working in the "Orlon" area of the Waynesboro Plant. Special attention was given to nature of exposure to DMF in the "Orlon" area.

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Background

DMF is used as a spinning solvent in the manufacture of "orlon" at the Waynesboro Plant. DMF (CAS Reg. No. 68-12-2) was first synthesized in 1893 from the reaction of carbon monoxide with dimethylamine. The high solvency of DMF makes it well suited as a solvent in industrial processes, especially those involving polar polymers such as PVC and polyacrylonitrile. (Kennedy, 1986).

DMF can be absorbed into the body by ingestion, skin contact, or inhalation. Exposure to DMF results in the excretion of N-methylformamide (MMF - CAS Reg. No. 123-39-7) in the urine. Recent experiments, however, indicate that the metabolism of DMF is more complex than a series of demethylation steps. The target organ for DMF toxicity is the liver (Kennedy, 1986).

Two clusters, one of three and one of four, testicular germ cell tumors have been reported in aircraft mechanics who had extensive exposure to a solution containing 80 percent DMF and 20 percent acetone (Ducatman, et al, 1986). The DMF solution was dripped from intravenous bags into the wing joints of F4 aircraft, principally during the Vietnam era. No protective equipment was used by mechanics engaged in the 'depotting' operation. Neither medical records nor DMF air or MMF metabolite monitoring data were available.

A cluster of three testicular cancers has recently been reported among leather tannery workers in New York State (Levin, et al, 1987). Each of the three tannery workers was reported to have had skin contact with DMF in the spray line operation at the same plant. No DMF air monitoring or MMF metabolite data were reported. Tannery workers are known to have exposure to a wide variety of agents, including nitrosamines, chromate pigments, benzidine-based direct dyes, formaldehyde, leather dust and aromatic organic solvents (Stern, et al, 1987).

Epididymitis is an inflammation of the epididymis, a duct along the border of the testicle, which provides for storage, transit and maturation of spermatozoa. Diagnosis of epididymitis is generally established by physical examination, urinalysis, urine culture and clinical course. The disease appears to fall into three categories: nonspecific bacterial epididymitis, sexually transmitted epididymitis and epididymitis of uncertain etiology (Krieger, 1984).

Orchitis, less common than epididymitis, involves inflammation of the adjacent testicle. Blood-borne dissemination is the major route of infection. Viral infections, mainly mumps orchitis, are associated with most cases. Since inflammation of the epididymis generally precedes inflammation of the testicle, and patients with clinical evidence of epididymitis usually have involvement of the testicle, most of these patients are classified as having epididymo-orchitis (Krieger, 1984).

Little is known about the epidemiology of epididymitis or orchitis. No general population incidence data are available since it is not a disease for which cases are required to be reported to any population-based registry. Acute epididymitis, however, is reported to be the most common disorder requiring admission at military urology clinics (Vordermark, 1985) and is responsible for more days lost from military service than any other disease (Krieger, 1984).

Methods

A self-administered questionnaire was offered in April, 1987 to all active male employees at the Waynesboro Plant irrespective of current assignment. At that time, there were 1,416 active male employees at the plant. The questionnaire was presented at three series of group meetings with a representative from plant Medical (either the physician or physician's assistant) present to answer any medical questions and to address any employee concerns.

The questionnaire shown in Figure 1 was used to gather information on history of testicular pain and diagnoses of epididymitis, orchitis, urethritis, prostatitis, hydrocele, varicocele and urinary tract infections as well as history of a vasectomy. Name of physician and date of occurrence were requested for each event to which the respondent answered "yes". Physician's name was used as a source to validate the diagnoses reported in the questionnaire and to obtain additional information where needed. Questionnaire data were computerized and the accuracy of the data was validated.

A work history was compiled for each study subject which included demographic data, each job title held at the plant, department or work area, and begin and end dates for each job title. The file of the Administrative Personnel Records System (APR) was the source of work histories for wage roll employees. The APR system, which is maintained at the Charlotte Computer Center, contains complete work history records on all wage roll employees and pensioners at the Waynesboro Plant. Work history records of salary roll employees were photocopied from hard copy records available in the personnel office. The salary work histories were computerized, job titles were standardized by work area and job codes were assigned to job title categories. Exposure to DMF as described in the following section was assessed for all wage and salary roll job titles.

Odds ratios were computed as a measure of the strength of the association between exposure to DMF and being a case. Mantel-Haenszel and logistic regression methods were used to assess relationships between various measures of exposure to DMF and risk of epididymitis. Odds ratios were adjusted for age at diagnosis (or end of follow-up), payroll class and either plant service date or year of birth. An odds ratio of 1.0 implies no association between exposure to DMF and being a case. Odds ratios greater than 1.0 indicate that the odds of a case being exposed to DMF are greater than that of a control while an odds ratio of less than 1.0 would indicate a negative association. Ninety percent confidence intervals on the odds ratios were computed as an indication of whether the odds ratios differed significantly from 1.00 at the 10% level (two-tailed).

Determination of Exposure to DMF

Exposure assessments developed for Waynesboro in a DMF case-control study of selected cancers being conducted at the Waynesboro, Camden, Belle and Washington Works plants were used for this survey. The procedure for assessing potential exposure to DMF was developed by a Project Team comprising KRD industrial hygienists P.G. Gilby and S.W. Dixon, and epidemiologist J. Walrath.

At the initial plant site visit, an orientation session included description of the plant layout and "Orlon" manufacturing process related to DMF use. Discussion with plant personnel included information on raw materials and processes used in the past and a description of the personnel organization and job titles relative to physical layout and processes. After the Project Team was directed on a plant tour of "Orlon" production areas, existing monitoring data by job title and/or work area were reviewed.

A plant history was developed which outlined the DMF process, including origin of and changes in buildings, departments, raw materials, process(es) and capacity. Changes in control measures (i.e. ventilation and protective equipment) were documented through discussion with long term plant personnel and review of design blueprints in plant engineering.

Data on DMF air measurements and NMF metabolite samples were utilized whenever possible. A total of 2,916 personal or area DMF samples were available for 1974-1986 at the Waynesboro Plant. In order to ensure uniformity over time, the area, job and task codes for each sample were assigned based on the coding systems currently in use at the plant. The following data were then entered onto specially developed computer screens: type of sample (i.e. personal or area), name and social security number (for personal samples), date of sample, area code, job code, task

code, type of personal protective equipment, duration of sample and concentration of DMF. For analyses, these data were grouped into unique categories based on combinations of area, job and task.

Measurements of concentrations of the urinary metabolite NMF were available on computer for 1980-1986. For earlier years, fragmentary data on NMF concentrations were obtained from industrial hygiene records. Values entered for each sample in the 1980-1986 data were: sample date, social security number, area, task, job, class and NMF concentration. After these data were edited and missing values and laboratory control samples were deleted, 50,744 NMF measurements were available for analysis by area, job and task categories.

DMF Exposure Ranks

The development of an exposure estimate for each job category was based on information assembled during the course of the study. This information included a job description, period of time in question, use of personal protective equipment, nature of dermal exposure, a list of other chemicals with potential for exposure, a summary of industrial hygiene measurements (both MMF and DMF) and the basis for the decision of the estimation of rank. The form in Figure 2 was used to record facts relevant to each job category classification that had potential for exposure to DMF.

Two estimates of the 8 hour time-weighted average (TWA) exposure to DMF were assigned to each job title category determined to have potential for exposure to DMF. One estimate considered average exposure to DMF and another estimate incorporated the maximum 8 hour TWA exposure to DMF. Average exposure was based on the geometric mean of the 8 hour TWA of DMF and/or MMF samples using the criteria in Table 1. The estimate taking into consideration the maximum exposure to DMF was based on the 95th percentile of the DMF and/or MMF 8 hour TWA sample measurements (Table 2). For each of these exposure estimates, a rank of P (present but not analytically detectable), 1, 2, or 3 was assigned based on available exposure data. Job titles previously determined to have no potential for exposure to DMF were assigned a rank of 0.

In the case of each type of exposure estimate, the final estimate of rank was based on the combined criteria for both DMF and MMF. A decision was made to assign the higher of the two ranks to a job category if the DMF- and MMF-based ranks differed. In instances where no exposure data were available, which was generally true in the earlier time periods, extrapolation was made using exposure data for later years, taking into consideration information recorded on the exposure determination form.

[illegible] spelling were changed wherever possible to standardize job title and area combinations. Job codes were added where needed for DMF-exposed jobs. An exposure dictionary was created which listed all unique combinations of area, job title and job code. The numbers of unique combinations of work area and job title were 539 for the wage and 2038 for the salary work history exposure dictionaries. An exposure profile was assigned to each of these unique job title/area combinations determined to have some potential for exposure to DMF. Each exposure profile included the two determinations of rank discussed earlier; one estimate for the mean DMF/MMF exposures and one estimate for the 95th percentile of the DMF/MMF exposure range. The exposure profiles also took into account any changes in exposure ranks over time.

After exposure profiles were completed for each plant, the dictionary with all job title/area combinations and corresponding exposure estimates was merged with the complete work histories of cases and controls. By this method, exposure classifications were assigned independently of case-control status.

Questionnaire Response Rates

Meetings, scheduled to cover all shift rotations, were held to describe the survey, explain medical terminology and give employees an opportunity to ask questions. During Session I, 867 or 61.2% of the target population of 1,416 male employees on the rolls attended a meeting. A second series (Session II) was scheduled in which an additional 186 men completed a questionnaire for a cumulative response rate of 74.4%. Session III was then held, adding 289 men to the study group and increasing the response rate to 1,342 (94.8%) male employees at the plant.

In Figure 3 are cumulative response rates by questionnaire session and payroll class. Response in Sessions I and II was lower among wage than salary employees. Participation by wage roll employees, however, increased considerably during Session III. Twenty-five percent of the target population of wage employees attended a meeting during Session III compared with 8.6% of the salary roll work force. This resulted in relatively comparable overall response rates of 93.9% and 97.5% for wage and salary roll, respectively.

Employees who attended Session I had a greater proportion of positive responses than employees who attended the latter two sessions (Figure 4). Over 13% of the men who attended the first session reported having had testicular pain severe enough to consult a physician compared with 5.9% of men who attended Session III. Overall, 11.1% reported a history of testicular pain. The proportion of employees with a reported diagnosis of epididymitis was also higher in Session I (8.1%) than in subsequent sessions (6.5% and 3.1% for Sessions II and III, respectively). The overall proportion of employees with a diagnosis of epididymitis was 6.8% in the study group.

Descriptive Data

A total of 1,342 male employees (94.8% of the target workforce) attended one of the meetings and completed the questionnaire. Of these, 149 men (11.1%) reported having had testicular pain severe enough to consult a physician (Table 3). Table 4 summarizes responses to questions related to epididymitis and orchitis. Eighty-five men reported a history of diagnosis of epididymitis and eighteen reported a diagnosis of orchitis. Since epididymitis and orchitis are considered to be one disease entity, i.e. epididymo-orchitis, those men with a positive history of either epididymitis or orchitis or both were grouped together and are referred to as epididymo-orchitis cases. Ninety-one men were included in the epididymo-orchitis group, representing 6.8% of the total study group. The proportion with a positive history of epididymitis was similar when examined by payclass; 6.9% for wage and 6.5% for salary roll.

Table 5 shows that 154 men (11.5%) who completed the questionnaire reported having been diagnosed with prostatitis. The proportions were similar by payclass; 11.3% among wage and 12.0% among salary roll. Positive diagnoses for urethritis and urinary tract infection comprised 3.7% and 14.6% of the study group, respectively.

Varicocele, a varicose condition of the veins in the testes, was reported to have been diagnosed among 35 men (2.5%) in the study group; 2.1% in the wage roll and 3.9% in the salary roll (Table 6). Nineteen men (1.4%) reported having had a hydrocele, a circumscribed collection of fluid in the testicle.

A total of 222 men (16.5% of the study group) reported having had a vasectomy. Proportions differed by payroll status, 13.0% among the wage and 25.5% among the salary roll (Table 7).

Fifty-six men responded positively to having had 'any other testicular condition.' These other testicular conditions as reported on the questionnaire are as follows (one case per condition unless otherwise noted): abnormality in testicle, ache, aseptic meningitis, benign prostatic hypertrophy, chlamydia infection, cyst (6), dilated veins, enlarged indurated epididymis, fatty tumor, fluid buildup, fluid in testicles, hematocele, hernia, kidney stones (3), low sperm count (2), lump-knot, lumps in epididymis, mass in scrotum, missing left testicle, mumps (7), mumps left testicle (3), mumps orchitis, nerves removed left testicle, physical strain, prostate gland, seminoma, small scrotal cyst, sperm buildup on side of testicle, spermatocele (5), swollen area on testicle, testicular cancer, undescended testicle (4), and water or fluid sac.

Confirmation of Diagnoses

An attempt was made to confirm the self-reported diagnoses of epididymitis, orchitis, prostatitis, hydrocele and varicocele. Each employee had the option of signing the questionnaire as indication of their granting permission for Du Pont Medical to contact their physician(s) for confirmation of diagnoses. A total of 1252 men (93.3%) gave permission. A confirmation form was sent to the physician, when noted, for each positive response to the above conditions. The diagnosis in question was stated on the form and the physician was asked for their diagnosis, date of diagnosis and additional comments. For a vasectomy, the physician was asked to verify that a vasectomy was performed and provide the date of the procedure. In each instance, a copy of the questionnaire was enclosed. To encourage a more complete response rate, a fee of $5.00 per completed form was paid to each participating physician's office.

A total of 230 confirmation forms was sent to 67 physicians. Forty-nine (73.1%) of the physicians responded with completed forms on 203 (88.2%) of the reported diagnoses. Du Pont medical records were consulted for the remainder of the diagnoses where either the physician was from Waynesboro Medical, no physician's name was given, the physician could not be located, or was no longer in practice.

A positive diagnosis was not changed in the case of lack of confirmation. Rather, these diagnoses were flagged as positive diagnoses with lack of confirmation and were included as cases in the analyses. Also, if a physician provided a diagnosis that was not reported on the questionnaire, this response was flagged as a positive diagnosis with lack of confirmation. The confirmation forms were especially useful in providing accurate dates of diagnoses and/or date of a vasectomy.

Sixteen (18.9%) of the 85 diagnoses of epididymitis were not confirmed by a physician and an additional fourteen were reported by a physician but not by the employee. Six (33.3%) of the 18 diagnoses of orchitis were not confirmed by a physician and five (27.8%) were ascertained through contact with physicians.

Case-Control Analyses

DMF Exposure and Epididymitis

Analyses were conducted to assess whether ever being exposed to DMF was a risk factor for epididymitis. Employees who ever held a job with a DMF exposure rank of P, 1, 2, or 3 were included in the 'ever exposed' category and those who never held a job with an exposure rank greater than 0 were in the 'never exposed' group. Separate analyses were conducted using the (1) geometric mean exposure rank as the criteria for exposure as defined in Table 1 and (2) 95th percentile as the criteria for exposure (Table 2).

Excluded from the group of epididymitis cases were those diagnosed before their initial date of employment at Waynesboro and those with missing dates of diagnosis. Excluded from the comparison group (hereafter referred to as controls) were individuals with a positive history of prostatitis and/or a history of testicular pain severe enough to consult a physician. These exclusions resulted in a case series of 78 individuals with a history of epididymitis while at Waynesboro and a control group of 1106. The median age at diagnosis for the epididymo-orchitis cases was 35. In Figure 5 is the distribution of the cases by year of diagnosis. Median year of diagnosis was 1978.

The number of men who were ever exposed to DMF based on the geometric mean rank was 956 (81% of the study group). Slightly more, 973 (82%), had ever been exposed based on the 95th percentile of the TWA. Odds ratios adjusted for age, payroll class and plant service date are 1.17 and .96 based on the geometric mean and 95th percentile ranks, respectively (Table 8).

The risk of developing epididymitis after exposure to DMF was examined using the highest exposure rank ever attained as the risk factor. Logistic regression analyses of the highest rank

ever attained (based on the geometric mean) show odds ratios of 1.50, 1.21 and 1.16 for those whose highest geometric mean exposure rank ever reached P, 1 or 2, respectively (Table 9). Similar analyses using the 95th percentile as a measure of exposure show no association with increasing rank (Table 10). Adjusted odds ratios are .74, .83, 1.14 and .82 among those whose 95th percentile DMF exposures ever reached categories P, 1, 2 or 3, respectively.

The risk of developing epididymitis was evaluated by the average DMF exposure experienced by each employee. Adjusted odds ratios are 1.29, 1.09 and 1.19 among those with average exposure ranks of P, 1 and 2, respectively, based on the geometric mean (Table 11). Using the 95th percentile average rank, adjusted odds ratios are 1.08, .85, .97 and 1.26 for average exposure ranks of P, 1, 2, or 3, respectively (Table 12). No trends are apparent and none of the odds ratios in either of these analyses is significantly different from 1.00.

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Vasectomy and Epididymitis

An additional hypothesis tested was the suggested relationship between having had a vasectomy and subsequent development of epididymitis (Walker et al, 1981 and Massey et al, 1984). In Table 13, the adjusted odds ratio for developing epididymitis after a vasectomy is 3.26 (90% confidence limits are 1.96, 5.43). Since there has been some debate over the years as to whether a preoperative vasectomy should be performed to decrease the risk of developing epididymitis in patients who have undergone a prostatectomy (Krieger, 1984), the analysis was repeated, excluding all cases of prostatitis. The resulting adjusted odds ratio of 4.01 was significantly elevated with 90% confidence limits of (2.08, 7.71).

Having had a vasectomy was added to the logistic regression model. Table 14 summarizes the contribution of this variable and all other components of the logistic regression model. The adjusted odds ratio for ever being exposed to DMF is 1.03 after adjustment for age, plant service date, payclass and history of a vasectomy. Age, plant service date and prior vasectomy each contribute significantly to the overall model. Odds ratios are relatively higher for the younger age groups, in the earlier plant service date categories, and in the vasectomized group.

In Table 15 is the summary of the model in which adjustment is made for year of birth rather than plant service date. The adjusted odds ratio for ever being exposed to DMF is 2.04 after adjustment for age, year of birth, payclass and history of vasectomy. Age, year of birth (before 1939), and prior vasectomy all contribute significantly to the overall model. Odds ratios again are relatively higher in the younger age groups, in the earlier year of birth categories, and in the vasectomized group.

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DMF Exposure and Prostatitis

Analyses were conducted to evaluate the odds of DMF exposure in prostatitis cases versus controls. The analyses included 133 prostatitis cases and 1106 controls. Excluded from the analyses were prostatitis cases who were diagnosed before their plant service date and excluded from controls were persons diagnosed with epididymitis and/or orchitis. The mean age at time of diagnosis for the prostatitis cases was 39 years. In Figure 6 is the distribution of the prostatitis cases by year of diagnosis. The median year of diagnosis was 1979.

In Table 16 are odds ratios, adjusted for age, payclass and plant service date, of 1.12 and .90 for prostatitis using the geometric mean and 95th percentile ranks, respectively, as an indication of ever having been exposed to DMF. Neither of these odds ratios are significantly different from 1.00.

Odds ratios for prostatitis by DMF exposure level were also calculated using the highest exposure rank ever attained. Adjusted odds ratios are .89, 1.44 and .94 for those whose highest exposure rank ever reached (based on the geometric mean) was P, 1 or 2, respectively (Table 17). Similar analyses in Table 18 using the highest 95th percentile rank show no association with increasing rank.

Analyses were conducted to test the possible association between exposure to DMF based on average exposure rank and prostatitis. Results using both the geometric mean and 95th percentile shown in Tables 19 and 20, respectively, show no patterns with respect to average exposure rank.

DMF Exposure and Testicular Pain

The epididymitis/orchitis case series was expanded to include persons who answered 'yes' to ever having had testicular pain severe enough to contact a physician. Although 149 men had a positive response to this question, not all could be included in the analyses because no date of diagnosis was associated with this question. The testicular pain question, being more subjective in nature, was intended only as an introduction to the questions on epididymitis and orchitis and therefore, no date was requested for the testicular pain. In an attempt to ascertain a case series of persons with testicular pain, those who answered 'yes' to the question were included as a case if they had a diagnosis date for epididymitis, orchitis, prostatitis, or 'other testicular condition.' Excluded from controls were men with a positive history of epididymitis, orchitis, or prostatitis but with no positive answer to the question on testicular pain. These selection criteria resulted in a case series of 109 cases and 1106 controls.

Odds ratios for ever being exposed to DMF were 1.30 and 1.09 for the geometric mean and 95th percentile exposure ranks, respectively (Table 21). Neither of these odds ratios were significantly different from 1.00. Analyses based on highest exposure rank ever attained showed elevated odds ratios for ranks 1 and 2 based on the geometric mean (Table 22). Neither of these odds ratios, however, were significantly elevated at the 10% level. No pattern in adjusted odds ratios was observed for the highest rank attained based on the 95th percentile (Table 23). Adjusted odds ratios for average exposure ranks of P, 1 and 2 based on geometric means were 1.37, 1.35 and 1.22, respectively (Table 24). Using the average exposure rank based on the 95th percentile resulted in adjusted odds ratios for testicular pain of 1.10, 1.17, 1.05 and 1.00 for ranks P, 1, 2 and 3, respectively (Table 25).

DBF Exposure and Hydrocele and Varicocele

The risk of developing either a hydrocele or varicocele was also computed. Odds ratios for hydrocele were 1.31 and 1.02 when determination of exposure was based on the geometric mean and 95th percentile ranks, respectively (Table 26). Odds ratios for varicocele were 2.11 and 1.84 based on the geometric mean and 95th percentile ranks, respectively (Table 27). None of these odds ratios was statistically significant.

Discussion

These questionnaire data provide estimates of the prevalence of epididymitis, orchitis and other related conditions in a population of employed men. Since neither epididymitis nor orchitis is a reportable disease, no prevalence or incidence data have been available. Of the active employees who completed the questionnaire, 6.8% had ever been diagnosed with epididymitis or orchitis.

Analyses of these survey data indicate the lack of an association between ever being exposed to DMF and the occurrence of epididymitis. Logistic regression analyses of the odds of developing epididymitis based on the highest exposure rank attained showed no association with increasing rank. Similarly, no pattern in odds ratios was seen when the average exposure rank was used as the measure of exposure.

Development of epididymitis appeared to be associated with both earlier year of birth and earlier plant service date, independent of exposure to DMF. Those who were born before 1940 and those who began work at the plant before 1970 were at greater risk of epididymitis. Since year of birth and plant service date are highly correlated, more work is needed to determine the relative importance of these two factors.

Within this study, age, year of birth and plant service date were considered to be what has been referred to as 'nuisance variables' (Breslow and Day, 1980). In reference to these so-called 'nuisance variables', Breslow and Day state that 'They are included only to ensure that the estimates of relative risk are free from possible confounding effects, and no specific meaning is to be attached to their coefficients.' To control for the confounding effects of these factors in our study, adjustment was made in the logistic regression analyses for age, year of birth and/or plant service date. Because of the high

collinearity among time-related variables such as plant service date, birth cohort, exposure duration and latency, unambiguous answers concerning these variables were not possible.

Having had a vasectomy was a significant risk factor for subsequent development of epididymo-orchitis. Results of a cohort study of 10,590 vasectomized men and paired controls showed an excess of epididymitis-orchitis among the vasectomized men (Massey et al, 1984). Walker and colleagues (1981) studied hospitalization rates among 6,092 vasectomized men and found that they had relatively high rates of hospitalization for diseases of the genitourinary system during the postoperative period.

History of prostatitis was not associated with exposure to DMF when exposure was characterized as ever versus never exposed to DMF, highest DMF exposure rank ever experienced or average DMF exposure rank.

Expanding the study group to include persons who reported testicular pain severe enough to contact a physician resulted in no discernible patterns of risk.

There was no association between ever being exposed to DMF and development of either a hydrocele or varicocele.

A cross-sectional survey such as this one has certain limitations. Potential bias may arise since the plant population as of the questionnaire date may not be representative of the composition of the plant workforce in the past. Excluded are pensioners, decedents, those who terminated without pension and transferees. It was not feasible to include these individuals in our study group because of problems in identifying all these persons and in obtaining their medical and work histories.

Questions may arise as to reliability of diagnoses from questionnaires. While this is a problem inherent in surveys

based on questionnaire data, considerable effort was made to confirm the diagnoses and to supplement information in the questionnaires when additional data were available.

Determination of historical exposures in the absence of actual exposure data is a source of potential bias in most epidemiologic studies. However, assessments of past DMF exposures in our study were made based on extensive DMF air and MMF metabolite data, taking into consideration well-documented information on changes in exposure controls and manufacturing processes.

Acknowledgements

Dr. Stadulis, Dave Snyder, Ann Hutchens and the rest of the Medical Staff at the Waynesboro Plant were of great assistance in the distribution of questionnaires at the numerous meetings and in many related administrative activities. Woodrow Carr was responsible for the smooth management of the questionnaire sessions and Betty Varner provided the salary roll work history data. Wayne Watson and Joe Parish at the Charlotte Computer Center and Freelyn Stanley at Waynesboro were most helpful in the dissemination of wage roll work history data from the APR system. Ruth Biddle supplied work history records for the technical salary roll employees. Ann Hutchens sent confirmation forms to physicians and Jen Biscoe arranged for payments to be made to participating physicians.

Ruth Quah provided invaluable programming expertise for the DMF and MMF exposure summary analyses, work history data management and assignment of exposure profiles. Donald Kiscaden with his years of industrial hygiene experience at Waynesboro was extremely helpful in the classification of job titles and in assisting Steve Dixon and Pat Gilby in their careful characterization of DMF exposures and assignment of DMF exposure ranks.

Mary Staats and Pauline Jordan provided expert data entry and Dr. Cherry Burke gave helpful advice.

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Figure 1

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PLEASE PRINT

Name: _____
Last name First name Middle initial

Circle one: Wage Salary Social Security Number _____

Birthdate: ___/___/___

A) Have you ever had pain in your testicles that was severe enough for you to contact a physician?

Yes _____ No _____ (if no, go to section B)

Did the physician tell you that you had any of the following diagnoses?

	Yes	No	If Yes: Name of Physician City, State	Month/Year
Epididymitis				
Orchitis				

B) Have you ever been told by a physician that you have had any of these diagnoses?

	Yes	No	If Yes: Name of Physician City, State	Month/Year
Urethritis				
Prostatitis				
Hydrocele				
Varicocele				

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C) Have you ever been told by a physician that you have had a urinary tract infection? Yes _____ No _____ (if no, go to section D)

When did this condition occur? (Month/Year) _____

Name of physician _____

Where is the physician located? _____
City State

D) Have you had a vasectomy? Yes ___ No ___ (If not, go to Section E)

When was the vasectomy performed? (Month/Year) _____

Name of physician _____

Where is the physician located? _____
City State

E) Have you ever been told by a physician that you have had any other testicular condition? Yes _____ No _____ (if no, go to section F)

Give name of condition _____

Name of physician _____ Date _____
Month/Year

Where is physician located? _____
City State

F) I give Du Pont Medical Division permission to contact any of the above physicians to obtain additional information concerning these diagnoses.

Date _____ Signature _____

Use reverse side for additional information, if necessary.

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5.B.5

Figure 2

Page ___ of ___

JOB EXPOSURE DATA
DMF STUDY

Plant Name _____ Code: ___ ___ ___ Date Coded: ___ ___ ___ ___
Mo Dy Yr

By: _____

Job Title _____ Code: ___ ___ ___ ___

Job Area _____ Code: ___ ___ ___ ___

Exposure Period: From: ___ ___ ___ ___ to ___ ___ ___ ___ TWA Rank: 0 P 1 2 3
No Dy Yr No Dy Yr 95% Rank =

DMF Exposure Job Description (Include % of time and exposure pattern)

Estimated Exposure (ppm or mg/m) Personal Protector (Enter Type)

Dermal Exposure

Basis for Estimating Rank Other Chemical Exposures(Inc.Dates)

FIGURE 3

CUMULATIVE ATTENDANCE RATES AMONG

ACTIVE MALE EMPLOYEES BY QUESTIONNAIRE SESSION

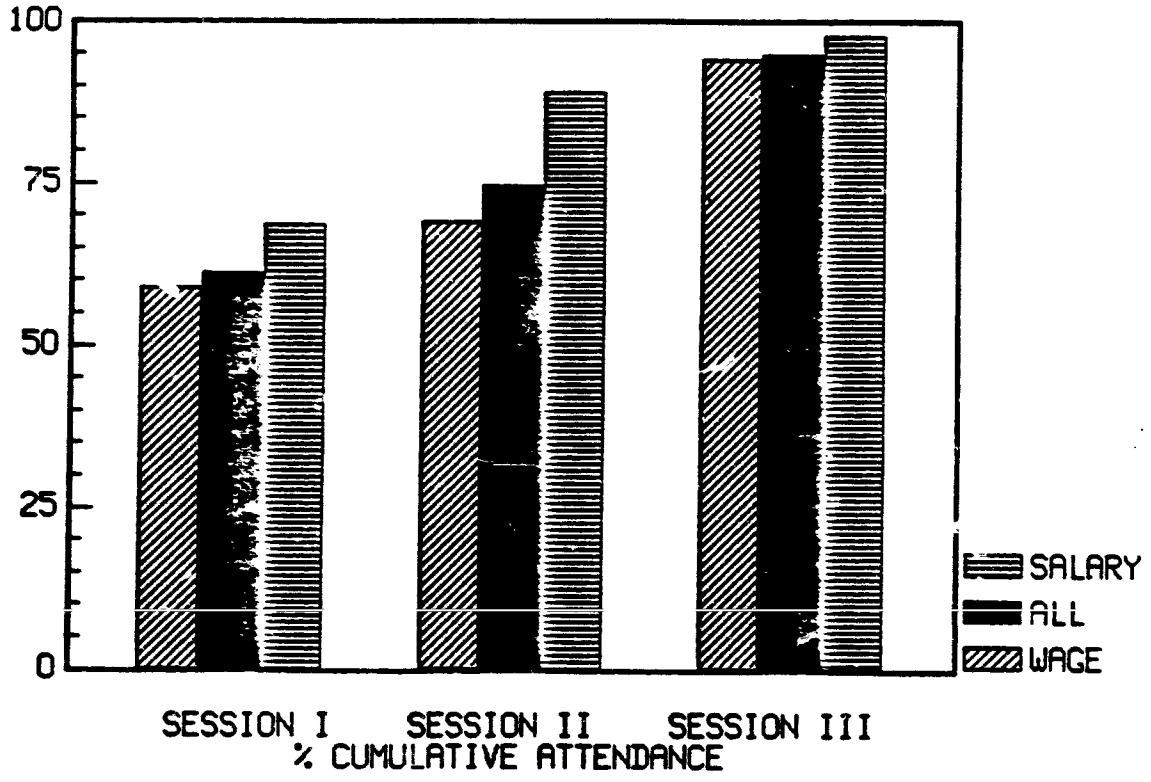
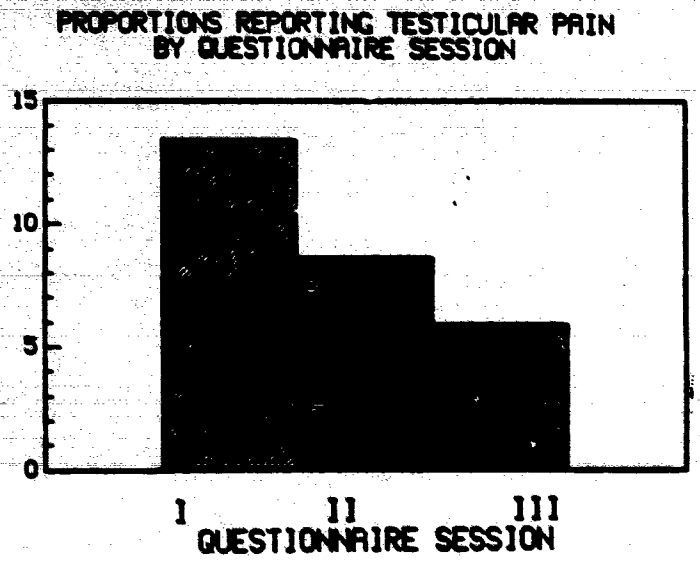


FIGURE 4

PROPORTIONS REPORTING TESTICULAR PAIN AND DIAGNOSES OF EPIDIDYMO-ORCHITIS BY QUESTIONNAIRE SESSION



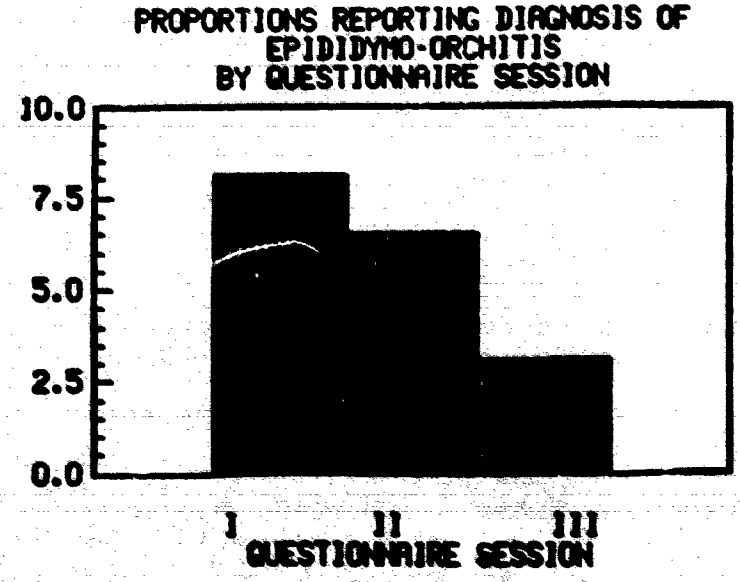


FIGURE 5

DISTRIBUTION OF EPIDIDYMO-ORCHITIS CASES

BY YEAR OF DIAGNOSIS

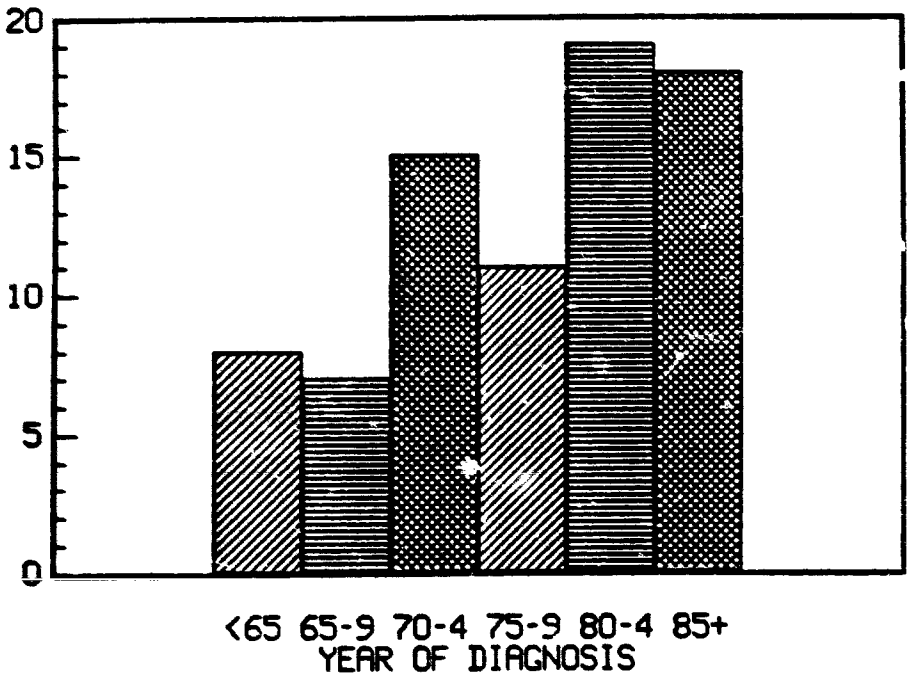


FIGURE 6

DISTRIBUTION OF PROSTATITIS CASES

BY YEAR OF DIAGNOSIS

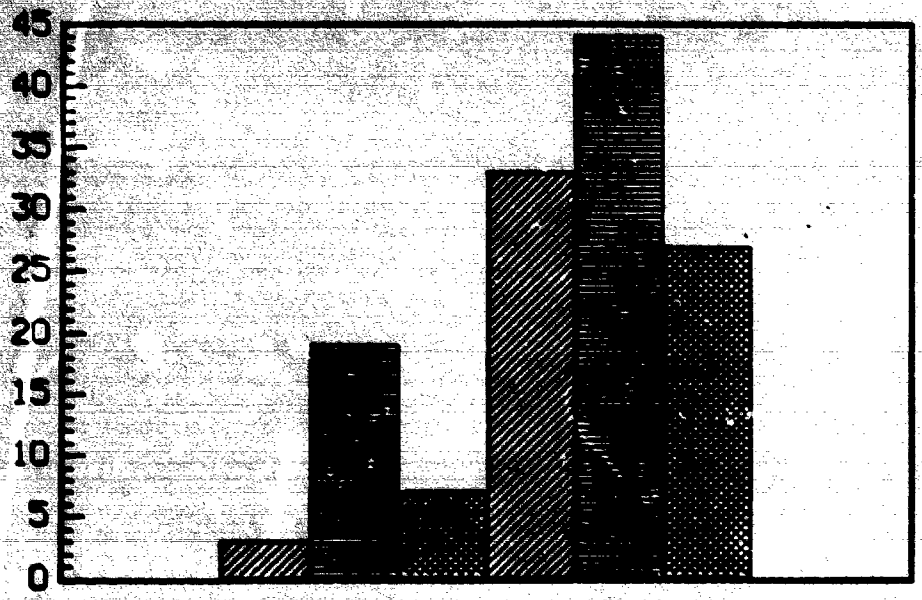


TABLE 1

CRITERIA FOR RANKING OF JOB EXPOSURES

BY GEOMETRIC MEAN

DMF in Air

Measured Exposure - Geometric Mean(ppm)	Rank
0	0 - None
< 1.0	P - Present, but not analytically detectable * or below 1 ppm
1.0 - < 2.0	1 - Low
2.0 - < 10.0	2 - Moderate
10.0 +	3 - High

MMF in Urine

Measured Exposure - Geometric Mean(ppm)	Rank
0	0 - None
< 1.0	P - Present, but not analytically detectable * or below 1 ppm
1.0 - < 5.0	1 - Low
5.0 - < 20.0	2 - Moderate
20.0 +	3 - High

* - Until 1985, minimum level of detection of both DMF and MMF was 1.0 ppm.

TABLE 2

CRITERIA FOR RANKING OF JOB EXPOSURES BY 95TH PERCENTILE

DNF in Air

Best estimate * of the 95th Percentile (ppm)	Rank
0	0 - None
< 5.0	P - Present, but not analytically detectable * or below 1 ppm
5.0 - < 10.0	1 - Low
10.0 - < 50.0	2 - Moderate
50.0 +	3 - High

NNF in Urine

Best estimate * of the 95th Percentile (ppm)	Rank
0	0 - None
< 5.0	P - Present, but not analytically detectable * or below 1 ppm
5.0 - < 25.0	1 - Low
25.0 - < 100.0	2 - Moderate
100.0 +	3 - High

* - Best estimate of the 95th percentile value is 5 times the geometric mean

TABLE 3

FREQUENCY OF REPORTED HISTORY OF TESTICULAR PAIN ON WAYNESBORO EPIDIDYMITIS SURVEY QUESTIONNAIRES, BY PAYCLASS

	Reported History of Testicular Pain		
	WAGE	SALARY	BOTH
YES	113 (11.8%)	36 (9.4%)	149 (11.1%)
NO	844	349	1193
TOTAL	957	385	1342

TABLE 4

FREQUENCY OF REPORTED DIAGNOSES OF EPIDIDYMITIS, ORCHITIS OR EITHER ON WAYNESBORO EPIDIDYMITIS SURVEY QUESTIONNAIRES, BY PAYCLASS

Reported History of Epididymitis

	WAGE	SALARY	BOTH
YES	65 (6.8%)	21 (5.5%)	86 (6.4%)
NO	892	364	1256
TOTAL	957	385	1342

Reported History of Orchitis

	WAGE	SALARY	BOTH
YES	9 (0.9%)	9 (2.3%)	18 (1.3%)
NO	948	376	1324
TOTAL	957	385	1342

Reported History of Either Epididymitis or Orchitis

(Epididymo-Orchitis)

	WAGE	SALARY	BOTH
YES	66 (6.9%)	25 (6.5%)	91 (6.8%)
NO	891	360	1251
TOTAL	957	385	1342

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TABLE 5

FREQUENCY OF REPORTED DIAGNOSES OF PROSTATITIS, URETHRITIS, AND URINARY TRACT INFECTION ON WAYNESBORO EPIDIDYMITIS SURVEY QUESTIONNAIRES, BY PAYCLASS

Reported Diagnosis of Prostatitis

	WAGE	SALARY	BOTH
YES	108 (11.3%)	46 (12.0%)	154 (11.5%)
NO	849	339	1188
TOTAL	957	385	1342

Reported Diagnosis of Urethritis

	WAGE	SALARY	BOTH
YES	39 (4.1%)	11 (2.9%)	50 (3.7%)
NO	918	374	1292
TOTAL	957	385	1342

Reported Diagnosis of Urinary Tract Infection

	WAGE	SALARY	BOTH
YES	132 (13.8%)	64 (16.6%)	196 (14.6%)
NO	825	321	1146
TOTAL	957	385	1342

TABLE 6

FREQUENCY OF REPORTED DIAGNOSES OF VARICOCELE AND HYDROCELE ON WAYNESBORO EPIDIDYMITIS SURVEY QUESTIONNAIRES, BY PAYCLASS

Reported Diagnosis of Varicocele

	WAGE	SALARY	BOTH
YES	20 (2.1%)	15 (3.9%)	35 (2.6%)
NO	937	370	1307
TOTAL	957	385	1342

Reported Diagnosis of Hydrocele

	WAGE	SALARY	BOTH
YES	14 (1.5%)	5 (1.3%)	19 (1.4%)
NO	943	380	1323
TOTAL	957	385	1342

TABLE 7

FREQUENCY OF HISTORY OF VASECTOMY ON WAYNESBORO EPIDIDYMITIS SURVEY QUESTIONNAIRES, BY PAYCLASS

	Reported History of Vasectomy		
	WAGE	SALARY	BOTH
YES	124 (13.0%)	98 (25.5%)	222 (16.5%)
NO	833	287	1120
TOTAL	957	385	1342

TABLE 8

CASE-CONTROL ANALYSES OF EPIDIDYMITIS CASES

(EVER VS. NEVER EXPOSED TO DMF)

BY GEOMETRIC MEAN AND 95TH PERCENTILE RANKS

Basis for Determining Exposure	No. of Cases Exposed	No. of Controls Exposed	Adjusted# Odds Ratio	90% Confidence Limits
Geometric Mean	66	890	1.17	(.60, 2.27)
95th Percentile	66	907	.96	(.48, 1.89)

- Adjusted for age, payclass and plant service date

TABLE 9

LOGISTIC REGRESSION ANALYSES OF EPIDIDYMITIS CASES BY HIGHEST RANK EVER ATTAINED (RANK BASED ON GEOMETRIC MEAN)

Highest Rank Attained	No. of Cases	No. of Controls	Adjusted# Odds Ratio	90% Confidence Limits
0 (No exposure)	12	216	1.00	
P	5	67	1.50	(.36, 3.12)
1	24	322	1.21	(.58, 2.52)
2	37	501	1.16	(.57, 2.35)

- Adjusted for age, payclass and plant service date.

TABLE 10

LOGISTIC REGRESSION ANALYSES OF EPIDIDYMITIS CASES BY HIGHEST RANK EVER ATTAINED (RANK BASED ON 95TH PERCENTILE)

Highest Rank Attained	No. of Cases	No. of Controls	Adjusted# Odds Ratio	90% Confidence Limits
0 (No exposure)	12	199	1.00	
P	5	74	.74	(.25, 2.21)
1	13	201	.83	(.36, 1.89)
2	31	389	1.14	(.55, 2.36)
3	17	243	.82	(.36, 1.88)

- Adjusted for age, payclass and plant service date

TABLE 11

LOGISTIC REGRESSION ANALYSES OF EPIDIDYMITIS CASES

BY AVERAGE EXPOSURE RANK

(RANK BASED ON GEOMETRIC MEAN)

Average Exposure Rank	No. of Cases	No. of Controls	Adjusted# Odds Ratio	90% Confidence Limits
0 (No exposure)	12	216	1.00	
P	14	157	1.29	(.56, 2.96)
1	23	336	1.09	(.52, 2.28)
2	29	397	1.19	(.57, 2.46)

- Adjusted for age, payclass and plant service date.

TABLE 12

LOGISTIC REGRESSION ANALYSES OF EPIDIDYMITIS CASES

BY AVERAGE EXPOSURE RANK

(RANK BASED ON 95TH PERCENTILE)

Average Exposure Rank	No. of Cases	No. of Controls	Adjusted# Odds Ratio	90% Confidence Limits
0 (No exposure)	12	199	1.00	
P	12	139	1.08	(.45, 2.54)
1	14	230	.85	(.38, 1.88)
2	37	505	.97	(.47, 2.00)
3	3	33	1.26	(.35, 4.60)

- Adjusted for age, payclass and plant service date.

TABLE 13

LOGISTIC REGRESSION ANALYSES OF EPIDIDYMITIS CASES BY HISTORY OF VASECTOMY

No. of Cases with Vasectomy	No. of Controls with Vasectomy	Adjusted# Odds Ratio	90% Confidence Limits
21	194	3.26 *	(1.96, 5.43)

Excluding prostatitis cases

No. of Cases with Vasectomy	No. of Controls with Vasectomy	Adjusted# Odds Ratio	90% Confidence Limits
13	172	4.01 *	(2.08, 7.71)

* - Statistically significant at the .10 level

- Adjusted for age, payclass and plant service date.

TABLE 14

ADJUSTED ODDS RATIOS AND CONFIDENCE LIMITS

FOR COMPONENTS OF MODEL FOR

LOGISTIC REGRESSION ANALYSIS OF EPIDIDYMO-ORCHITIS

Variable in Model	Adjusted & Odds Ratio	90% Confidence Limits
Never exposed to DMF	1.00	
Exposed to DMF @	1.03	(.53, 2.02)
Age less than 30 years	1.00	
Age 30 - 34 years	.75 *	(.33, .71)
Age 35 - 44 years	.04 *	(.01, .10)
Age 45 or more years	.003 *	(.001, .01)
Payclass - wage	1.00	
Payclass - salary	.87	(.50, 1.52)
P.S.D. # before 1960	1.00	
P.S.D. 1960 - 1964	.22 *	(.10, .48)
P.S.D. 1965 - 1969	.09 *	(.04, .22)
P.S.D. 1970 or later	.005 *	(.002, .01)
No prior vasectomy	1.00	
Prior vasectomy	3.32 *	(1.98, 5.58)

* - Statistically significant at the 10% level

@ - Exposure determined by geometric mean rank

- Plant Service Date

& - Adjusted for other independent variables in model

TABLE 15

ADJUSTED ODDS RATIOS AND CONFIDENCE LIMITS FOR COMPONENTS OF MODEL FOR LOGISTIC REGRESSION ANALYSIS OF EPIDIDYMO-ORCHITIS

Variable in Model	Adjusted & Odds Ratio	90% Confidence Limits
Never exposed to DMF	1.00	
Exposed to DMF @	2.04	(.97, 4.29)
Age less than 30 years	1.00	
Age 30 - 34 years	.69	(.31, 1.52)
Age 35 - 44 years	.07 *	(.03, .15)
Age 45 or more years	.001 *	(.0001, .003)
Payclass - wage	1.00	
Payclass - salary	.99	(.55, 1.81)
Birthyear before 1935	1.00	
Birthyear 1935-1939	.83	(.38, 1.78)
Birthyear 1940-1944	.02 *	(.005, .08)
Birthyear 1945 and later	.001 *	(.0003, .005)
No prior vasectomy	1.00	
Prior vasectomy	3.10 *	(1.79, 5.62)

* - Statistically significant at the 10% level

@ - Exposure determined by geometric mean rank

& - Adjusted for other independent variables in model

TABLE 16

LOGISTIC REGRESSION ANALYSES OF PROSTATITIS CASES

(EVER VS. NEVER EXPOSED TO DMF)

BY GEOMETRIC MEAN AND 95TH PERCENTILE RANKS

Basis for Determining Exposure	No. of Cases Exposed	No. of Controls Exposed	Adjusted# Odds Ratio	90% Confidence Limits
Geometric Mean	114	890	1.12	(.65, 1.91)
95th Percentile	114	907	.90	(.52, 1.57)

- Adjusted for age, payclass and plant service date.

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TABLE 17

LOGISTIC REGRESSION ANALYSES OF PROSTATITIS CASES

BY HIGHEST RANK EVER ATTAINED

(RANK BASED ON GEOMETRIC MEAN)

Highest Rank Attained	No. of Cases	No. of Controls	Adjusted# Odds Ratio	90% Confidence Limits
0 (No exposure)	19	216	1.00	
P	12	67	.89	(.36, 2.10)
1	48	322	1.44	(.81, 2.56)
2	54	501	.94	(.53, 1.67)

- Adjusted for age, payclass and plant service date.

TABLE 18

LOGISTIC REGRESSION ANALYSES OF PROSTATITIS CASES

BY HIGHEST RANK EVER ATTAINED

(RANK BASED ON 95TH PERCENTILE)

Highest Rank Attained	No. of Cases	No. of Controls	Adjusted# Odds Ratio	90% Confidence Limits
0 (No exposure)	19	199	1.00	
P	12	74	.64	(.27, 1.52)
1	32	201	1.24	(.66, 2.34)
2	38	389	.82	(.45, 1.50)
3	32	243	.89	(.46, 1.71)

- Adjusted for age, payclass and plant service date.

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TABLE 19

LOGISTIC REGRESSION ANALYSES OF PROSTATITIS CASES

BY AVERAGE EXPOSURE RANK

(RANK BASED ON GEOMETRIC MEAN)

Average Exposure Rank	No. of Cases	No. of Controls	Adjusted# Odds Ratio	90% Confidence Limits
0 (No exposure)	18	218	1.00	
P	26	158	1.35	(.69, 2.67)
1	34	342	.88	(.47, 1.64)
2	35	402	.89	(.48, 1.65)

- Adjusted for age, payclass and plant service date.

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TABLE 20

LOGISTIC REGRESSION ANALYSES OF PROSTATITIS CASES

BY AVERAGE EXPOSURE RANK

(RANK BASED ON 95TH PERCENTILE)

Average Exposure Rank	No. of Cases	No. of Controls	Adjusted# Odds Ratio	90% Confidence Limits
0 (No exposure)	18	201	1.00	
P	22	139	.93	(.45, 1.88)
1	26	233	.82	(.42, 1.58)
2	45	513	.74	(.40, 1.36)
3	2	34	.42	(.09, 1.85)

- Adjusted for age, payclass and plant service date.

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TABLE 21

LOGISTIC REGRESSION ANALYSES OF TESTICULAR PAIN CASES

(EVER VS. NEVER EXPOSED TO DMF)

BY GEOMETRIC MEAN AND 95TH PERCENTILE RANKS

Basis for Determining Exposure	No. of Cases Exposed	No. of Controls Exposed	Adjusted Odds Ratio	90% Confidence Limits
Geometric Mean	96	890	1.30	(.70, 2.44)
95th Percentile	97	907	1.09	(.57, 2.08)

- Adjusted for age, payclass and plant service date.

TABLE 22

LOGISTIC REGRESSION ANALYSES OF TESTICULAR PAIN CASES
BY HIGHEST RANK EVER ATTAINED
(RANK BASED ON GEOMETRIC MEAN)

Highest Rank Attained	No. of Cases	No. of Controls	Adjusted# Odds Ratio	90% Confidence Limits
0 (No exposure)	13	216	1.00	
P	7	67	.96	(.35, 2.59)
1	39	322	1.42	(.72, 2.86)
2	50	501	1.26	(.65, 2.44)

- Adjusted for age, payclass and plant service date.

TABLE 23

LOGISTIC REGRESSION ANALYSES OF TESTICULAR PAIN CASES BY HIGHEST RANK EVER ATTAINED (RANK BASED ON 95TH PERCENTILE)

Highest Rank Attained	No. of Cases	No. of Controls	Adjusted# Odds Ratio	90% Confidence Limits
0 (No exposure)	12	199	1.00	
P	8	74	.77	(.29, 2.06)
1	24	201	1.14	(.54, 2.41)
2	39	389	1.18	(.59, 2.32)
3	26	243	1.04	(.49, 2.21)

- Adjusted for age, payclass and plant service date.

TABLE 24

LOGISTIC REGRESSION ANALYSES OF TESTICULAR PAIN CASES

BY AVERAGE EXPOSURE RANK

(RANK BASED ON GEOMETRIC MEAN)

Average Exposure Rank	No. of Cases	No. of Controls	Adjusted# Odds Ratio	90% Confidence Limits
0 (No exposure)	13	216	1.00	
P	21	157	1.37	(.64, 2.91)
1	38	336	1.35	(.82, 2.67)
2	37	397	1.22	(.62, 2.40)

- Adjusted for age, payclass and plant service date.

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TABLE 25

LOGISTIC REGRESSION ANALYSES OF TESTICULAR PAIN CASES

BY AVERAGE EXPOSURE RANK

(RANK BASED ON 95TH PERCENTILE)

Average Exposure Rank	No. of Cases	No. of Controls	Adjusted# Odds Ratio	90% Confidence Limits
0 (No exposure)	12	199	1.00	
P	17	139	1.10	(.49, 2.43)
1	27	230	1.17	(.57, 2.38)
2	50	505	1.05	(.53, 2.08)
3	3	33	1.00	(.28, 3.50)

- Adjusted for age, payclass and plant service date.

TABLE 26

LOGISTIC REGRESSION ANALYSES OF HYDROCELE CASES

(EVER VS. NEVER EXPOSED TO DMF)

BY GEOMETRIC MEAN AND 95TH PERCENTILE RANKS

Basis for Determining Exposure	No. of Cases Exposed	No. of Controls Exposed	Adjusted# Odds Ratio	90% Confidence Limits
Geometric Mean	10	1065	1.31	(.26, 6.68)
95th Percentile	10	1083	1.02	(.19, 5.35)

- Adjusted for age, payclass and plant service date.

TABLE 27

LOGISTIC REGRESSION ANALYSSS OF VARICOCELE CASES

(EVER VS. NEVER EXPOSED TO DMF)

BY GEOMETRIC MEAN AND 95TH PERCENTILE RANKS

Basis for Determining Exposure	No. of Cases Exposed	No. of Controls Exposed	Adjusted# Odds Ratio	90% Confidence Limits
Geometric Mean	17	1054	2.11	(.46, 9.74)
95th Percentile	17	1072	1.84	(.39, 8.75)

- Adjusted for age, payclass and plant service date.

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CONTAINS NO CBI

A CASE-CONTROL STUDY OF CANCER AMONG DU PONT EMPLOYEES WITH POTENTIAL FOR EXPOSURE TO DIMETHYLFORMAMIDE

Judy Walrath, Ph.D.
Epidemiologist

William E. Fayerweather, Ph.D., M.P.H.
Manager, Epidemiology

Pat G. Gilby, C.I.H.
Occupational Health Consultant

May 10, 1988

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ABSTRACT

This study's objective is to determine whether the risk of developing cancers of the buccal cavity and pharynx, liver, prostate, testis, or skin (malignant melanoma) is related to exposure to dimethylformamide (DMF). This case-control study includes male employees at the following plants: Belle (Agricultural Chemicals), Camden (Textile Fibers), Washington Works (Polymer Products) and Waynesboro (Textile Fibers). DMF is produced at the Belle, West Virginia plant, and is used at the Waynesboro and May plants as a spinning solvent, and at the Washington Works and Fayetteville plants as a solvent for inks.

Cases are defined as all incident cases of cancers of the buccal cavity and pharynx, liver, prostate, testis, or skin (malignant melanoma) that have been reported to the Du Pont Cancer Registry among active male employees at the study plants during the period 1956-1985. The 138 cancer cases are distributed by anatomic site as follows: 39 buccal cavity and pharynx, 6 liver, 43 prostate, 11 testis and 39 malignant melanoma.

For each case, 2 controls were selected, matched on sex, payroll, year of birth and plant. Complete work histories were obtained for all but 1 case (malignant melanoma at Waynesboro) and 4 controls. To determine whether an employee could have been exposed to DMF during his career at the plant, all jobs with potential for exposure to DMF were identified. Each of these jobs was assigned an exposure ranking based on DMF industrial hygiene air monitoring, N-methyl-formamide (NMF) metabolite monitoring and knowledge of the evolution of manufacturing processes and workplace exposure controls. Each employee's DMF exposure pattern during his career at each plant was then characterized as (a) ever versus never having been exposed to DMF, and (b) highest DMF exposure experienced.

Summary analyses for all plants combined show no statistically significant association between ever having been exposed to DMF and subsequent development of cancers of the buccal cavity and pharynx, liver, malignant melanoma, prostate and testis.

When odds ratios are examined by plant site, prostate cancer at Washington Works is significantly elevated, based on three cases exposed out of four. No statistically significant association is observed among employees similarly exposed to DMF in the other three plants. The recency of exposure to DMF, the low exposures received and the absence of similar excesses at other plants argue against a causal association between DMF exposure and prostate cancer at Washington Works.

Assessment of highest DMF exposure rank, duration of exposure and latent period show no patterns suggestive of an association between DMF and cancers of the buccal cavity and pharynx, liver, malignant melanoma, prostate or testis. Cancer risk also appears to be unrelated to a history of having worked as a mechanic.

In summary, these data suggest that there is no causal relationship between exposure to DMF and any of the cancers studied.

A CASE-CONTROL STUDY OF CANCER AMONG DU PONT EMPLOYEES WITH POTENTIAL FOR EXPOSURE TO DIMETHYLFORMAMIDE

OBJECTIVE

This study's objective is to determine whether the risk of developing cancers of the buccal cavity and pharynx, liver, prostate, testis, or skin (malignant melanoma) is related to exposure to dimethylformamide (DMF).

RATIONALE

Cancers at these five sites are included for the following reasons. Cancers of the buccal cavity and pharynx and malignant melanoma were statistically significantly elevated in a cohort of May plant workers exposed to DMF, but not ACN (acrylonitrile) (Chen, 1986). Prostate cancer was statistically significantly elevated in a cohort of workers exposed to both DMF and ACN at the May plant (Chen, 1986). Two small clusters of testicular cancer were reported among aircraft repairmen who had potential for exposure to DMF (Ducatman, 1986). DMF is known to be a liver toxin (Kennedy, 1986).

BACKGROUND

DMF (CAS Reg. No. 68-12-2) was first synthesized in 1893 from the reaction of carbon monoxide with dimethylamine. The high solvency of DMF makes it well suited as a solvent in industrial processes, especially those involving polar polymers such as polyvinyl chloride and polyacrylonitrile (Kennedy, 1986). DMF can be absorbed into the body by ingestion, skin contact or inhalation. Exposure to DMF results in the excretion of the urinary metabolite N-methyl-formamide (MMF - CAS Reg. No. 123-39-7). Recent experiments, however, indicate that the metabolism of DMF is more complex than a series of demethylation steps. The target organ for DMF toxicity is the liver (Kennedy, 1986).

DMF is produced at the Belle, West Virginia plant, and is used at the Waynesboro and May plants as a spinning solvent in the manufacture of acrylic fiber, and at the Washington Works and Fayetteville plants as a solvent for inks used to tint plastic sheeting.

Pell and others (1973) investigated the health effects of DMF at the May and Waynesboro plants, with special attention given to liver, cardiovascular and gastrointestinal disorders. No statistically significant excess was found for any chronic disease (including liver disease), sickness absenteeism or laboratory test abnormalities at either plant. Seven cases of cancer were observed compared with an expected value of 9.7 among 370 workers with exposure to DMF at Waynesboro. No data on cancer were presented for the May plant.

An epidemiologic study of workers exposed to ACN at the May plant in Camden, South Carolina revealed an increased incidence of respiratory cancer (O'Berg, 1980). To determine whether the elevated cancer was associated with exposure to DMF, ACN, or a combination of DMF and ACN, a cohort study was conducted on 5005 male employees at the May plant (Chen, 1986).

The cohort was comprised of 2530 employees exposed to DMF but not to ACN, 1329 exposed to both DMF and ACN, 16 exposed to ACN but not DMF and 1130 with no exposure to either DMF or ACN. The incidence of cancers of the buccal cavity and pharynx and melanoma was significantly elevated among wage employees exposed to DMF but not to ACN. The excess of malignant melanoma was statistically significant when the comparison group was the general U.S. population but not when Du Pont rates were used as the comparison. Prostate cancer was significantly elevated among wage employees exposed to both ACN and DMF.

Results of an update of the study of workers exposed to ACN at the May plant (O'Berg et al, 1985) showed a statistically significant excess of prostate cancer based on 6 observed cases. There was also an excess of respiratory cancer, but this excess was not statistically significant.

At the Waynesboro plant, a non-significant excess of prostate cancer was reported in a cohort of 1083 workers exposed to acrylonitrile (Chen et al, 1987). Exposure patterns among employees exposed to ACN at the May plant are similar to those among employees at the Waynesboro plant in that most employees exposed to ACN are also exposed to DMF.

Two clusters of three and four testicular germ cell tumors have been reported in aircraft mechanics who had exposure to a solution containing DMF and acetone (Ducatman et al, 1986). Neither medical records nor DMF air exposure or NMF metabolite data were available.

A study on testicular cancer among Navy personnel (Garland et al, 1988) reported statistically significantly elevated testicular cancer among aviation support equipment technicians, enginemen and construction mechanics. Potential exposures mentioned for these occupations are lubricating oils, paints (including chromate-based), degreasing agents, other solvents

and internal combustion exhaust emissions from diesel and gasoline engines.

A cluster of three testicular cancers has been reported among leather tannery workers in New York State (Levin et al, 1987). Each of the three tannery workers was reported to have worked in the same operation in the same plant. This particular operation involved exposure to several chemicals, including DMF. No air monitoring or metabolite data were reported. Tannery workers are known to have exposure to a wide variety of agents, including nitrosamines, chromate pigments, benzidine-based direct dyes, formaldehyde, leather dust and aromatic organic solvents (Stern et al, 1987).

An unpublished paper by the State of New York Department of Health (1988) reported a statistically significantly elevated risk of testicular cancer among persons employed in the leather industry in Fulton County, New York. The Fulton County study was prompted by Levin's report (Levin et al, 1987) of a cluster of three testicular cancers among tannery workers. Ten testicular cancers in the county were identified in the State Cancer Registry, and controls were selected from other cancer sites within the Registry. Lifetime occupational histories were obtained for the testicular cancer cases while usual occupation was determined for the controls through cancer report forms or death certificates.

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STUDY DESIGN

This case-control study includes male employees at the following plants: Belle (Agricultural Chemicals), Camden (Textile Fibers), Washington Works (Polymer Products), and Waynesboro (Textile Fibers). Fayetteville plant (Polymer Products) is not included in the study because of the recency of potential exposure to DMF.

DMF production began at Belle plant in 1961. DMF use began in 1950 at May plant and in 1958 at Waynesboro and Washington Works plants.

Cases are defined as all incident cases of cancers of the buccal cavity and pharynx, liver, prostate, testis, or skin (malignant melanoma) that have been reported to the Du Pont Cancer Registry among active male employees at the four study plants during the period 1956-1985. The 138 cancer cases which meet these criteria are distributed by anatomic site as follows: 39 buccal cavity and pharynx, 6 liver, 43 prostate, 11 testis, and 39 malignant melanoma (Table 1). The population from which these cancers are identified averages 8724 per year during 1956-1985. Average mid-year population by plant during this time period is: Belle - 2052, May - 2276, Washington Works - 2150 and Waynesboro - 2246 (Table 1).

For each case, the first two eligible controls were selected from the roster corresponding to plant and year of diagnosis of the case. Each control was matched to its respective case according to year of birth (+ or - 3 years), sex, payroll class (wage or salary), and plant.

Work histories were computerized for each study subject. Each work history includes demographic data, every job title held while at the plant, department or work area and begin and end dates for each job.

ASSESSMENT OF EXPOSURE TO DMF

A system for assessing potential exposure to DMF was developed by a Project Team comprising Employee Relations Department industrial hygienists P.G. Gilby and S.W. Dixon, and epidemiologist J. Walrath, and applied in a standard manner across the study plants.

The Project Team made a site visit to each plant which began with an orientation of the plant layout and manufacturing processes related to DMF production or use. Discussion with plant personnel centered upon types of raw materials and processes used in the past and description of the plant personnel organization and job titles relative to physical layout and process(es). A plant tour was conducted of areas involving DMF production or products using DMF.

After the plant tour, existing monitoring data by job title and/or work area were reviewed. When feasible, copies of all sampling data were obtained at the initial plant visit. Job descriptions were obtained for all job titles with potential for exposure to DMF. Work histories for study subjects were developed from personnel records. At Belle, personnel records had been destroyed for some employees, in compliance with the plant's routine guidelines for records retention. In these instances, seniority rosters, medical records and interviews with long-term co-workers were used to ascertain work histories.

A plant history was developed for each plant site which outlined the DMF process, including origin of and changes in buildings, departments, raw materials, process(es) and capacity. Changes in control measures (i.e. ventilation and protective equipment) were documented through discussion with long term plant personnel and review of design blueprints in plant engineering.

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DMF AND NMF EXPOSURE MONITORING DATA

Data on DMF air measurements and NMF urinary metabolite concentrations were utilized whenever possible. The following sections outline the extent to which exposure data were available for each plant site.

WAYNESBORO AND MAY PLANTS

Totals of 2916 and 2718 personal or area samples of DMF were available for 1974-1986 for the Waynesboro and May plants, respectively. Fragmentary DMF data were available for the earlier years, beginning in 1952. In order to ensure uniformity over time, the area, job and task codes for each sample were assigned based on the coding systems currently in use at each plant. The following data were then entered onto specially developed computer screens: plant code, type of sample (i.e. personal or area), name and social security number (for personal samples), date of sample, area code, job code, task code, type of personal protective equipment, duration of sample and concentration of DMF. For analyses, these data were grouped into unique categories based on combinations of area, job and task.

For Waynesboro, measurements of concentrations of the urinary metabolite NMF were available on computer tape for 1980-1986. Data values entered for each sample were: plant code, sample date, social security number, area, task, job, class and NMF concentration. After these data were edited and invalid values (i.e. analytical standards) and incomplete entries were deleted, 60,744 NMF measurements were available for analyses by area, job and task categories at Waynesboro. For earlier years, fragmentary NMF data were obtained from medical records of study subjects and from industrial hygiene records.

Approximately 70,000 MMF concentrations for May plant employees were available on computer printout for the years 1975-1986. Due to the large amount of data, only 25% of the measurements were entered. In order to compensate for seasonal variations in MMF metabolite data (Dixon et al, 1983), a rotating sample was taken in which data for the first month of each quarter (i.e. January, April, July and October) were selected for each subsequent year. For example, data were entered for January in 1975, April in 1976, July in 1977, October in 1978 and so on. After the data were edited and missing values were deleted, a total of 11,985 measurements were available for analysis by area, job and task at the May plant.

WASHINGTON [illegible]

Personal DMF air monitoring data were available by individual and by task on computer tape from 1974-1986. MMF metabolite data were available from 1978. A total of 2,361 DMF and 2,037 MMF samples were available for analysis.

BELLE

Area monitoring data were available from 1975. While these data were from area samples, attempts were made to locate the sampling device at breathing zone level in some cases. Personal DMF monitoring data were available from 1979-1986 and MMF urine samples were available from 1975-1979. A total of 167 personal DMF samples, 107 MMF urine samples and 14 DMF area samples were available for analysis.

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RANKING OF JOB EXPOSURES

The development of an exposure estimate for each job category was based on information assembled during the course of the study. This information included a job description, period of time in question, use of personal protective equipment, nature of dermal exposure, a list of other chemicals with potential for exposure, a summary of industrial hygiene measurements (both MMF and DMF) and the basis for the decision of the estimation of rank. The form in Figure 1 was used to record facts relevant to each job category classification that had potential for exposure to DMF.

Two estimates of 8 hour time-weighted average (TWA) exposure to DMF were assigned to each job title category determined to have potential for exposure to DMF. One estimate considered average exposure to DMF and another estimate incorporated the peak 8 hour TWA exposure to DMF. Average exposure was based on the geometric mean of the 8 hour TWA of DMF and/or MMF samples using the criteria in Table 2. The estimate taking into consideration peak 8 hour TWA exposures to DMF was based on the 95th percentile of the DMF and/or MMF 8 hour TWA sample measurements (Table 3). For each of these exposure estimates, a rank of P (present but not analytically detectable), 1, 2 or 3 was assigned based on available exposure data. Jobs titles previously determined to have no potential for exposure to DMF were assigned a rank of 0.

For each type of exposure estimate, the final estimate of rank was based on the combined criteria for both DMF and MMF. A decision was made to assign the higher of the two ranks to a job category if the DMF- and MMF-based ranks differed. In instances where no exposure data were available, which was generally true in the earlier time periods, extrapolation was made, using exposure data for later years and taking into consideration information recorded on the exposure determination form.

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Work history data were reviewed separately for each plant and minor variations in spelling were changed wherever possible to standardize job title and area combinations. Job codes were added where needed for DMF-exposed jobs. An "exposure dictionary" was created for each plant which listed all unique combinations of area, job title and job code. The numbers of unique combinations of job title and area ranged from 597 for Washington Works to 1352 for Waynesboro. For each of the four plants in the study, an exposure profile was assigned to each unique job title/area combination with potential for exposure to DMF. Each exposure profile included the two determinations of rank; one estimate for the mean DMF/MMF exposure and one estimate for the 95th percentile of the DMF/MMF exposure range. The exposure profiles also took into account changes in exposure ranks by time period. Exposure profiles for each plant are presented in Appendices A, B, C and D for Belle, May, Washington Works and Waynesboro, respectively.

After exposure profiles were completed for each plant, the dictionary with all job title/area combinations and corresponding exposure estimates was merged with the complete work histories of the cases and controls. By this method, exposure classifications were assigned independently of case-control status.

STATISTICAL METHODS

For each cancer site, the association between ever being exposed to DNP and cancer risk is assessed by individual plant using Mantel-Haenszel matched analyses. Test-based 90% confidence intervals on the odds ratios are computed as an indication of whether or not the odds ratio differs significantly from 1.00 at the 10% probability level (two-tailed). That is, if the 90% confidence interval does not include 1.00, the odds ratio is assumed to be different from the null value of 1.00 and the odds ratio is said to be statistically significant. In situations for which the Mantel-Haenszel estimates were mathematically not defined, the logit procedure was used to estimate the odds ratio and 90% confidence limits. The logit estimate adds a correction factor of 0.5 to each cell of a table that contains a zero.

Mantel-Haenszel and multiple logistic regression methods are used to compute a summary odds ratio over all strata. Stratification in the Mantel-Haenszel analyses is based on matched triplet. Stratification in the logistic regression analyses is based on the matching variables of plant, payclass, year of diagnosis and age at diagnosis.

For each cancer site, the Breslow-Day test for heterogeneity of odds ratios is computed to determine whether odds ratios differ significantly across strata. Statistical significance for this test indicates that the odds ratios are heterogeneous across strata, that stratum-specific effects should be examined and that the summary statistic across all plants should therefore be regarded cautiously.

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The potential for DMF exposure was categorized according to:

- Ever versus never exposed to DMF based on the geometric mean of the TWA and on the 95th percentile of the TWA.

- Exposure level based on the job with the highest geometric mean exposure rank.

- Exposure duration based on the total number of days spent in DMF jobs with geometric mean exposure ranks greater than zero.

- Latent period -- exposure was defined and analyzed according to each of three assumptions about latent period: (1) no latent period; (2) 3-year minimum latent period; (3) 10-year minimum latent period.

Exposure was assessed for each case and matched control from the date the respective case or control was hired at the plant to the case's date of diagnosis. Analyses of DMF exposure based on the 95th percentile of the TWA produced results that were similar to those for the geometric mean and are not presented in the tables.

Exploratory analyses of jobs in the category of mechanic/craftsman were also performed to see if there was any indication that these workers were at a higher cancer risk.

Assessment of effect by exposure level, latent period and duration of exposure were performed by multiple logistic regression techniques with stratification on the matching variables of plant, payclass, year of diagnosis and age of diagnosis. For all analyses, two-tailed 90% confidence intervals on odds ratios were calculated.

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RESULTS AND DISCUSSION

The average age of the cancer cases was 62.8 and ranged from 59.8 at Washington Works to 65.5 at Belle. Work histories were unavailable for one cancer case (malignant melanoma at Waynesboro) and four controls.

The distribution of study subjects by highest geometric mean exposure category ever attained (none, present, low and moderate) shows that none of the job titles at any of the plants falls into the highest geometric mean exposure rank (Table 4). DMF exposure patterns vary considerably by plant. The proportion exposed to DMF ranges from 6.9% at Belle to 83.2% at the May plant. All study subjects exposed to DMF at Belle and the majority of those exposed at Washington Works are in the "Present" category. At the May plant, more than half of the DMF-exposed employees are in the "Moderate" category. Exposed study subjects are relatively evenly distributed by exposure category at Waynesboro.

BUCCAL CAVITY AND PHARYNX CANCERS

Thirty-nine cases of cancers of the buccal cavity and pharynx are included in the analyses. Median age at diagnosis is 51. Distribution of cancer cases by plant site is as follows: Belle-11, May-11, Washington Works-9 and Waynesboro-8.

Visual inspection of the plant-specific odds ratios (Table 5) reveals marked heterogeneity. Adjusted odds ratios range from 0.50 at the May plant to 15.0 at Belle. Only Belle shows an elevated odds ratio, and this elevation is based on a single exposed case. The test for heterogeneity of the odds ratios is statistically significant (p-value = 0.041), which also suggests that the odds ratios are heterogeneous over strata. Summary estimates over all plants should therefore be interpreted with caution.

The Mantel-Haenszel all-plants odds ratio (Table 6, odds ratio = 0.89) is not statistically significantly different from 1.00. Analyses of exposure by highest DMF exposure category attained show odds ratios of less than 1.00 in all three exposure categories.

In a cohort study at May plant (Chen, 1986), cancer of the buccal cavity and pharynx was statistically significantly elevated among employees exposed to DMF but not to ACN compared with expected numbers based on Company or U.S. rates. Routine cancer incidence surveillance for the period 1956-1983 showed a statistically significant excess of buccal cavity and pharynx cancer among May plant employees relative to the entire Company. Routine mortality surveillance for the period 1957-1984 showed a slight but statistically nonsignificant excess for this cancer site.

The buccal cavity and pharynx cancer component of the present study was added because of the buccal cavity cancer excesses at May plant noted above. In contrast to Chen's study that relied upon external comparison groups (e.g., U.S. rates), the present study compares DMF-exposed May plant employees to May plant employees who never worked in DMF areas. These internal comparisons show that buccal cavity cancer risk is no higher in DMF-exposed than non-exposed employees (OR = 0.50, 90% CI = 0.05, 4.89). These findings suggest that there may be a local excess of buccal cavity cancer at May plant that is unrelated to DMF exposure.

As Chen observed (Chen, 1986), this plant-wide excess may be attributable to a disproportionate amount of tobacco use in South Carolina where the May plant is located. All eleven buccal cavity and pharynx cancer cases were heavy smokers for a long duration (at least 20 years), and two of them were heavy drinkers. Information on use of chewing tobacco and snuff was not ascertained. Use of tobacco (including smokeless tobacco) and alcohol are important risk factors for cancers of the buccal cavity and pharynx (Mahboubi and Sayed, 1982).

LIVER CANCER

Only six liver cancer cases are available for analysis: 4 are from Belle and 2 from Washington Works. All six cases were wage roll employees. Ages at diagnosis range from 45 to 61 and years of diagnosis are from 1964 to 1978. Only one case and one control were ever exposed to DMF at Belle and none of the cases and controls at Washington Works was exposed to DMF (Table 7). The highest exposure level attained at Belle by exposed liver cancer cases and controls is the "Present, < 1 ppm level" (Table 8). The logit estimate of 3.00 is not statistically significantly different from 1.00.

Liver cancer is relatively rare in the United States. Suspected etiologic factors for this disease are hepatitis B virus, alcohol and aflatoxin (Falk, 1982).

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Malignant Melanoma

The malignant melanoma study group is comprised of 38 cases with a median age at diagnosis of 46. Nine cases are from Belle, 11 from May, 12 from Washington Works and 6 from Waynesboro. Cases were diagnosed from 1963 through 1985 with a median year of 1979.

Analyses of the malignant melanoma cases by individual plant (Table 9) show odds ratios that range from 1.00 at Waynesboro to 3.50 at Belle. The test for heterogeneity of the odds ratios is not statistically significant (p = 0.19).

The summary odds ratio of 1.70 for all plants combined (Table 10) is not statistically significantly different from 1.00 (90% CI = 0.52, 5.51).

Logistic regression analyses by highest exposure attained show a slight trend with increasing exposure category (Table 10), but the odds ratio at the highest exposure level is not statistically significant.

In a cohort study at May plant (Chen, 1986), malignant melanoma was statistically significantly elevated among employees exposed to DNF but not to ACW. The excess of malignant melanoma was statistically significant when the comparison group was the general U.S. population but not when Du Pont rates were used as the comparison.

The malignant melanoma component of the present study was initiated because of the malignant melanoma excesses at May plant noted above. In contrast to Chen's study that relied upon external comparison groups (e.g., U.S. rates), the present study compares DNF-exposed employees at May plant to employees at May plant who never worked in DNF areas. These internal

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comparisons show that malignant melanoma risk is no higher in DMF-exposed than non-exposed employees (OR = 1.02, 90% CI = 0.14, 7.32). These findings suggest that there is an excess of malignant melanoma at May plant that is unrelated to DMF exposure. This local excess might be due to regional differences in medical surveillance, diagnostic thoroughness or lifestyle. It might also be due to undetermined factors responsible for the Company-wide excesses of malignant melanoma reported from cancer surveillance data (Pell et al, 1978 and O'Berg et al, 1987).

Chemical exposures have not been regarded as important risk factors for malignant melanoma. However, some studies have raised this possibility, and interest in this area is increasing. Possible etiologic factors associated with malignant melanoma include exposure to sunlight, eye and hair color, skin tone, ability to tan, family history, previous skin cancer, precursor lesions, latitude of residence and ethnicity (Lee, 1982).

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PROSTATE CANCER

The following analyses include a total of 43 cases of cancer of the prostate. Median age at diagnosis is 57, with a range from age 40 to 64. Median year of diagnosis is 1974. Distribution of the prostate cancer cases by plant site is as follows: Belle-16, May-13, Washington Works-4 and Waynesboro-10.

Mantel-Haenszel analyses by plant site (Table 11) show odds ratios of 0.40, 1.43 and 2.00 at May, Waynesboro and Belle, respectively. The odds ratio of 8.04 (based on the logit estimate) for Washington Works is statistically significantly elevated (90% CI = 1.04, 62.3).

The test for heterogeneity of the odds ratio is statistically significant (p = .020). Visual inspection of odds ratios by plant reveals marked heterogeneity, suggesting that a summary odds ratio over all plants may be misleading.

When data from all four plants are combined (Table 12), the Mantel-Haenszel odds ratio of 1.47 is elevated, but not statistically significant (90% CI = 0.66, 3.30). This elevated odds ratio is largely due to the Washington Works plant where 3 of the 4 cases were exposed to DMF compared with only one of the 8 controls. Excluding this plant results in an odds ratio of 0.93 with 90% CI = 0.38, 2.32.

Logistic regression analysis of dose-response (Table 12) shows an odds ratio of 1.11 in the "Present" group and an odds ratio in the "Moderate" category that is elevated (odds ratio = 1.75), but not statistically significant at the 90% level.

The odds ratio for prostate cancer is statistically significantly elevated at Washington Works, but the summary odds ratio over all plants combined is not statistically significantly elevated. At Washington Works, two cases (DMF exposure durations of 13 and 135 months) were exposed in the <1.0 ppm DMF range and the third exposed case (exposure duration of 33 months) had been exposed to DMF levels in the 2.0-<10.0 ppm range (Table 13). The Company's cancer incidence surveillance data for 1956-1985 show that Washington Works has a slight deficit of prostate cancer cases compared with the number expected based on Company incidence rates.

The DMF-exposed cases at Washington Works have 12-16 years of elapsed time between date first exposed and date of diagnosis. With few exceptions (e.g., radiation-induced leukemia), most known occupationally induced malignancies show at least a twenty-year latency between exposure and disease. Thus, the recency of exposure to DMF, the low DMF exposures received, the lack of similar excesses at other plants and the absence of an overall prostate cancer excess at Washington Works argue against a causal association between DMF and prostate cancer at Washington Works.

Prostate cancer incidence was shown by O'Berg (1985) to be statistically significantly elevated among a May plant ACN-exposed cohort relative to the entire Company. Essentially all workers exposed to ACN at this plant were also exposed to DMF. In a follow-up study at the same plant (Chen, 1986), prostate cancer incidence was statistically significantly elevated among employees exposed to both DMF and ACN. The higher incidence observed in the cohort exposed only to DMF was not statistically significant. Routine cancer incidence surveillance data for the period 1956-1983 show a statistically significant excess of prostate cancer among May plant employees relative to the entire Company. Mortality surveillance data for 1957-1984 show no excess of genitourinary cancer.

The prostate cancer component of the present study was initiated because of the prostate cancer excesses at May plant noted above. In contrast to the earlier studies that relied upon external comparison groups (e.g., U.S. rates), the present study compares DMF-exposed May plant employees to May plant employees who never worked in DMF areas. These internal comparisons show that prostate cancer risk is no higher in DMF-exposed than non-exposed May plant employees (OR = 0.67, 90% CI = 0.10, 4.39). These findings are suggestive of a local excess of prostate cancer at May plant that is unrelated to DMF. This local excess might be due to regional differences in medical surveillance, diagnostic thoroughness or lifestyle.

The incidence of prostate cancer is known to increase with age, to be higher among black than among white men and to show a positive socioeconomic gradient (Greenwald, 1982). Other than occupational exposure to cadmium and zinc, prostate cancer is generally recognized as having no known occupational etiology. Other suspected etiologic factors include sexually-transmitted viruses.

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TESTICULAR CANCER

Analyses on testicular cancer include 11 cases ranging in age from 25 to 54 at time of diagnosis. Median age at diagnosis is 32. Four cases each were diagnosed at Belle, four at Washington Works, one at the May plant and two at Waynesboro.

Data by individual plant are sparse (Table 14). Adjusted odds ratios for May, Waynesboro and Washington Works are 3.00, 0.33 and 0.33, respectively. Belle plant's adjusted odds ratio is elevated (OR = 15.0 by the logit method), but not statistically significantly different from 1.00 (90% CI = 0.37, 608.). The Breslow-Day test for heterogeneity of the odds ratios is not statistically significant.

The Mantel-Haenszel summary odds ratio for testicular cancer is 0.99 with 90% confidence limits of (0.22, 4.44) (Table 15). The logistic regression summary odds ratio is 0.91 using the matched control series (90% CI = 0.11, 7.76). Data for testicular cancer are sparse when examined by exposure level (Table 15). The odds ratios for the "Low" and "Present, but not detectable" groups were both less than 1.00. The "Moderate" category shows an elevated odds ratio (11.6) based on 2 cases and 2 controls (90% CI = 0.47, 386.). To give another perspective on the statistical variability of these data, one less case in the "Moderate" category would have reduced the adjusted odds ratio for this category from 11.6 to close to 1.0.

Only three of the eleven testicular cancer cases in our study were exposed to DMF (Table 16). One wage roll employee (age 32 at diagnosis) was exposed for three months in the "Present, but not detectable" range and developed his cancer less than 4 years after he was first exposed. Two wage roll employees (ages 32 and 36 at diagnosis) were exposed for 35 and

105 months to levels in the 2.0-10.00 ppm range and developed their cancers within 8 and 17 years, respectively, of first exposure. It is interesting to note that 8 of the 11 testicular cancer cases in our study are from the two plants with the lowest frequencies and levels of DMF exposure (Belle and Washington Works). Although Ducatman (1986) and Levin (1987) reported testicular cancer clusters among workers exposed to DMF, our results provide no support for a suggested causal link between DMF and testicular cancer.

Testicular cancer is the most common cancer among white males aged 20 to 34. Etiologic factors that have been suggested in the literature include undescended testis, familial history, viral orchitis and testicular trauma. Although testicular cancer occurs more frequently among white collar than blue collar occupational groups, no specific high-risk occupations have been identified (Schottenfeld and Warshauer, 1982).

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ANALYSES BY LATENCY AND DURATION

Mantel-Haenszel matched analyses were conducted with three latency assumptions: (1) no latent period, (2) three-year latency and (3) ten-year latency. Analyses based on minimum latency assumptions of 3 and 10 years do not produce any notable differences in odds ratios (Table 17). The three-year latent period was chosen not because we condoned this methodology, but to permit comparison with two testicular cancer clusters (Ducatman et al, 1988) for which cases with minimum latencies of 3 years were allowed. Although it is more traditional to assume a twenty-year than ten-year latent period when studying malignancies with possible occupational etiology (radiation-induced leukemia excepted), a minimum twenty-year latency assumption results in no DMF-exposed testicular cancer cases and therefore was not used.

Logistic regression analysis by duration of exposure (Table 18) generally show lower adjusted odds ratios among those with ten years or more duration of exposure than among those with less than ten years of exposure.

ANALYSIS OF MECHANICS

Clusters of testicular cancer have been reported among mechanics by Ducatman (1986) and Garland (1988). To determine whether there was increased cancer risk among mechanics in our study, exposure was redefined as ever having worked as a mechanic. Summary odds ratios by cancer site (Table 19) show odds ratios ranging from 0.40 for liver cancer to 1.50 for testicular cancer. None of the odds ratios is statistically significant.

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GENERAL DISCUSSION

The statistical power of this study is limited due to small numbers of study subjects, especially for cancers of the liver and testis. Cancer cases for various sites are confined to those diagnosed among men while actively employed at Du Pont. Cancer cases which occurred among pensioners are not included since pensioners are not included in the Du Pont cancer registry and their disease status could not be ascertained in a complete manner.

The cancer registry was established in 1956 to study cancer morbidity among Company employees. Cases are identified by accident and health insurance claims and death certificates that accompany life insurance claims. Beginning in 1977, Du Pont introduced a cancer registry report to be submitted by Company physicians on any employee who develops cancer. The purposes of this form are to report cases that may not have been included among the insurance claims, such as those persons who (1) are not covered by the accident and health insurance plan, or (2) develop basal or squamous cell cancer of the skin that does not result in disability of more than seven days, as required by the insurance plan; and, to provide us with information not always available on other documents, such as histologic type, procedures used to establish the diagnosis, smoking history, occupational history, and history of actual or potential exposure to known or suspected carcinogenic agents. The cancer morbidity data are confined to newly diagnosed cases that occur among active employees. The data do not include cases which are first diagnosed after the person's employment is terminated, as a result of either retirement on a company pension, resignation, layoff, or discharge. If, after an employee's first episode of disability from cancer, the primary site shown on subsequent accident and health insurance claims or the death certificate does not agree with the primary site on the original claim, the Company physician at the employee's

work location is contacted to ascertain the correct primary site. This is done by the Company physician or the hospital where the employee was treated (Pell et al, 1978).

Determination of historical exposures in the absence of actual exposure data is a potential source of error in epidemiologic studies. Assessments of past DMF exposures in our study were made based on extensive DMF air and MMF metabolite data, and took into consideration well-documented information on changes in exposure controls and manufacturing processes and use of personal protective equipment.

Buccal cancers and malignant melanoma were included in our study as a result of findings of statistically significant elevations of these cancers among cohorts of workers exposed to DMF at the May plant. Prostate cancer was included based on a statistically significant excess reported among workers exposed to both DMF and ACN at the May plant. Inclusion of these index cases in the current study may have biased the results towards positive findings for these cancers.

Other occupational, lifestyle and hereditary risk factors may have been acting as confounders in this study. As in studies of this kind, confounders could have spuriously inflated the observed odds ratios or masked a causal association between DMF exposure and disease.

Several clusters of 3-4 testicular cancer cases have been reported among aircraft mechanics (Ducatman et al, 1986) and tannery workers (Levin et al, 1987). A subsequent unpublished investigation of testicular cancer centered on the county (Fulton County) where the leather tannery cluster was identified. This study reported a statistically significantly elevated odds ratio for testicular cancer among workers in the leather tannery industry (State of New York, 1988). The Fulton County investigation has a number of shortcomings. Problems

include inclusion of index cases in analysis, differences in occupational history ascertainment between cases and controls, large disparity in age distribution of cases and controls, failure to include 9 testicular cancer cases (all non-exposed) and controls from neighboring Montgomery County, lack of DMF monitoring data and lack of consideration of other chemicals present in leather tanneries.

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SUMMARY

Summary analyses over all plants combined show no statistically significant association between ever having been exposed to DMF and subsequent development of cancers of the buccal cavity and pharynx, liver, malignant melanoma, prostate and testis.

When odds ratios are examined by plant site, prostate cancer at Washington Works is statistically significantly elevated, based on three cases exposed out of four. No statistically significant association is observed among employees similarly exposed to DMF in the other three plants. The recency of exposure to DMF, the low exposures received and the absence of similar excesses at other plants argue against a causal association between DMF exposure and prostate cancer at Washington Works.

Assessment of highest DMF exposure rank, duration of exposure and latent period show no patterns suggestive of an association between DMF and cancers of the buccal cavity and pharynx, liver, malignant melanoma, prostate or testis. Cancer risk also appears to be unrelated to a history of having worked as a mechanic.

In summary, these data suggest that there is no causal relationship between exposure to DMF and any of the cancers studied.

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Figure 1

JOB EXPOSURE DATA
DMF Study

Page ___ of ___

Plant Name _____ Code: ___ ___ ___ Date Coded: ___ ___ ___ ___
Mo Dy Yr

By: _____

Job Title _____ Code: ___ ___ ___ ___

Job Area _____ Code: ___ ___ ___ ___

Exposure Period: From: ___ ___ ___ ___ to ___ ___ ___ ___ TWA Rank: 0 P 1 2 3
Mo Dy Yr Mo Dy Yr 95% Rank =

DMF Exposure Job Description (Include % of time and exposure pattern)

Estimated Exposure (ppm or mg/m)

Personal Protector (Enter Type)

Dermal Exposure

Basis for Estimating Rank

Other Chemical Exposures(Inc.Dates)

TABLE 1

NUMBERS OF CANCER CASES BY CANCER SITE AND PLANT, AMONG MALE EMPLOYEES, 1956 - 1985

Cancer site	Plant				
	Belle	May	Washington Works	Waynesboro	Total
Buccal cavity and pharynx	11	11	9	8	39
Liver	4	0	2	0	6
Malignant melanoma	9	11	12	7	39
Prostate	16	13	4	10	43
Testis	4	1	4	2	11
All cases	44	36	31	27	138
Average number of employees 1956-1985	2052	2276	2150	2246	8724

TABLE 2

CRITERIA FOR RANKING OF JOB EXPOSURES
BY GEOMETRIC MEAN

DMF in Air

Measured Exposure - Geometric Mean (ppm)	Rank
0	0 - None
< 1.0	P - Present, but not analytically detectable * or below 1 ppm
1.0 - < 2.0	1 - Low
2.0 - < 10.0	2 - Moderate
10.0 +	3 - High

MMF in Urine

Measured Exposure - Geometric Mean (ppm)	Rank
0	0 - None
< 1.0	P - Present, but not analytically detectable * or below 1 ppm
1.0 - < 5.0	1 - Low
5.0 - < 20.0	2 - Moderate
20.0 +	3 - High

* - Until 1985, minimum level of detection of both DMF and MMF was 1.0 ppm.

TABLE 3

CRITERIA FOR RANKING OF JOB EXPOSURES BY 95TH PERCENTILE

DMF in Air

Best estimate * of the 95th Percentile (ppm)	Rank
0	0 - None
< 5.0	P - Present, but not analytically detectable * or below 1 ppm
5.0 - < 10.0	1 - Low
10.0 - < 50.0	2 - Moderate
50.0 +	3 - High

MMF in Urine

Best estimate * of the 95th Percentile (ppm)	Rank
0	0 - None
< 5.0	P - Present, but not analytically detectable * or below 1 ppm
5.0 - < 25.0	1 - Low
25.0 - < 100.0	2 - Moderate
100.0 +	3 - High

* - Best estimate of the 95th percentile value is 5 times the geometric mean

TABLE 4

DISTRIBUTION OF STUDY SUBJECTS ACROSS EXPOSURE CATEGORIES, BY PLANT

Plant	Percent By Exposure Category				Total % Exposed
	None	Present	Low	Moderate	
May	16.8	25.7	8.9	48.5	83.2
Waynesboro	55.3	11.8	14.5	18.4	44.7
Washington Works	81.5	13.0	3.3	2.2	18.5
Belle	93.1	6.9	0.0	0.0	6.9
All Plants	63.9	14.0	5.8	16.3	36.1

TABLE 5

ODDS RATIOS FOR

CANCERS OF THE BUCCAL CAVITY AND PHARYNX

BY INDIVIDUAL PLANT

Plant	Cases # Exposed/ Total #	Controls # Exposed/ Total #	Crude Odds Ratio	Mantel-Haenszel Odds Ratio	90% CI on Adjusted Odds Ratio
May	9/11 (81.8%)	19/22 (86.4%)	0.71	0.50	(0.05, 4.89)
Waynesboro	3/8 (37.5%)	8/16 (50.0%)	0.60	0.50	(0.08, 3.03)
Washington Works	2/9 (22.2%)	4/17 (23.5%)	0.93	1.00@	(0.18, 5.69)
Belle	1/11 (9.1%)	0/21 (0.0%)	N.D.	15.0@	(0.37, 608.)

@Logit estimate

TABLE 6

ADJUSTED ODDS RATIOS FOR BUCCAL CAVITY & PHARYNX BASED ON HIGHEST GEOMETRIC MEAN EXPOSURE CATEGORY EVER ATTAINED

Highest Exposure Attained	No. of Cases	No. of Controls	Mantel-Haenszel Adjusted Odds Ratio with 90% CI	Logistic Adjusted Odds Ratio with 90% CI
None	24	45	1.00	1.00
Present, but not detectable	6	10	--	0.68 (0.21, 2.24)
Low	1	8	--	0.17 (0.03, 1.16)
Moderate	8	13	--	0.81 (0.23, 2.81)
Any Exposure	15	31	0.89 (0.35, 2.29)	0.95 (0.39, 2.36)

TABLE 7

ODDS RATIOS FOR CANCERS OF THE LIVER

BY INDIVIDUAL PLANT

Plant	Cases # Exposed/ Total #	Controls # Exposed/ Total #	Crude Odds Ratio
May	0/0	0/0	N.D.
Waynesboro	0/0	0/0	N.D.
Washington Works	0/2 (0.0%)	0/4 (0.0%)	N.D.
Belle	1/4 (25.0%)	1/8 (12.5%)	2.33

N.D. - Not Defined

TABLE 8

ADJUSTED ODDS RATIOS FOR LIVER CANCER

BASED ON HIGHEST GEOMETRIC MEAN EXPOSURE CATEGORY

EVER ATTAINED

Highest Exposure Attained	No. of Cases	No. of Controls	Mantel-Haenszel Adjusted Odds Ratio with 90% CI	Logistic Adjusted Odds Ratio with 90% CI
None	5	11	1.00	1.00
Present, but not detectable	1	1	--	N.D.
Low	0	0	--	N.D.
Moderate	0	0	--	N.D.
Any exposure	1	1	3.00[@] (0.11, 80.5)	2.70 (0.16, 45.8)

N.D. - Not Defined

[@]Logit estimate

TABLE 9

ODDS RATIOS FOR MALIGNANT MELANOMA

BY INDIVIDUAL PLANT

Plant	Cases # Exposed/ Total #	Controls # Exposed/ Total #	Crude Odds Ratio	Mantel-Haenszel Odds Ratio	90% CI on Adjusted Odds Ratio
May	9/11 (81.8%)	17/21 (81.0%)	1.06	1.02@	(0.14, 7.32)
Waynesboro	3/6 (50.0%)	6/12 (50.0%)	1.00	1.00@	(0.10, 10.2)
Washington Works	2/12 (16.7%)	3/24 (12.5%)	1.40	2.00	(0.12, 32.6)
Belle	2/9 (22.2%)	1/17 (5.9%)	4.57	3.50	(0.45, 27.5)

@Logit estimate

TABLE 10

ADJUSTED ODDS RATIOS FOR MALIGNANT MELANOMA

BASED ON HIGHEST GEOMETRIC MEAN EXPOSURE CATEGORY

EVER ATTAINED

Highest Exposure Attained	No. of Cases	No. of Controls	Mantel-Haenszel Adjusted Odds Ratio with 90% CI	Logistic Adjusted Odds Ratio with 90% CI
None	22	47	1.00	1.00
Present, but not detectable	4	9	--	0.85 (0.19, 3.80)
Low	3	6	--	1.86 (0.47, 7.34)
Moderate	9	12	--	3.11 (0.81, 11.9)
Any exposure	16	27	1.70 (0.52, 5.51)	1.95 (0.77, 4.98)

TABLE 11

ODDS RATIOS FOR CANCERS OF THE PROSTATE

BY INDIVIDUAL PLANT

Plant	Cases # Exposed/ Total #	Controls # Exposed/ Total #	Crude Odds Ratio	Mantel-Haenszel Odds Ratio	90% CI on Adjusted Odds Ratio
May	9/13 (69.2%)	21/26 (80.8%)	0.54	0.40	(0.07, 2.28)
Waynesboro	4/10 (40.0%)	6/18 (33.3%)	1.33	1.43	(0.41, 5.01)
Washington Works	3/4 (75.0%)	1 (12.5%)	21.0	8.04*@	(1.04, 62.3)
Belle	1/16 (6.3%)	1/32 (3.1%)	2.07	2.00	(0.20, 19.6)

* - Statistically significant at the 10% level.

@Logit estimate

TABLE 12

ADJUSTED ODDS RATIOS FOR PROSTATE CANCER

BASED ON HIGHEST GEOMETRIC MEAN EXPOSURE CATEGORY

EVER ATTAINED

Highest Exposure Attained	No. of Cases	No. of Controls	Mantel-Haenszel Adjusted Odds Ratio with 90% CI	Logistic Adjusted Odds Ratio with 90% CI
None	26	55	1.00	1.00
Present, but not detectable	9	14	--	1.11 (0.39, 3.19)
Low	0	4	--	0.0 N.D.
Moderate	8	11	--	1.75 (0.54, 5.70)
Any exposure	17	29	1.47 (0.66, 3.30)	1.48 (0.59, 3.74)

N.D. - Not Defined

TABLE 13

DESCRIPTIVE DATA ON PROSTATE CANCER CASES

AT WASHINGTON WORKS

Plant	Payclass	Year First Exposed to DMF	Months in DMF	Highest Exposure Rank	Age at Diagnosis	Year of Diagnosis	Mechanic
Washington Works	Salary	--	0	0	40	1971	Yes
	Wage	1960	33	Moderate	64	1974	Yes
	Wage	1968	135	Present	58	1980	
	Wage	1968	13	Present	53	1984	

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TABLE 14

ODDS RATIOS FOR TESTICULAR CANCER

BY INDIVIDUAL PLANT

Plant	Cases # Exposed/ Total #	Controls # Exposed/ Total #	Crude Odds Ratio	Mantel-Haenszel Odds Ratio	90% CI on Adjusted Odds Ratio
May	1/1 (100.0%)	1/2 (50.0%)	N.D.	3.00[@]	(0.11, 80.5)
Waynesboro	1/2 (50.0%)	3/4 (75.0%)	0.33	0.33[@]	(0.01, 8.93)
Washington Works	0/4 (0.0%)	2/8 (25.0%)	N.D.	0.33[@]	(0.03, 3.41)
Belle	1/4 (25.0%)	0/8 (0.0%)	N.D.	15.0[@]	(0.37, 608.)

N.D. - Not Defined

[@]Logit estimate

TABLE 15

ADJUSTED ODDS RATIOS FOR TESTICULAR CANCER BASED ON HIGHEST GEOMETRIC MEAN EXPOSURE CATEGORY EVER ATTAINED

Highest Exposure Attained	No. of Cases	No. of Controls	Mantel-Haenszel Adjusted Odds Ratio with 90% CI	Logistic Adjusted Odds Ratio with 90% CI
None	8	16	1.00	1.00
Present, but not detectable	1	3	--	0.86 (0.09, 8.58)
Low	0	1	--	0.01 N.D.
Moderate	2	2	--	11.6 (0.47, 286.)
Any exposure	11	22	0.99@ (0.22, 4.44)	0.91 (0.11, 7.76)

N.D. - Not Defined

@Logit estimate

TABLE 16

DESCRIPTIVE DATA ON TESTICULAR CANCER CASES

Plant	Payclass	Year First Exposed to DEP	Months in DEP	Highest Exposure Rank	Age at Diagnosis	Year of Diagnosis	Mentioned
Belle	Salary	--	0	0	25	1968	
	Wage	--	0	0	54	1970	Yes
	Wage	--	0	0	51	1972	Yes
	Wage	1981	3	Present	32	1984	Yes
May	Wage	1965	35	Moderate	32	1972	Yes
Washington Works	Salary	--	0	0	28	1963	
	Salary	--	0	0	44	1967	
	Wage	--	0	0	43	1969	Yes
	Wage	--	0	0	31	1983	
Waynesboro	Salary	--	0	0	25	1970	
	Wage	1960	105	Moderate	36	1976	Yes

TABLE 17

MANTEL-HAENSZEL ODDS RATIOS WITH
90% CONFIDENCE INTERVALS
BY ASSUMED LATENT PERIOD, ALL PLANTS COMBINED

Cancer Site	No Minimum Latency Mantel-Haenszel Odds Ratio	Minimum Latency of 3 Years Mantel-Haenszel Odds Ratio	Minimum Latency of 10 Years Mantel-Haenszel Odds Ratio
Buccal cavity and pharynx	0.89 (0.35, 2.29)	0.50 (0.20, 1.27)	0.99@ (0.26, 3.82)
Liver	3.00@ (0.11, 80.5)	3.00@ (0.11, 80.5)	3.00@ (0.11, 80.5)
Malignant melanoma	1.70 (0.52, 5.51)	1.50 (0.53, 4.26)	1.33 (0.44, 3.99)
Prostate	1.47 (0.66, 3.30)	1.26 (0.54, 2.94)	1.65 (0.72, 3.74)
Testicular	0.99@ (0.22, 4.44)	1.50 (0.23, 9.89)	0.50 (0.03, 8.14)

@Logit estimate

TABLE 18

LOGISTIC REGRESSION ODDS RATIOS WITH
90% CONFIDENCE INTERVALS
BY DURATION OF EXPOSURE, ALL PLANTS COMBINED

	No Exposure	≤10 Year Duration	≥10 Year Duration
Cancer Site	Logistic Regression Odds Ratio	Logistic Regression Odds Ratio	Logistic Regression Odds Ratio
Buccal cavity and pharynx	1.00	1.10 (0.41, 2.95)	0.71 (0.21, 2.45)
Liver	1.00	0.00 N.D.	2.20 (0.18, 26.4)
Malignant melanoma	1.00	2.48 (0.93, 6.59)	0.90 (0.23, 3.62)
Prostate	1.00	1.99 (0.71, 5.58)	0.89 (0.26, 3.04)
Testicular	1.00	1.28 (0.14, 1.16)	0.00 N.D.

N.D. - Not Defined

TABLE 19

MANTEL-HAENSZEL ADJUSTED ODDS RATIOS

WITH 90% CONFIDENCE INTERVALS

FOR MECHANICS, ALL PLANTS COMBINED

Cancer Site	Cases # Mechanics/ Total #	Controls # Mechanics/ Total #	Mantel-Haenszel Adjusted Odds Ratio	90% CI on Adjusted Odds Ratio
Buccal cavity and pharynx	14/39 (35.9%)	34/76 (44.7%)	0.71	(0.35, 1.42)
Liver	2/6 (33.3%)	7/12 (58.3%)	0.40@	(0.08, 1.96)
Malignant melanoma	10/38 (26.3%)	30/74 (40.5%)	0.53	(0.26, 1.08)
Prostate	20/43 (46.5%)	32/82 (38.1%)	1.48	(0.78, 2.84)
Testicular	6/11 (54.6%)	10/22 (45.5%)	1.50	(0.47, 4.77)

@Logit estimate

APPENDIX A

DMF EXPOSURE PROFILES FOR THE BELLE PLANT

BY AREA AND JOB TITLE

AREA	JOB TITLE	GM AND 95% * DMF EXPOSURE RANKS [95% RANK IN ()] FOR 1961-12/31/86
C&P East	Amines/Amide Operator	P (P)
C&P East	Amines Field (Loader) Opr	P (P)
C&P East	Drum Plant Utility Worker	P (P)
C&P East	Amines Environmental Opr	P (P)
C&P East	DME/DMS Operator	P (P)
C&P East	Amines Maintenance Coordinator/Helper	P (P)
C&P East	Drum Plant Coordinator	P (P)
C&P East	Maintenance Coordinator	P (P)
C&P East	M-2 Mechanic	P (P)
C&P East	Drum Plant Mechanic	P (P)
Main Plant Lab	Lab Technician	P (P)

*GM is Geometric Mean of TWA
95% is 95th Percentile of TWA

APPENDIX B

DMF EXPOSURE PROFILES FOR THE MAY PLANT

BY AREA, JOB TITLE AND TIME PERIOD

AREA	JOB TITLE	GM AND 95% * DMF EXPOSURE RANKS [95% RANK IN ()] BY TIME PERIOD		
		01/01/50-05/31/68	06/01/68-05/31/78	06/01/78-12/31/86
Project Crew	Maint Mechanic	P (1)	P (1)	P (1)
Services	Maint Mechanic	P (1)	P (1)	P (1)
Polymer-Recovery	Maint Mechanic	P (2)	P (2)	P (1)
Soln Prep-Spinning	Maint Mechanic	1 (3)	P (2)	P (2)
Wash-Draw-Finish	Maint Mechanic	P (1)	P (1)	P (1)
Control Equipment	Mechanic	P (1)	P (1)	P (P)
Service	Operator	P (2)	P (1)	P (1)
Control Lab	Labratorian	P (1)	P (1)	P (1)
Wash Draw	Draw Operator	1 (3)	P (2)	P (1)
Finishing	Operator	P (1)	P (1)	P (1)
Soln Prep	Operator	P (1)	P (1)	P (1)
Spinning	Operator	2 (2)	2 (2)	2 (2)
Polymer	Operator	P (1)	P (1)	P (1)
Recovery	Operator	P (1)	P (1)	P (1)
Maintenance	Supervisor	P (P)	P (P)	P (P)
Acrylic Fiber Recovery	Supervisor	P (P)	P (P)	P (P)

*GM is Geometric Mean of TWA
95% is 95th Percentile of TWA

APPENDIX B (cont'd)

DMF EXPOSURE PROFILES FOR THE MAY PLANT

BY AREA, JOB TITLE AND TIME PERIOD

AREA	JOB TITLE	GM AND 95% * DMF EXPOSURE RANKS [95% RANK IN ()] BY TIME PERIOD		
		01/01/50-05/31/68	06/01/68-05/31/78	06/01/78-12/31/86
Acrylic Fiber Polymer	Supervisor	P (P)	P (P)	P (P)
Acrylic Fiber Solution Prep	Supervisor	P (P)	P (P)	P (P)
Acrylic Fiber Spinning	Supervisor	P (1)	P (1)	P (1)
Acrylic Fiber Wash Draw	Supervisor	P (P)	P (P)	P (P)
Acrylic Fiber Finishing	Supervisor	P (P)	P (P)	P (P)
Control Laboratory	Supervisor	P (P)	P (P)	P (P)

*GM is Geometric Mean of TWA
95% is 95th Percentile of TWA

APPENDIX C

DMF EXPOSURE PROFILES FOR THE WASHINGTON WORKS PLANT

BY AREA, JOB TITLE AND TIME PERIOD

AREA	JOB TITLE	GM AND 95% * DMF EXPOSURE RANKS [95% RANK IN ()] BY TIME PERIOD 01/01/58-12/31/77	01/01/78-12/31/86
Plastic Sheeting	Mechanic	1 (2)	P (2)
Ink Preparation	Day Relief Opr Tinting Ink Prep Opr	2 (2)	1 (1)
EPC East (formerly C&P)	Service Opr Color Prep	P (1)	P (1)
Plastic Sheeting	Tinting Coordinator	P (P)	P (P)
Plastic Sheeting	Packout & Warehouse Opr	P (P)	P (P)
Plastic Sheeting	Warehouse Opr	P (P)	P (P)
Plastic Sheeting	Warehouse Coordinator	P (P)	P (P)
Plastic Sheeting	Powder Windup Opr LVF (Ex-Powder Windup, Dryer Opr, & Slitter)	P (P)	P (P)
Plastic Sheeting Tinting	Unwind Operator	2 (2)	1 (1)
Plastic Sheeting Tinting	Windup Operator	2 (2)	1 (1)
Plastic Sheeting	Inspector	2 (2)	1 (1)
Plastic Sheeting	Tinting Relief Opr	2 (2)	1 (1)
Plastic Sheeting	Tinting Relief Foreman	1 (1)	1 (1)
	Extrusion Relief Foreman - Tinting	P (P)	P (P)

*GM is Geometric Mean of TWA
95% is 95th Percentile of TWA

APPENDIX C (cont'd)

DMF EXPOSURE PROFILES FOR THE WASHINGTON WORKS PLANT

BY AREA, JOB TITLE AND TIME PERIOD

AREA	JOB TITLE	GM AND 95% * DMF EXPOSURE RANKS [95% RANK IN ()] BY TIME PERIOD 01/01/58-12/31/77	01/01/78-12/31/86
Plastic Sheeting	Tinting Operator	2 (2)	1 (1)
Plastic Sheeting	Tinting Printing Opr	2 (2)	1 (1)
Plastic Sheeting	LOF Tint-Print Opr (or Tint/Print Relief Opr)	2 (2)	1 (1)
Plastic Sheeting	Foreman/Supervisor	P (P)	P (P)
C&P	Lab Operator	0 (0)	0 (0)

*GM is Geometric Mean of TWA
95% is 95th Percentile of TWA

APPENDIX D

DMF EXPOSURE PROFILES FOR THE WAYNESBORO PLANT

BY AREA, JOB TITLE AND TIME PERIOD

AREA	JOB TITLE	GM AND 95% ** DMF EXPOSURE RANKS [95% RANK IN ()] BY TIME PERIOD 04/01/58-05/31/68	06/01/68-08/31/74	09/01/74-12/31/86
Control Equipment	Mechanic	1 (2)	P (1)	P (1)
Maint Polymer	Mechanic	2 (2)	1 (2)	P (2)
Control Equipment - Poly Recovery	Mechanic	P (P)	P (P)	P (P)
Recovery	Mechanic	P (1)	P (1)	P (P)
Finishing	Mechanic	P (1)	P (1)	P (1)
Control Lab	Labratorian	P (P)	P (P)	P (P)
*Benger Laboratory	Semiworks Opr	2 (2)	2 (2)	0 (0)
Acrylic Fiber Polymer	Soln Prep Opr	1 (2)	1 (2)	1 (2)
Acrylic Fiber Spinning	Spinning Opr	2 (3)	2 (3)	2 (2)
Acrylic Fiber Drawing	Draw Opr	2 (3)	2 (2)	2 (2)
Acrylic Fiber Finishing	Finishing Opr	1 (1)	1 (1)	1 (1)
Recovery	Recovery-Waste Treatment Opr	P (P)	P (P)	P (P)

*Time periods for Benger Lab are: 01/01/46-12/31/51, 01/01/52-12/31/66, and 01/01/67-12/31/86

**GM is Geometric Mean of TWA
95% is 95th Percentile of TWA

ATTACHMENT D (cont'd)

DMF EXPOSURE PROFILES FOR THE WAYNESBORO PLANT

BY AREA, JOB TITLE AND TIME PERIOD

AREA	JOB TITLE	GM AND 95% ** DMF EXPOSURE RANKS [95% RANK IN ()] BY TIME PERIOD		
		04/01/58-05/31/68	06/01/68-08/31/74	09/01/74-12/31/86
Spin-Draw	Area Mechanic	1 (2)	P (1)	P (1)
Control Equip-SDF	Mechanic	1 (1)	P (1)	P (1)
Maintenance	Supervisor	P (P)	P (P)	P (P)
Acrylic Fiber Polymer	Supervisor	P (P)	P (P)	P (P)
Acrylic Fiber Spinning	Supervisor	1 (1)	1 (1)	1 (1)
Acrylic Fiber Drawing	Supervisor	1 (1)	1 (1)	1 (1)
Acrylic Fiber Finishing	Supervisor	P (P)	P (P)	P (P)
Recovery	Supervisor	P (P)	P (P)	P (P)
Control Equipment	Supervisor	P (P)	P (P)	P (P)
*Benger Laboratory	Supervisor	1 (1)	1 (1)	0 (0)
Labor & Transporatation	Laborer	0 (P)	0 (P)	0 (P)

*Time periods for Benger Lab are: 01/01/46-12/31/51, 01/01/52-12/31/66, and 01/01/67-12/31/86

**GM is Geometric Mean of TWA
95% is 95th Percentile of TWA

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