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September 14, 1995

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Dear Sir:

Here is a copy of the final report entitled "Cancer Incidence Study of Workers Handling Mono and Di-arylamines Including Dichlorobenzidine, Ortho-tolidine, and Ortho-dianisidine."

Please contact the undersigned if you have any questions or comments at (616) 323-4746.

Sincerely yours,

Jeffrey Mehring

Jeffrey S. Mehring, Ph.D.
Program Manager
Environmental Health Sciences

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Cancer Incidence Study

Of Workers Handling Mono- and Di-arylamines Including Dichlorobenzidine, Ortho-tolidine, and Ortho-dianisidine

September 14, 1995

SRA Technologies, Inc.
8110 Gatehouse Road, 600 West
Falls Church, Virginia 22042

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Cancer Incidence Study

Of Workers Handling Mono- and Di-arylamines Including Dichlorobenzidine, Ortho-tolidine, and Ortho-dianisidine

Prepared for:
The Upjohn Company

September 14, 1995

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Executive Summary

A cancer incidence study was undertaken on workers employed at a chemical plant where arylamines had been produced since the plant's inception in the mid-1940s. Benzidine was produced at the plant prior to mid-1965, but use and production of other mono- and di-arylamines occurred until 1989. In 1985, the company became aware of three cases of bladder cancer in non-benzidine workers. An epidemiologic study of 704 workers first employed at the site between July 1, 1965, and December 31, 1989, was undertaken to assess cancer incidence during the study period.

In this cohort, 27 confirmed cancer cases were ascertained through the Connecticut Tumor Registry, a worker survey, death certificates, and a company health surveillance program. A statistically significant increase in the standardized incidence ratio (SIR) was observed for cancer of the bladder (males only) and testis. An elevated, but not statistically significant, SIR was found for breast cancer. The elevated risk for cancers of the testis and breast was based on three or fewer observed cases and was not associated with arylamine exposure. As a result, the association between arylamine exposure and these cancers was not evaluated further. The SIR for bladder cancer among males was 8.3 (95% confidence interval (CI) = 3.3 - 17.0) in which seven cases were observed and 0.85 were expected. Another bladder cancer case was recently identified, after the study cut-off date, and is discussed in Section 6, Epilogue.

An exposure classification system was developed by a panel of former and current employees who were knowledgeable about historical operations at the plant. This system focused on arylamine exposures, but could not segregate workers by type of arylamine exposure because production of all arylamines occurred in the same facilities at various times. Bladder cancer risks among males demonstrated an exposure-effect relationship (SIRs = 0.0, 5.5, 16.4, for none, low, or moderate levels of exposure, respectively).

All bladder cancer cases were known to be current or former cigarette smokers. Consequently, smoking appears to be directly associated with the increase in cancer risks. An occupational etiology for the observed association with bladder cancer was supported by the substantive level of risk (>800%), the exposure-effect trend, the relatively young age of the cases at the time of diagnosis (52 years), and biological plausibility.

The protocol and draft report for this study were peer-reviewed by a panel of nationally-recognized epidemiologists who were not involved in carrying out the study.

Section 1

Introduction and Background

The North Haven Fine Chemical (NHFC) plant was a specialty chemicals manufacturing facility that started operations in North Haven, Connecticut, in the mid-1940s as the Carwin Company. Arylamine chemicals were produced at the facility for over 40 years. Among its first products were 3,3' dichlorobenzidine (DCB), benzidine, o-dianisidine, and o-tolidine (Griffeth 1989). DCB was always the largest volume arylamine at the plant, followed by benzidine, o-dianisidine, and o-tolidine. The approximate production volume ratios from start-up until mid-1965, when benzidine production was discontinued, were 10:5:4:1, respectively. After 1965, DCB and other arylamine production continued at the plant until 1989, when the DCB process was sold to another firm. The approximate production volume ratios between 1965 and 1989 were 9:4:1 for DCB, o-dianisidine, and o-tolidine, respectively. All production operations at the NHFC plant ceased in 1993.

Operations at the plant have never required a large work force. There were three employees plus the principals when operations began. By 1962 when the plant was acquired by Upjohn, there were approximately 135 production and administrative workers. From 1975 to the time that operations wound down in 1993, there were no more than 202 employees at the plant at any given time. All told, there have been approximately 1,710 individuals employed at the plant since it started.

A permanent biological monitoring program was instituted in 1949 that continued up to the time that arylamine operations terminated. In 1951, investigators from nearby Yale University published a method to monitor worker exposures using chloramine-T for measuring arylamine compounds in the urine (Glassman and Meigs 1951). Throughout the plant's history, the urinary amine program involved a portion of the work force and was used for monitoring the effectiveness of exposure control strategies. At the time of the program's inception, Meigs and his colleagues (1951) reported on the biological monitoring program in which urine samples were collected during June and December 1950. The investigators found that urinary amine levels increased during warm months and that personal hygiene and the use of clean clothes were factors affecting levels. Meigs et al. (1954) later published another report on plant workers confirming the importance of skin as an exposure route.

Other measures were implemented over time by the plant management to assess worker health status. In 1956, a cystoscopy program was initiated that had the goal of early detection of bladder tumors. Many employees participated in the program when it started, but the dropout rate was high. By 1964, the plant provided cytology testing for employees with five or more years of service and by 1966 the program was a routine part of the plant's medical surveillance program. Former employees, however, were not tested until a recall program was initiated in 1977 to locate all former employees who had been exposed to benzidine and invite them to participate in the cytology surveillance program. The company was able to trace 94% of 581 employees. The surveillance continues to this day. In 1994, the company initiated a bladder tumor surveillance program for post-1965 workers. All current and former workers were invited for an annual screening to identify potential malignant changes in bladder cells. In addition to the bladder cancer surveillance programs for benzidine- and non-benzidine-era employees, the company has maintained a routine medical surveillance program for all active workers.

In 1986, Meigs et al. published a study of the cancer incidence experience of workers at the NHFC plant employed during the period 1945 to mid-1965, with followup to the end of 1978. An elevated SIR was reported for stomach (1.9), lung (1.5), prostate (1.7), colon (1.5), and bladder cancer (3.4). Only the excess of bladder cancer among workers first employed prior to the end of benzidine production in mid-1965 was statistically significant (SIR = 3.4; 95% confidence interval (CI) = 1.5-6.8). Bladder cancer cases were concentrated among men with high exposure to benzidine as determined qualitatively by an exposure assessment committee; no statistically significant elevation in risk was noted for other cancer sites. Risks for bladder cancer appeared to be higher for men employed during the earliest years of plant operation (1945–1949) compared to those employed later. The SIR for the earlier period was 9.8 (95% CI = 2.6 - 25.0), compared to 2.1 (95% CI = 0.0 - 11.8) for those first employed during the period 1950–1954. Meigs et al. (1986) attributed the risk to benzidine exposure, notwithstanding that men were probably exposed to other arylamines.

Benzidine has been recognized by several organizations, including the U.S. Environmental Protection Agency (EPA), the National Toxicology Program (NTP), and the World Health Organization (WHO), as a known human carcinogen (U.S. EPA 1995a; NTP 1991; the International Agency for Research on Cancer (IARC) 1987, 1982a). Among the epidemiologic studies that IARC cites as supportive of an etiologic relationship between benzidine and bladder cancer is the study by Meigs et al. (1986) on NHFC plant workers. On the other hand, other arylamines such DCB, o-dianisidine, or o-tolidine have not been adequately studied in epidemiologic investigations, in part, because cohorts exposed to these substances alone, and not benzidine, are difficult to find in sufficiently large numbers. Three epidemiologic studies (discussed in Section 5) have been conducted on DCB and each reported a lack of association between exposure and health effects. There are no studies in the literature on workers uniquely exposed to o-dianisidine or o-tolidine. Thus, the study reported here is relevant to the question of the carcinogenicity of arylamines other than benzidine.

Section 2

Study Rationale and Objectives

In 1985, the Upjohn medical department received information indicating that three workers first employed at the NHFC plant after benzidine operations were discontinued in mid-1965 had developed bladder tumors. A preliminary assessment of the cases indicated that an epidemiologic study was appropriate (Rench and Unger 1989). Based on this assessment, Upjohn initiated the study reported here. The primary objective of this study was to determine whether the incidence of cancer was higher than expected among non-benzidine workers first employed at the NHFC plant after mid-1965. Another purpose of the study was to identify workers and types of cancers that should be considered in a preventive medical recall program, if one was needed. The study was undertaken with the knowledge that the worker cohort would be very small and that a limited period of followup would exist, because only those workers starting employment after June 1965 would be enrolled.

Section 3

Methods

3.1 Cohort Identification

The study cohort consisted of 704 NHFC workers, 585 males and 119 females, first employed at the NHFC plant between June 15, 1965, and December 31, 1989. Only workers never exposed to benzidine at the NHFC plant were selected. Work histories and demographic information were identified using the corporate database at Upjohn headquarters and the personnel records at the plant. Because the corporate database was computerized only in 1974, active employees with work histories prior to 1974 had their records updated manually. Work histories for employees who terminated prior to 1974 also had their work histories reconstructed manually from the records at the plant. All records were matched against the Meigs data tapes (workers first employed prior to mid-1965) to identify any worker first employed prior to the cessation of benzidine production.

To make sure that no worker had been missed, the assembled database was verified against the listings appearing on the Internal Revenue Service (IRS) 941 Forms. The forms have been used in other studies as a reliable means of validating the completeness of an occupational study cohort (Marsh and Enterline 1979). Two random samples of workers were generated from the IRS forms and were compared to the list of workers in the assembled database. Twenty-seven names from the 941 forms were missing from the cohort database. The missing workers were identified either as employees of Donald S. Gillmore Laboratories, located in a separate facility in the NHFC plant complex, or as staff who, although not NHFC plant employees, were administratively assigned to the plant but were actually working at a facility in Texas. Texas workers were excluded from the study cohort. Donald S. Gillmore Laboratories' workers were considered members of the study cohort only if they had also actually worked at the NHFC plant after mid-1965 and were included only for the actual time spent in the plant.

3.2 Cancer Identification

Three sources were used to identify cancer cases for the incidence study in addition to the ongoing surveillance by Upjohn. These methods included matching the cohort roster with the cancer cases registered at the Connecticut Tumor Registry (CTR), reviewing the death certificates of deceased workers, and identifying and confirming reported cancers through a mail survey of all members of the study cohort having a current address. Cancers were considered confirmed if the cancer was reported by CTR; if it was reported on the death certificate either as the cause of death, a contributing cause of death, or as an additional condition; or if a self-reported cancer was confirmed by the treating physician.

3.2.1 Connecticut Tumor Registry

A list of all the NHFC workers in the cohort was submitted to the CTR in November 1992. The name, date of birth, and Social Security number of the cohort members were matched against the CTR database. Although CTR is a reliable source of cancer identification, only the cancers diagnosed and reported in Connecticut prior to and during 1990 were available through this source. No information was available for cancers diagnosed among former workers who had moved out of state, or cancers diagnosed after 1990 in Connecticut. To obtain cancer information on workers living outside the State of Connecticut, and to obtain information on more current cancers, a mail survey was initiated in 1993. If the worker reported a cancer, the worker was again contacted to obtain the name and address of the diagnosing physician. Attempts were made to confirm all the reported cancers diagnosed after NHFC employment.

3.2.2 Death Certificates

As another potential source of identifying cancer cases, death certificates were reviewed to identify any cancer cases that were missed by the other two sources. Death certificates were requested from the vital statistics office in the state of death for each worker identified as deceased through the tracing activities undertaken by the Equifax company, the corporate retirement records, or the worker survey. Death certificates were obtained for all but one worker. If a cancer was recorded as a cause of death, as contributing to the cause of death, or as an additional condition on the death certificate, the worker was classified as a cancer case in the incidence study. The date of death was used for the date of diagnosis when the date of diagnosis was unavailable from other cancer sources.

3.2.3 Worker Survey

Because the CTR was limited to identifying cancers diagnosed in Connecticut residents only and for cancers reported during 1990 or earlier, a survey of all current and former NHFC employees in the cohort was undertaken. Efforts to obtain a current mailing address and telephone number for each worker were initiated before the questionnaire was sent. Once a current address was obtained for each worker, a questionnaire was mailed requesting information on the diagnosis of any cancer, smoking, other possible risk factors for bladder cancer, and work histories. An additional mailing and a telephone followup were initiated for nonrespondents.

Tracing: Records of 654 workers were initially submitted to Equifax for tracing using their mortality database, credit report database, and manual searching methods. The remaining 50 were current workers whose addresses were already known. The tracing activities started in May 1992 and continued throughout the survey. Initially, Equifax was requested not to contact the workers but to use other means to obtain a current address and telephone number for each worker. This task was made more difficult by records without dates of birth, Social Security numbers, and work history dates. Equifax was then given more latitude to find the difficult-to-locate workers. When given permission to speak to the individuals being sought, the success rate increased. Records of workers who could not be traced directly by Equifax were compared to the IRS 941 Forms for Social Security number accuracy, and were compared to NHFC plant records to identify potential discrepancies. The records were resubmitted to Equifax for further followup. Addresses and telephone numbers were not obtained for 21 workers.

Survey: The questionnaire (Appendix A) was mailed on July 27, 1993, to the 683 workers having a current address. A second questionnaire was sent by registered mail with a signature requested on September 22, 1993, to all nonrespondents. Finally, an abbreviated questionnaire was administered by telephone to all remaining nonrespondents with active telephone numbers. Data entry of the questionnaire information was completed during February 1994. Data verification (100%) was completed by mid-March. The error rate was less than 0.01%.

3.3 Exposure Classification

In addition to the work histories available through the corporate database, two other sources of information were used to assess potential exposures to arylamines at the plant: the urinary arylamine database and the information developed by an exposure assessment committee convened for this study. Job titles, tenure, unit numbers, and work status information were obtained from the computerized corporate database and supplemented with plant personnel records for the 704 study cohort members. More accurate job title information was available for jobs held after 1973. Information on the building where each cohort member worked could be derived for the chemical operators from the unit number found in the corporate database. Unit numbers also were used to assess exposure potential for the administrative staff and other workers in areas that were very unlikely to have had any arylamine exposure. Mechanics and engineers, on the other hand, worked in all buildings as needed, and were potentially exposed to nearly all chemicals manufactured, processed, or used at the plant. Unit numbers were not as useful for these workers. Unit numbers and corresponding job titles are listed in Appendix B.

3.3.1 Urinary Arylamine Data

Urinary arylamine measurements were initiated as a result of the Yale University monitoring study published in 1951. The urinary arylamine records, dated between 1966 and 1976, were reviewed to assess their usefulness in determining job-specific arylamine exposure levels. Records for the years beyond 1977 were less useful for determining job-specific exposure levels because urinary arylamine levels were usually below the detection limit as a result of the plant having introduced exposure control measures. The urinary arylamine data could not be used for the exposure assessment in this study because urine samples were only taken from a subset of highly exposed workers (usually operators) each week; also, the tested workers were not representative of workers from each job category. In addition, because of the lack of detail available in the work history, the urinary amine data could only be associated with general job titles such as operators and would not have provided information on other workers. Finally, false positives were common in the program because the use of a number of over-the-counter medications provided a positive result.

3.3.2 Exposure Assessment Committee

An Exposure Assessment Committee (EAC), consisting of four senior NHFC staff knowledgeable about NHFC work processes and potential exposures, was assembled after identification of the work histories but prior to the analysis to review job-specific exposures and assign exposure scores. Prior to their meeting, a matrix of arylamine production and use, by month for the years between 1965 and 1989, was prepared by the staff at the plant and provided as a reference point for the EAC assessment. The objective of the EAC was to develop an exposure score for each job title based on the members' knowledge of jobs, buildings, and production records for this time period. The exposure scoring system took into consideration the exposure-control measures introduced at the plant. The committee focused only on the arylamines listed in Table 1. The EAC committee met once and clarified resulting issues by conference calls. The product of their deliberations was the exposure assessment matrix appearing in Appendix C.

The exposure scoring system developed by the EAC was based on two components: intensity of exposure and frequency of contact. For lack of any monitoring data on exposure intensity to the individual worker, the intensity score of exposure to arylamines consisted of a scale from 0 to 5 where 0 referred to no exposure and 5 to the greatest exposure. A linear scale was used for exposure intensity; no information was available to suggest that a nonlinear scale would be more appropriate.

Table 1. Arylamines Handled at the NHFC Plant

Chemical Name	CAS Number	Other Names Used by NHFC Plant Personnel and Related Compounds
Dichlorobenzidine (DCB)	91-94-1	3,3'-dichlorobenzidine; dichlorobenzidine dihydrochloride; C; CL; CD; chlor; DCB Base Wet; CBW; DCB Free Base; C-126
o-dianisidine	91-93-0	3,3'-dimethoxybenzidine; ortho-dianisidine; dianisidine base; dianisidine free base (wet or dry); DBI; DFB; DB; DBW
o-tolidine	119-93-7	3,3'-dimethylbenzidine; ortho-tolidine; diortho-tolidine
o-toluidine	95-53-4	2-methyl benzeneamine; ortho-toluidine
o-chloroaniline	95-51-2	ortho-chloroaniline; OCA

Frequency, on the other hand, reflected the time spent at the exposed location and was 100% if the worker spent all his or her time in a location where arylamines were present and 0% if no time was spent in an area where arylamines were used. When the exact dates of production or use were unknown, but records showed that production or use did occur during a few months of that year, the job was considered exposed at 100% for the whole year. The EAC committee preferred erring in the direction of overestimating exposure.

The EAC first developed the exposure scoring system for chemical operators, the group believed to be most heavily exposed. The EAC also reviewed all other jobs in units with potential exposure such as the mechanics, engineers, shipping clerks, and chemists. It was determined that some of these workers were heavily exposed when in contact with the production systems, but the frequency of contact was unpredictable. The assigned scores reflected the reduced frequency of exposure. Because the same facilities were used to produce arylamine products, mechanics, engineers, and laboratory workers were potentially exposed to multiple arylamines, and their exposure scores indicated overall arylamine exposure. For this reason, it was not possible for this study to evaluate chemical-specific effects for each arylamine used at the plant. For workers assigned to units in which the EAC determined that no exposure to arylamines had occurred, the assigned intensity and frequency exposure scores were zero.

3.3.3 Average Daily Exposure Scores and Annual Cumulative Exposure Score

The exposure scores assigned by the EAC were used to calculate an average daily exposure (ADE) value for each work interval in the employee's work history (Appendix D). The ADE consisted of summing the product of the intensity of the exposure, the frequency with which the arylamine was used, and the duration (in days) the worker spent in an exposed job; the sum was then divided by the total number of days spent at that exposure. A master exposure time table array was generated as a time line from the exposure matrix developed by the EAC which provided the frequency and the intensity. A worker's work interval was then divided into smaller intervals that coincided with the master exposure time table and compared to the master array. The score for each small interval was then summed over that work interval and divided by the number of days spent in that job interval to obtain an average daily exposure score for each job. The analytical program, described in Section 3.4.1, then summed the ADEs to obtain a total cumulative exposure score for each worker over the worker's work history. This cumulative exposure score was divided by 365.25 to provide an annual cumulative exposure score.

3.4 Analysis

The data for this study were analyzed using a modified version of OCMAP/PC computer software package using the life table analytical approach, and SAS's Proc Freq, Proc Means, and Cox's Proportional Hazard Model (SAS 1990). For all analyses, several definitions or restrictions were imposed on the study cohort and the cases to minimize bias. These definitions and restrictions are listed below.

- The person-years of observation for a cancer case were accumulated until the date of cancer diagnosis, if the case was still alive, or the date of death, if the cancer case could only be identified from the death certificate. Because only two cancer cases were identified solely through the death certificate, no adjustment was made to account for the lag between cancer diagnosis and death.
- The person-years of observation for a deceased worker who died of a cause other than cancer was accumulated until the time of death.
- Workers with confirmed diagnosed cancers prior to the date of Upjohn employment were eliminated from the analysis (n = 6, two males and four females).
- Three workers diagnosed with non-melanoma skin cancer contributed person-years of observation but were not considered as cancer cases in the analyses of malignant cancers.
- Person-years of observation for all other workers were accumulated until the date last worked, the date when the mail interview was completed, the date of the last known activity identified during the tracing, or, if still working, the last day of the followup period (August 31, 1994), whichever was most recent.

3.4.1 Survival Analyses

The survival analyses were carried out using Module 1 of the OCMAP/PC program developed by the University of Pittsburgh (Marsh et al. 1[illegible]) and adapted for use with cancer incidence data. Cancer incidence rates from the State of Connecticut were applied to the person-years of observation in the study population to obtain the expected number of cancers in that population. Five-year Connecticut cancer incidence rates were used for the comparison group through 1990. The 1990 rates were also used for the period extending through the end of the study. The SIR was calculated as the ratio of observed to expected cases. A cumulative exposure score for all arylamines was calculated by the program for each worker using the average daily exposure score described in Section 3.3.3. The total cumulative exposure score for each worker, calculated in days by OCMAP/PC, was divided by 365.25 to give an annual cumulative exposure score for each worker. Analyses were carried out for males and females separately and for workers with less than five years of followup and five or more years. Three cumulative exposure groups were developed and included: a cumulative exposure score of 0, a score greater than 0 but less than 2.5, and a score of 2.5 or more. Because the CTR does not provide race-specific cancer incidence rates, this study did not estimate race-specific cancer risks.

3.4.2 Incidence Density Rates and Cox's Proportional Hazard Regression

The incidence density of bladder cancer (cases per 1,000 person-years of observation) was examined for three exposure groups: no cumulative exposure, less than 2.5, and 2.5 or more. The association between exposure and incidence density was evaluated with a chi-square test for linear trend (Dean et al. 1990). This was done separately for all males and for male smokers only.

Cox's proportional hazard regression model was used to account for confounders. The time variable used was the length of followup in years. For this study, the hazard ratio reflected the annual probability of each worker developing cancer per year of observation. The model considered other factors (independent variables) that influence the occurrence of cancer. The independent variables introduced into the model included the cumulative arylamine exposure score discussed above, sex, smoking (never smoked, ever smoked, and smoking status unknown), and age at hire. Both continuous and categorical values were used for the exposure scores.

Section 4

Results

4.1 Survey Results

Of the 704 workers in the cohort study, an address was not available for 21 workers, some of whom were deceased, leaving 683 (97%) workers available to participate in the mail survey. The 21, who were not sent a questionnaire, were included in the analysis because the corporate database and the NHFC files provided sufficient data to include these workers. Accumulation of the person-years of observation was terminated for the 21 employees at the time they ended employment if they had a missing address, or at the time of death if they were deceased.

During the first mailing, 302 (44.2%) workers completed the questionnaires, three (0.4%) refused, and 52 (7.6%) questionnaires were undeliverable as addressed. The response rates of the survey are summarized in Table 2. Additional mailings were made when updated address information became available. Among the workers who could not be located, two workers appeared to have moved out of the country. During the second mailing, 291 (77.4%) signed and returned the certified receipt, 248 (66.0%) completed the questionnaire, and 18 (4.8%) workers refused to participate. Nonrespondents were surveyed by telephone. To maximize cooperation, only the questions on cancer, smoking, and coffee use were asked. Of the 110 telephoned, 98 (89.1%) completed the interview. Information on coffee consumption, use of medications and sweeteners, and other job and hobby exposures was collected in the survey. This information has not been included in the analyses because of the small number of positive responses and the large number of instances in which responses were not provided.

Table 2. Responses to the Mailed Survey

Activity	Number	Outcome	Number	Percent of Surveyed	Percent of Total Cohort[1]	Cumulative (%)
Mailing 1	683	Responded	302	44.2	42.9	42.9
		Refused/Other	3	0.4	0.4	
		Undeliverable	52	7.6	7.4	
		No Response	326	47.7	46.3	
Mailing 2	376	Responded	248	66.0	35.2	78.1
		Refused/Other	18	4.8	2.6	
		Undeliverable	19	5.1	2.7	
		No Response	91	24.2	12.9	
Telephone	110	Responded	98	89.1	13.9	92.0
		Refused/Other	10	9.1	1.4	
		No Response	2	1.8	0.3	

[1] based on n = 704

4.2 Cohort Characteristics

Table 3 summarizes worker attributes included in the analysis. Of the original 704 members of the worker cohort, six were eliminated from the analysis because they had developed cancer prior to NHFC plant employment. Of the 698 remaining workers, 583 (83.5%) were males and 115 (16.5%) were females. Information on race was available for only 69% of the cohort. The average age at followup was 46 years. The males were employed on the average 4.5 years and the females for 3.1 years. The workers were followed for approximately 14 years, on average.

The primary source of smoking information was the mail questionnaire and from those who chose to complete the smoking history question. Of the 698 workers, 30.7% reported never having smoked (Table 4) with females (38.3%) more likely than males (29.2%) to report never having smoked. More males declined to report their smoking status (30.5%) than females (27.8%). Male smokers were slightly older than nonsmokers at the time of hire (29.6 years compared to 27.3 years; $p < 0.002$), tended to have worked longer (6 years compared to 4 years; $p < 0.007$), and tended to have a higher cumulative exposure score than nonsmokers (4.7 compared to 2.2; $p < 0.0001$). No such differences were observed among the females. Information on smoking was available for 16 of the 24 confirmed cancer cases (66.7%) and all of the bladder and breast cancer cases. Smoking histories from both the mail survey and the medical records were reviewed for the bladder cancer cases. One bladder cancer case did not respond to the smoking question in the survey; however, smoking history data were available on the medical record. A different bladder cancer case had a missing medical record. Smoking histories for all other bladder cancer cases were identical when medical records and survey results were compared.

Table 3. Worker Characteristics, NHFC Plant Epidemiology Study

Characteristics	Males	Females	Total
Total Cohort	585	119	704
Cancer Diagnosis Prior to Employment	2	4	6
Number of Workers in Analysis	583	115	698
Race (%)			
White	53.7	65.2	55.6
Nonwhite	13.6	11.3	13.2
Unknown	32.8	23.5	31.2
Average Age at Hire (yrs)	28.2 ± 7.8	29.2 ± 9.8	28.2 ± 8.3
Employment Duration (yrs)	4.5 ± 6.5	3.1 ± 4.7	4.3 ± 6.3
Average Followup (yrs)	14.1 ± 8.3	13.7 ± 8.0	14.0 ± 8.3

Table 4. Smoking Status Among Workers, NHFC Plant Epidemiology Study

	Males		Females		Total	
Smoking Status	**N**	**%**	**N**	**%**	**N**	**%**
Never Smoked	170	29.2	44	38.3	214	30.7
Ever Smoked	200	34.3	39	33.9	239	34.2
Status Unknown[1]	213	36.5	32	27.8	245	35.1
Total	583	100.0	115	100.0	698	100.0

[1]Includes workers who did not receive a questionnaire because of missing address and telephone information.

4.3 Cancer Cases

As a result of the cancer identification activities by the CTR, the mail survey, and the review of the death certificates, a total of 27 cancer cases were identified by all sources and confirmed, 23 among male workers and four among female workers. Three of the 23 male cancer cases were non-melanoma skin cancers. They were not considered as cases for this study leaving 24 malignant cancer cases for the analysis. The source of identification for these cancers is described below.

Fifteen cancer cases were identified by the CTR (Appendix E), six of which were uniquely reported by this source. Two of the six uniquely reported cases were diagnosed prior to NHFC employment (cancer of the urethra in a male worker, and cancer of the colon in a female worker).

Thirty-two potential cancers were self-reported as a result of the worker survey, 25 of which were uniquely reported by this source (Appendix E). Attempts were made to confirm the self-reported cancers with the diagnosing physicians for the cancers diagnosed after NHFC employment (n = 24). Workers were telephoned to obtain the names and addresses of the diagnosing physicians. The medical provider was then contacted to confirm the report. Ten cancers were confirmed as reported, eight were not confirmed by a physician, and in the remaining cases, physicians did not respond or the worker refused or could not provide the name or address of the diagnosing physician. One worker reported a different cancer on the questionnaire (cancer of the cervix diagnosed in 1978) than the one reported by CTR (cancer of the colon diagnosed in 1962 and prior to NHFC employment).

Several discrepancies occurred among the various sources. Five workers reported as having cancer by CTR reported no cancer on the questionnaire. Two of these had been diagnosed prior to NHFC employment (cancer of the urethra and cancer of the colon). The remaining three included a cancer of the bladder, a melanoma, and a breast cancer.

Twenty-one workers were identified as deceased. Six cancers were reported on the death certificates. Two of the six cancers (multiple myeloma and cancer of the pancreas) were reported only on the death certificate.

For the study, then, 20 cancers were reported among males and four among females (three non-melanoma skin cancers were not considered in the analysis as malignant cancers but contributed to person-years of observation). Details on the cancer cases are presented in Table 5. The average age at diagnosis for all cancers was 51 years for males and 43 years for females. The average age at diagnosis for bladder cancer among males was 52 years compared to the average age of 68 years for Connecticut males (CTR 1986). For breast cancer among females, the average age at diagnosis was 32 years compared to the average age at diagnosis of 59 for Connecticut females.

Smoking histories for the breast and bladder cancer cases were obtained from the questionnaire and/or the medical records. Between the two sources, it was determined that all bladder cancer cases smoked currently (n = 1) or in the past (n = 6). Two of the three breast cancer cases smoked currently (n = 1) or in the past (n = 1), the other breast cancer case reported on the questionnaire that she never smoked.

Two of the bladder cancers among males were diagnosed in workers first employed after 1972, four were first employed at the age of 40 or older, and five worked at least five years or more. All bladder cancers had a followup period of at least eight years or more.

4.4 Person-years of Observation

If all the workers had been followed to the end of the study, 8,890 person-years of observation would have accrued for males and 1,704 person-years for females. Had the study relied solely on the information available in the company records, the males would have contributed 5,744 person-years of observation. As a result of the worker survey, the information on followup yielded 8,624 person-years of observation (6,714 among the exposed and 1,910 among the nonexposed) for the males, an increase of 50.1% over that generated by the company records alone and 97.0% of the maximum. The female workers contributed 1,660 person-years of observation for this analysis or 97.0% of the maximum.

4.5 Cumulative Exposure

Annual cumulative exposure scores were calculated for each worker. The scores ranged from 0 to 64.4. Among the NHFC workers, 20.4% of the males and 71.3% of the females had no exposure to arylamines. Forty-seven percent of the males had a cumulative exposure score greater than 0 and less than 2.5. Figure 1 shows the distribution of cumulative exposure scores for males. The cohort was categorized into three groups: the nonexposed (workers with cumulative exposure scores of 0); the low exposure group (workers with cumulative exposure scores of greater than 0

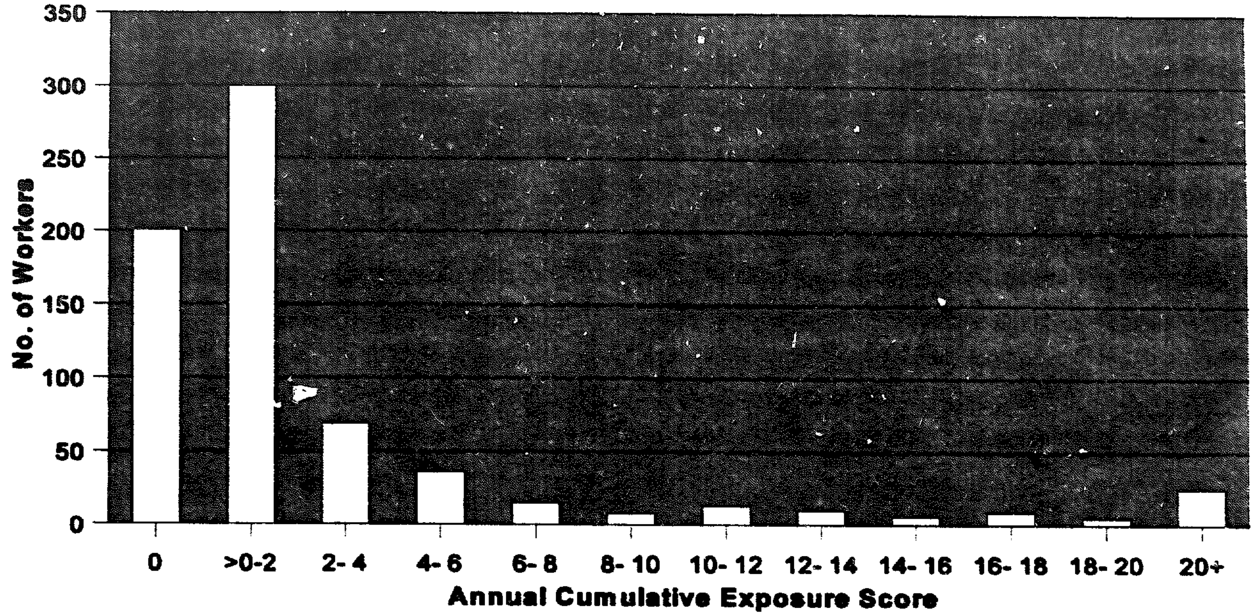
Table 5. Male and Female Cancer Cases, NHFC Plant Epidemiology Study

ID	Type	Code	Year of Birth	Year of Hire	Age at Cancer	Years Worked	Exposure Score	Followup[1] (years)	Smoking Status
Males									
3034	Testis	186.9	1960	1986	33.1	<0.1	0.00	6.5	no
3068	Myeloma	203.0	1923	1972	53.1	0.2	0.21	3.4	unk
3110	Stomach	151.9	1958	1976	33.7	0.2	0.15	15.6	no
3165	Testis	186.9	1935	1965	34.3	3.9	0.00	3.9	no
3176	Bladder	188.4	1927	1970	51.1	8.7	3.07	8.7	yes
3275	Bladder	188.2	1963	1984	31.2	2.3	2.23	9.8	yes
3283	Myeloma	203.0	1897	1966	86.4	5.3	0.00	17.9	unk
3324	Bladder	188.9	1939	1968	55.6	0.5	2.26	26.4	yes
3356	Soft Palate	145.3	1925	1970	64.2	<0.1	0.05	18.7	yes
3410	Kidney	189.0	1932	1969	57.1	<0.1	0.16	19.8	yes
3416	Lymph nodes	196.8	1953	1971	37.1	0.1	0.68	18.9	yes
3450	Bladder	188.9	1930	1973	55.2	10.0	4.03	12.0	yes
3459	Brain/CNS	192.1	1924	1971	51.0	0.1	0.10	4.1	unk
3475	Pancreas	157.5	1931	1970	48.4	1.6	1.58	9.1	unk
3510	Prostate	185.0	1944	1965	49.1	27.9	11.45	27.9	yes
3571	Lip	140.9	1919	1978	70.6	10.0	4.84	11.5	yes
3633	Bladder	188.2	1942	1970	45.7	5.2	16.19	17.2	yes
3658	Bladder	188.9	1922	1966	63.4	17.9	50.00	19.2	yes
3684	Bladder	188.9	1927	1968	61.5	20.5	10.13	20.5	yes
3687	Melanoma	172.5	1954	1979	34.9	9.2	16.78	9.2	unk
Females									
3344	Uterine	182.0	1911	1972	76.8	0.4	0.00	15.4	unk
3546	Breast	174.9	1949	1983	44.0	0.7	0.25	9.6	yes
3606	Breast	174.9	1939	1970	49.4	5.2	0.00	18.2	no
3670	Breast	174.4	1952	1985	33.2	0.7	0.00	0.7	yes

[1] Number of years from date of employment to occurence of cancer.

but less than 2.5); and the high exposure group (workers with cumulative exposure groups of 2.5 or more). A score of 2.5 was used as a cut-off, prior to data analysis, because of the obvious break in the number of workers with scores above and below this value. This score also provided sufficient person-years of observation for meaningful exposure-effect analyses. The scoring, as mentioned previously, was based on the observations of an exposure assessment committee and, therefore, the scoring approach was consistent across all exposure groups.

Figure 1. Annual Cumulative Exposure Scores Among NHFC Male Workers



4.6 Survival Analyses

Table 6 summarizes the observed SIRs for the survival analyses. Males had an elevated SIR for all cancers, cancer of the buccal cavity, cancer of the bladder, cancer of the kidney, cancer of the brain, and cancer of the testis. Only cancer of the bladder (SIR = 8.3; 95% CI = 3.3 - 17.1) and cancer of the testis (SIR = 11.4; 95% CI = 1.4 - 41.1) were statistically significant, however. The confidence intervals were very wide for cancers of the mouth, brain, kidney, and testis due to the small number of cases observed in each of those groups. For bladder cancer, the SIR remained elevated even when the bladder case reported only by CTR is excluded (SIR = 7.1; 95% CI = 2.6 - 15.4). Among females, only four cancers were reported: one cancer of the corpus uteri and three breast cancers. The only elevated SIR among females was for breast cancer, but the increase was not statistically significant (SIR = 1.9; 95% CI = 0.4 - 5.6).

Among males, the two workers with diagnosed cancer of the testis had no exposure to arylamines and one worked only 15 days. All bladder cancer cases were potentially exposed to arylamines.

All breast cancers among females occurred in the nonexposed group. As a result of the initial analyses, the cancer among females and testicular cancer among males were not analyzed further.

Table 6. Standardized Incidence Ratios by Selected Cancer Type (Males), NHFC Plant Epidemiology Study

Cancer Type (ICD Code)	Observed	Expected	SIR	95% Confidence Interval
All cancers[1]	20	14.1	1.4	0.9 - 2.2
Buccal cavity (140-149)	2	0.8	2.5	0.3 - 9.1
Digestive (150-159)	2	2.9	0.7	0.1 - 2.5
Melanoma (172)	1	1.0	1.0	0.0 - 5.5
Prostate gland (185)	1	1.0	1.0	0.0 - 5.3
Bladder (188, 189.9)	7	0.9	8.3	3.3 - 17.1
Kidney (189 except 189.9)	1	0.5	1.9	0.5 - 10.7
Brain (191)	1	0.4	2.9	0.0 - 16.1
Hematopoietic (200-207)	2	1.8	1.1	0.1 - 4.1
Testis (186)	2	0.2	11.4	1.4 - 41.1

[1] Includes the lymph node cancer not specified in table. Non-melanoma skin cancers are excluded as malignant cancers for the study.

To assess the influence of employment at the NHFC plant on the development of bladder cancer, two groups of workers were considered: workers with less than five years of followup and workers with five or more years of followup. No bladder cancer cases occurred in the group with less than five years of followup. The SIR was greater among workers with cumulative exposure scores of 2.5 or greater and in the group with five or more years of followup (SIR = 17.3; 95% CI = 5.6 - 40.5).

Exposure-effect relationships were examined between exposure to arylamines and the development of cancer. No association was observed between exposure and all cancers for all workers. The SIR among exposed males for all cancers was 1.5 (95% CI = 0.8 - 2.7) and was 1.4 (95% CI = 0.6 - 2.7) for nonexposed. The SIR for bladder cancer increased with increasing exposure (Table 7). Workers with no exposure to arylamines had no observed excess bladder cancer risk. The SIR for bladder cancer among males with a cumulative exposure score greater than 0 and less than 2.5 was 5.5 (95% CI = 0.7 - 19.8), and for workers with cumulative exposure scores of 2.5 or more was 16.4 (95% CI = 5.3 - 38.2). The experience was similar when the bladder cancer case reported only by CTR was omitted from the analysis; the SIR was 0 for the no-exposure group, 5.5 (95% CI = 0.7 - 19.8) with exposure scores between 0 and 2.5, and 13.1 (95% CI = 3.6 - 33.5) for exposure scores of 2.5 or greater. The excess bladder cancer cases were concentrated among chemical operators and mechanics. Chemical operators worked with the arylamines and their exposure occurred over a long period of time. Mechanics came into close contact with the chemicals when they repaired the equipment. The exposure is believed to have been of short duration but intense.

Table 7. Standardized Incidence Ratios for Bladder Cancer by Annual Cumulative Exposure Groups and by Years of Followup (Males), NHFC Plant Epidemiology Study

Length of Followup	Annual Cumulative Exposure Score: No Exposure			< 2.5			2.5+		
	n	SIR	CI	n	SIR	CI	n	SIR	CI
< 5 Years	0	0.0	—	0	—	—	0	—	—
5+ Years	0	0.0	—	2	6.4	(0.8 - 23.1)	5	17.3	(5.6 - 40.5)
Total	0	0.0	—	2	5.5	(0.7 - 19.8)	5	16.4	(5.3 - 38.2)

Because bladder cancer is strongly associated with smoking (American Cancer Society 1995), an attempt was made to assess the contribution of smoking among the exposed workers and to determine the associated SIR. Despite the fact that nearly 37% of the male cohort did not report their smoking status on the questionnaire survey, smoking status was known for all the bladder cases: one worker was a current smoker and six were former smokers.

All but one bladder cancer case reported smoking more than six cigarettes per day and most reported smoking at least one pack (20 cigarettes) per day. On the average, the cases smoked for 32 years. The smoking history provided in the medical records was similar to that reported in the survey questionnaire. Table 8 shows the SIR for bladder cancer among smokers only. The SIRs for the cumulative exposure groups of less than 2.5 (SIR = 11.6; 95% CI = 1.4 - 41.8) and 2.5 or more (SIR = 23.6; 95% CI = 7.7 - 55.2) were much greater than for the total cohort. The confidence intervals were wider, however, because the total number or the person-years of observation was smaller.

4.7 Incidence Density Rates and Cox's Proportional Hazard Model

Annual incidence density rates were calculated for this population. When all males were considered, there was a significant linear trend for increasing bladder cancer incidence with increasing exposure ($p = 0.015$). While the annual incidence for the nonexposed was zero, it was 0.47 (per 1,000 person-years followup) for those with a cumulative exposure score of less than 2.5, and 2.05 per 1,000 for those with a cumulative exposure score of 2.5 or greater.

A similar pattern was found among male smokers except that the incidence for all exposed groups was higher than for all males combined (smokers and nonsmokers). Again, among the nonexposed, the incidence was zero, but it was 0.64 in the lower exposure group, and 4.5 for those in the higher exposure group, with a significant linear trend ($p = 0.015$). The limited data restrict

Table 8. Standardized Incidence Ratios for Bladder Cancer by Annual Cumulative Exposure Groups and by Years of Followup in Smokers Only (Males), NHFC Plant Epidemiology Study

Length of Followup	Annual Cumulative Exposure Score: No Exposure			< 2.5			2.5+		
	n	SIR	CI	n	SIR	CI	n	SIR	CI
< 5 Years	0	0.0	—	0	—	—	0	—	—
5+ Years	0	0.0	—	2	13.7	(1.7 - 49.5)	5	25.0	(8.1 - 58.4)
Total	0	0.0	—	2	11.6	(1.4 - 41.8)	5	23.6	(7.7 - 55.2)

additional analyses of any association between smoking, occupational exposure, and bladder cancer.

The data were then submitted to Cox's proportional hazard regression. The results for total cancer in the model were similar to those obtained using the survival analysis. For total cancers, no association was observed between cumulative exposure and the development of cancer. A confounder, age at hire, explained much of the variance in the data set. The model failed, however, when bladder cancer was considered because there were no bladder cancer cases among nonsmokers and the hazard ratio approached infinity among smokers.

Section 5

Discussion

5.1 Technical Perspective

This study was undertaken to determine the incidence of bladder cancer among workers employed after benzidine operations terminated in mid-1965. It was not possible to evaluate cancer risks for specific arylamines in this study. Workers were likely to have been exposed to more than one arylamine during their tenure at the plant. Of the three principal arylamines produced at the facility during the study period, DCB has been studied the most. DCB was the principal arylamine produced at the facility. DCB has been designated by U.S. EPA as a probable human carcinogen and by the NTP as a substance which "may reasonably be anticipated to be a carcinogen." These conclusions were based on studies in which tumors were found in rats, mice, hamsters, and dogs following exposures by the oral route (U.S. EPA 1995b, NTP 1991, IARC 1987).

Three epidemiologic studies of workers have considered the carcinogenic potential of DCB (MacIntyre 1975; Gadian 1975; Gerarde and Gerarde 1974). None of these investigations reported an association between exposure to DCB and cancer incidence; however, each of these studies had limitations such as small study cohorts, brief exposure periods, and limited cohort followup, and therefore, have not been regarded as adequate evidence for demonstrating no increased risk between DCB exposure and bladder cancer (IARC 1982b). In a letter to the editor by Leeser and Cowan (1993), it was noted that additional followup of the cohort studied by MacIntyre (1975) indicated that four bladder cancer cases had occurred; however, an association of the cases with DCB exposure was uncertain as the cohort had a more mixed exposure history than previously thought. It was also found that some cohort members had more limited exposures than previously reported and that some cohort members were missed in the original analysis.

Cohorts of workers that have been exposed only to o-dianisidine or o-tolidine, two other arylamine compounds produced at the NHFC plant, have not been evaluated in any epidemiologic studies reported in the literature. Two investigations by Delzell et al. (1989) and Schulte et al. (1986) have found elevated cancer risks in occupational populations exposed principally to β-naphthylamine or benzidine, but exposures to other arylamines such as o-dianisidine or o-tolidine may have occurred. Sinks et al. (1992) found an elevated SIR for renal cell cancers (SIR = 3.7, 95% CI = 1.4 - 8.1) in paperboard printing workers. The risk could not be linked with any department or process, but the plant had used pigments containing congeners of DCB and o-tolidine. Other investigators have speculated on the possible role of substituted benzidines in bladder cancer. Myslak and coworkers (1991) conducted a case-control study of bladder cancers occurring in Germany and found that painters were over-represented among the cases. The authors noted that chemical exposures in painters can be diverse, but they speculated on the possible role of azo dyes which had been used extensively in German paints. Many of the azo dyes were developed from benzidine, DCB, o-dianisidine, or o-tolidine.

Even though the epidemiologic literature has not provided convincing evidence of a carcinogenic hazard associated with benzidine-related compounds, occupational advisories have been issued on the possibility of such a hazard. The Occupational Health and Safety Administration and the National Institute for Occupational Safety and Health (OSHA/NIOSH 1981) published their health hazard alert on benzidine-, o-tolidine-, and o-dianisidine-based dyes in 1981. In that alert, OSHA/NIOSH warned the public about the potential cancer hazard of these substances and the need to reduce worker exposures. In the United Kingdom, the British Association of Urological Surgeons Subcommittee on Industrial Bladder Cancer has issued guidance to clinicians warning about the possible cancer hazards of certain occupations and certain arylamines including DCB, o-dianisidine, and o-tolidine (BAUS 1988). NTP (1991) regards o-dianisidine and o-tolidine as substances which may be anticipated to be carcinogenic.

5.2 Significance of NHFC Plant Results

In this study we observed an association between jobs with arylamine exposure and bladder cancer. The results are inconsistent with the other epidemiologic studies on DCB workers in which an association with bladder cancer was not found. One possible difference between this and earlier studies is that exposures in this study were to a variety of arylamines of which DCB was one; it is not known if the association observed in this investigation was with a particular arylamine or a mixture of substances. The positive results of this study are noteworthy from the perspective that exposures to arylamines for the cohort were believed to be considerably greater in the late 1960s for the first seven years of the 24-year employment period and dropped dramatically in the early 1970s when exposure control strategies were implemented. Exposures during the mid- to late 1970s were considered to be at very low levels. These changes in exposure are supported by the decreases seen in urinary amine levels over this time period. We observed that five of the seven cancer cases started employment prior to 1972 when arylamine operations were moved to a building with improved exposure controls, although workers employed after 1972 had a shorter followup period. SIRs were not developed at this time because of the limited number of person-years of observation and the shorter latency period in the cohort employed after 1971.

There are several factors that could have influenced the magnitude of the bladder cancer risks observed in this study. The cases were identified primarily through three sources—a review of the Connecticut Tumor Registry records (current to 1990), a worker survey during the summer of 1993, and an on-going medical surveillance program that was operational at the close of the study in August 1994 when person-years of observation for the cohort were no longer accrued (Table 9).

Table 9. Bladder Cancer Cases by Source of Identification, NHFC Plant Epidemiology Study

ID	Year of Diagnosis	Company's Initial Identification Source	Study Identification Source
3176	1978	Surveillance	CTR, surveillance, questionnaire
3275	1994	Private MD, Workers' Compensation Claim	Workers' Compensation Claim
3324	1994	Surveillance	Surveillance
3450	1985	Private MD, CTR	CTR
3633	1987	Private MD, CTR prior to study	CTR, questionnaire
3658	1985	Surveillance	CTR, surveillance, questionnaire
3684	1988	Private MD, Self-reported to company	CTR, surveillance, questionnaire

Expected numbers of bladder cancer cases in this study were estimated from cancer incidence rates in the State of Connecticut. It is possible that cancer risks were overestimated in the study, because the company medical surveillance program identified cases diagnosed after 1990 that would not have been reported to the CTR. There is also the possibility that the existence of the company's medical surveillance program provided a level of surveillance that is not typical throughout Connecticut and, therefore, may have influenced the magnitude of the observed risks. A comparison of the average stage of disease in the cases from this study with that from the tumor registry would have been useful but was not available. We do not believe that this possible source of bias affects the overall conclusions of the study.

Strengths of this study include its focus on cancer incidence rather than mortality, complete followup of a substantial portion of the cohort, and categorization of workers by exposure to arylamines. The results argue in favor of a relationship between bladder cancer and arylamine exposure. First, the bladder cancer risk among all males in the cohort was substantial and statistically significant with risks being over 800% greater than expected (SIR = 8.3; 95% CI = 3.3 - 17.1). Data from a biological monitoring program could not be used for quantifying worker exposures. However, analyses using a committee-developed arylamine exposure classification system indicated an exposure-effect relationship with bladder cancer and increasing risk with higher exposure categories (SIRs = 0, 5.5, or 16.4 for exposure categories of none, low, or moderate, respectively). Another factor supporting the association is that exposures to arylamines in this population were known to have occurred because of the positive urinary amine test results (Section 3.3.1). A positive association was observed in workers involved in arylamine operations. An occupational influence in this study is suggested by the younger average age at time of diagnosis (52 years) among the NHFC plant bladder cancer cases, when compared to the average age of diagnosis in the State of Connecticut (68 years). Also, the excess bladder cancer risks were found among those workers in which an adequate latency period (more than five years of observation since initial exposure) had occurred.

There is biological plausibility that arylamine exposure at the plant, rather than exposures to other substances, could be associated with the observed excess of bladder cancer. It is recognized that some arylamines such as β-naphthylamine and benzidine are metabolized, probably by N-hydroxylation, to an ultimate carcinogen (Shulte et al. 1990). N-hydroxyarylamines have been found to be carcinogenic in several laboratory species. It has been postulated that N-hydroxylation occurs in the liver and that this proximate carcinogen is conjugated with glucuronide before being released into the systemic circulation. The kidneys collect the conjugate that is passed to the acidic environment of the bladder where it is postulated that the N-hydroxylamine is released and an electrophilic arylnitrenium ion is formed (Shulte et al. 1990). This ion is presumably the ultimate carcinogen that reacts with nucleic acids. There is also reason to believe that N-acetylation of arylamines is involved in occupational bladder cancer (Shulte et al. 1990). Several studies have reported associations between slow acetylator phenotype and bladder cancer risks among workers exposed to arylamines. With respect to this form of cancer, acetylation may be a detoxifying process and those individuals who have reduced acetylation capacity and are exposed to arylamines are at an increased risk. The acetylator phenotype of the cases and noncases at the NHFC plant is unknown.

Elevated cancer risks were observed in this study for cancer of the testis and breast. However, these risks were based on a limited number of observations (three or fewer cases for each type of cancer). An analysis of these cancer types indicated that they occurred among employees with no evidence of exposure to arylamines, and therefore, we conclude that they are probably not associated with exposures to arylamine compounds.

5.3 Influence of Smoking Status

All of the bladder cancer cases were current or ex-smokers. Smoking is known to be related to bladder cancer and increases the risk by approximately a factor of two (American Cancer Society 1995). It is unlikely that smoking alone explains the highly elevated bladder cancer risks seen in this study. It is possible that smoking and arylamine exposures are additive or synergistic. A final analysis of the impact of smoking on the development of cancer in the exposed population can only be evaluated when the cohort is older and has accrued more years of followup and bladder cancer has developed among nonexposed individuals.

Section 6

Epilogue

After the study cutoff date of August 31, 1994, the company surveillance program identified an additional bladder cancer case in 1995. The worker, employed between November 1965 and February 1966, was a male who worked at a job associated with arylamine exposure. Because of his short work history, his exposure score would have been in the moderate range. Consistent with the smoking histories of the other cases in this study, the worker had been a heavy smoker.

Section 7

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