Bladder Cancer Incidence in Arylamine Workers

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Cancer incidence was investigated in a cohort of 700 workers employed at a Connecticut chemical plant between mid-1965 and 1989. The plant poduced a variety of chemicals, including arylamines such as dichlorobenzidine (DCB), o-dianisidine, o-tolidine, but not benzidine. Benzidine production ceased prior to mid-1965. The principal finding was a statistically significant increase in the standardized incidence ratio (SIR) for bladder cancer in men (SIR = 8.3; confidence interval, 3.3 to 17.0). Based on an exposure classification system developed by a panel of former and current employees, the observed association between bladder cancer cases and exposure to arylamines increased with increasing exposure (SIRs = 0.0, 5.5, 16.4, for none, low, or moderate levels of exposure, respectively). Smoking probably contributed to the bladder cancer risk, as all case subjects were known to be current or former cigarette smokers.

In this investigation, the study cohort came from a specialty chemicals manufacturing facility that started operations in the mid-1940s. 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.[1] 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 plant ceased in 1993. Operations at the plant have never required a large work force. All told, there have been approximately 1710 individuals employed since plant operations started.

As early as 1949, plant management became concerned about the possible association between benzidine exposure and the development of bladder cancer. A permanent biological monitoring program was instituted at that time and continued up to the time that benzidine operations ceased in 1965. Urinary amine levels were found to increase during warm months? Skin contact was found to be the most important exposure route.[3] Other measures implemented over time by plant management in-

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cluded a cystoscopy program in 1956 to detect early bladder tumors, a cytology program in 1964 to test employees with 5 or more years of service, and the introduction of safety equipment and protective clothing. Former employees, however, were not tested until a recall program was initiated in 1977. In 1993, 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.

Meigs et al[4] reported the cancer incidence experience of workers employed at the plant between 1945 and mid-1965, with follow-up to the end of 1978. An elevated standardized incidence ratio (SIR) was reported for cancer of the stomach (1.9), lung (IS), prostate (1.7), colon (1.5), and bladder (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 to 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 to 1949) compared with those employed later. The SIR for the earlier period was 9.8 (95% CI, 2.6 to 25.0), compared with 2.1 (95% CI, 0.0 to 11.8) for those first employed during the period 1950 to 1954. Meigs et al[4] attributed the risk to benzidine exposure.

In 1985, the plant's medical department received information indicating that three workers tirst employed at the 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.[5] Based on this assessment, the company initiated the study reported here. The primary objective of the study was to determine whether the incidence of cancer was higher than expected among arylamine workers who were never exposed to benzidine and who were first employed at the plant after benzidine production ceased. 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 follow-up would exist, because only those workers starting employment after June 1965 would be enrolled.

Methods

The study cohort consisted of 704 workers, 585 men and 119 women, first employed at the plant between June 15, 1965, and December 31, 1989. Only workers never exposed to benzidine at the plant were selected. Work histories and demographic information were identified using the corporate database and the personnel records at the plant. Records were matched against the data tapes of workers first employed prior to mid-1965 to eliminate any worker employed prior to the cessation of benzidine production. To assure that no worker had been missed, the assembled database was verified against the listings appearing on the Internal Revenue Service 941 Forms. Missed workers were added to the cohort. The forms have been used **in** other studies as a reliable means of validating the completeness of an occupational study cohort.[6] Considerable effort was expended to locate a current address and to make vital status determinations for each member **of** the cohort (93% living; 3% deceased; 4% unknown).

Cancer Identification

Three sources were used to identify cancer cases for the incidence study in addition to the ongoing surveillance by the company's medical department. These methods included matching the cohort roster with the cancer cases registered at the Connecticut Tumor Registry (CTR) through 1990, reviewing the death certificates of deceased workers, and identifying and confirming reported cancers through a mail survey in 1993 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. Only confirmed cancer cases were considered in the analysis.

The mail survey consisted of sending a questionnaire to each worker for whom we had a valid address. The questionnaire requested information on the diagnosis of any cancer, smoking, other possible risk factors for bladder cancer, and work histones. An additional mailing and a telephone follow-up were initiated for nonrespondents. An abbreviated questionnaire was administered by telephone to nonrespondents for whom we had active telephone numbers.

Exposure Classification

An Exposure Assessment Committee (EAC), consisting of four former or current workers knowledgeable about work processes and potential exposures, was assembled after identification of the work histories but before the analysis to review job-specific exposures and assign exposure scores. Before their meeting, a matrix of arylamine production and use, by month for the years between 1965 and 1989, was prepared by the

TABLE 1
Arylamines Handled at the Plant

Chemical Name	CAS* Number	Related Compounds and Other Names Used by Plant Personnel
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-rnethvl benzeneamine; ortho-toluidine
o-chloroaniline	95-51-2	ortho-chloroaniline; OCA

* CAS, Chemical Abstracts Service.

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. It was not possible for this study to evaluate chemical-specific effects for each arylamine handled at the plant. The EAC committee met once and clarified resulting issues by conference calls. Job titles, tenure, unit numbers, and work status information were available from the computerized corporate database and plant personnel records for the 704 study cohort members.

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 because no information was available to suggest that a nonlinear scale would be more appropriate. For workers assigned to units in which the EAC determined that no exposure to arylamines had occurred, both the assigned intensity and frequency exposure scores were zero.

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's approach erred in the direction of overestimating exposure.

The exposure scores assigned to each job over the study period by the EAC were used as a master matrix to calculate an average daily exposure value for each work interval in the employee's work history. The average daily exposure was determined by 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.

Analysis

For all analyses, several definitions or restrictions were imposed on the study cohort and the cases to minimize bias. These definitions and restrictions included the following:

- The person-years of observation for a cancer case subject were accumulated until the date of cancer diagnosis, if the case subject was still alive, or the date of death, if the cancer case subject could only be identified from the death certificate. Because onlv two cancer case subjects were identified solely by death certificates, 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 were accumulated until the time of death.
- Workers with cancers confirmed before the date of employment at the plant were eliminated from the analysis ($n = 6$, two men and four
- Three workers diagnosed with non-melanoma skin cancer contributed person-years of observation but were not considered as cancer case subjects in the analysis 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 follow-up period (August 31, 1994), whichever was most recent.

Survival ***analyses.*** The survival analyses were carried out using Module 1 of the OCMAP/PC program developed by the University of Pittsburgh[7] 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 cohort to obtain the expected number of cancers. 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 for each worker using the average daily exposure score. 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 men and women separately and for workers with less than 5 years of follow-up and 5 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.

Incidence density rates and Cox's proportional hazard regression. The incidence density of bladder cancer (cases per 1000 person-years of observation) was examined for three exposure groups: no cumulative exposure, scores of less than 2.5, and scores of 2.5 or more. The association between exposure and incidence density was evaluated with a chi-squared test for linear trend.[8] The linearity test was performed separately for all men and for male smokers only. Cox's proportional hazard regression model was used to account for confounders such as sex, smoking, and age at hire.'

Results

Of the original 704 members of the worker cohort, six were eliminated from the analysis because they had developed cancer before plant employment (Table 2). If all of the workers had been followed-up to the end of the study, 8890 person-years of observation would have accrued for men and 1704 person-years for women. As a result of the worker survey, the information on follow-up yielded 8624 person-years of observation for a follow-up rate of 97% among the male employees and 1660 person-years of observation for a follow-up rate of 97% among women.

TABLE 2
Cohort Characteristics

Characteristics	Men	Women	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 (years)	28.2 ± 7.8	29.2 ± 9.8	28.2 ± 8.3
Employment Duration (years)	4.5 ± 6.5	3.1 ± 4.7	4.3 ± 6.3
Average Follow-Up (years)	14.1 ± 8.3	13.7 ± 8.0	14.0 ± 8.3

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. Details on the cancer cases are presented in Table 3.

The average age at diagnosis for all cancers was 51 years for men and 43 years for women. The average age at diagnosis for bladder cancer among men was 52 years. The average age for Connecticut men is 68 years.'" For breast cancer among women, the average age at diagnosis was 32 years. The average age at diagnosis for breast cancer among Connecticut women is 59 years. Two of the bladder cancers among men were diagnosed in workers first employed after 1972, four were first employed at the age of 40 or older, and five worked at least 5 years or more. All bladder cancers had a follow-up period of 8 years or more.

Cumulative Exposure

Annual cumulative exposure scores were calculated for each worker. The scores ranged from 0 to 64.4. Among the workers, 20.4% of the men and 71.3% of the women had no exposure to arylamines. Forty-seven percent of the men had a cumulative exposure score greater than 0 and less than 2.5. Figure 1 shows the distribution of cumulative exposure scores for men. The cohort was categorized into three groups: the non-exposed (workers with cumulative exposure scores of 0), the low exposure group (workers with cumulative exposure scores of greater than 0 but less than 2.5), and the high exposure group (workers with cumulative exposure scores of 2.5 or more). A score of 2.5 was used as a cut-off, prior to data analysis, because of an obvious break in the number of workers with scores above and below this value. This score also provided a sufficient number of person-years of observation for meaningful exposure-effect comparisons.

Survival Analyses

Table 4 summarizes the observed SIRs for the survival analyses. Men 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 to 17.1) and cancer of the testis (SIR = 11.4; 95% CI, 1.4 to 41.1) were statistically significant. Among women, only four cancers were reported: one uterine cancer and three breast cancers. The only elevated SIR among

TABLE 3
Male Cancer Cases

Type	ICD Code	Age at Cancer	Years Worked	Exposure Score	Follow-Up* (years)	Smoking Status†
Testis	186.9	33.1	<0.1	0.00	6.5	No
Myeloma	203.0	53.1	0.2	0.21	3.4	Unk
Stomach	151.9	33.7	0.2	0.15	15.6	No
Testis	186.9	34.3	3.9	0.00	3.9	No
Bladder	188.4	51.1	8.7	3.07	8.7	Yes
Bladder	188.2	31.2	2.3	2.23	9.8	Yes
Myeloma	203.0	86.4	5.3	0.00	17.9	Unk
Bladder	188.9	55.6	0.5	2.26	26.4	Yes
Soft Palate	145.3	64.2	<0.1	0.05	18.7	Yes
Kidney	189.0	57.1	<0.1	0.16	19.8	Yes
Lymph Nodes	196.8	37.1	0.1	0.68	18.9	Yes
Bladder	188.9	55.2	10.0	4.03	12.0	Yes
Brain/CNS	192.1	51.0	0.1	0.10	4.1	Unk
Pancreas	157.5	48.4	1.6	1.58	9.1	Unk
Prostate	185.0	49.1	27.9	11.45	27.9	Yes
Lip	140.9	70.6	10.0	4.84	11.5	Yes
Bladder	188.2	45.7	5.2	16.19	17.2	Yes
'Bladder	188.9	63.4	17.9	50.00	19.2	Yes
Bladder	188.9	61.5	20.5	10.13	20.5	Yes
Melanoma	172.5	34.9	9.2	16.78	9.2	Unk

* Number of years from date of employment to occurrence of cancer.
† ICD, International Classification of Diseases; Unk, unknown; CNS, central nervous system.

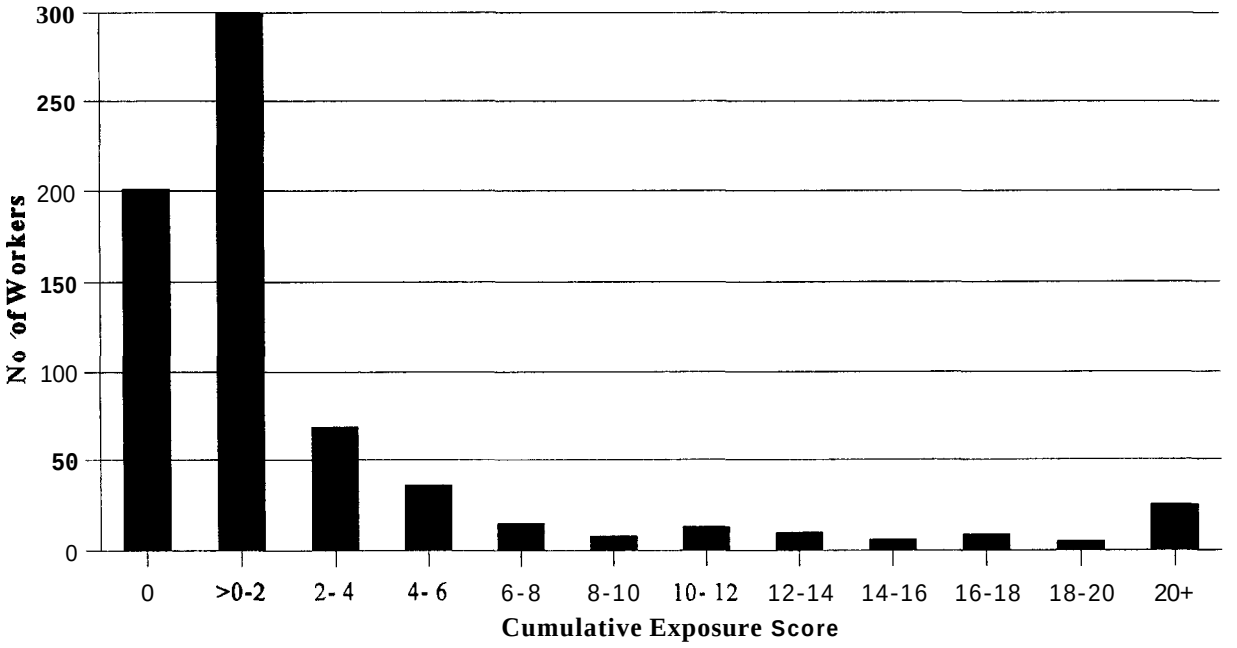

Fig. 1. Cumulative exposure scores among male workers.

women was for breast cancer, but the increase was not statistically significant (SIR = 1.9; 95% CI, 0.4 to 5.6). The two workers with diagnosed cancer of the testis had no exposure to arylamines and one had worked only 15 days. All bladder cancer case subjects were potentially exposed to arylamines. All breast cancers among women occurred in the non-exposed group. As a result of the initial analyses, the cancer among women and testicular cancer among men were not analyzed further.

To assess the influence of employment at the plant on the development of bladder cancer, two groups of workers were considered: workers with less than 5 years of follow-up and workers with 5 or more years. No bladder cancer cases occurred in

TABLE 4
Standardized Incidence Ratios (SIR) by Selected Cancer Type (Men)

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

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

TABLE 5
Standardized Incidence Ratios (SIR) for Bladder Cancer by Annual Cumulative Exposure Groups and by Years of Follow-up (Men)*

Length of Follow-Up	Annual Cumulative Exposure Score: No Exposure n	SIR	CI	<25 n	SIR	CI	2.5+ n	SIR	CI
<5 Years	0.0	0.00		0	0.0		0	0.0	
5+ Years	0.0	0.00		2	6.4	(0.8 to 23.1)	5	17.3	(5.6 to 40.5)
Total	0.0	0.00		2	5.5	(0.7 to 19.8)	5	16.4	(5.3 to 38.2)

• CI, confidence interval.

the group with less than 5 years of follow-up, but the SIR was greater among workers with cumulative exposure scores of 2.5 or greater and 5 or more years of follow-up (Table 5).

Exposure-effect relationships were examined between exposure to arylamines and the development of cancer. No association was observed between exposure to arylamines and all cancers for workers. The SIR for all cancers was 1.5 (95% CI, 0.8 to 2.7) among exposed men and was 1.4 (95% CI, 0.6 to 2.7) for non-exposed. The SIR for bladder cancer increased with increasing exposure (Table 5). 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 and, although the exposure is believed to have been of short duration, it may have been intense.

Because bladder cancer is strongly associated with smoking," 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 of the bladder cancer case subjects: one worker was a current smoker and six were former smokers. All but one bladder cancer case subject reported smoking more than six cigarettes per day and most reported smoking at least one pack (20 cigarettes) per day. On the average, the case subjects smoked for 32 years. The smoking history provided in the medical records was similar to that reported in the survey questionnaire. As expected, the bladder cancer SIRs among smokers for the cumulative exposure groups of less than 2.5 (SIR = 11.6; 95% CI, 1.4 to 41.8) and 2.5 or more (SIR = 23.6; 95% CI, 7.7 to 55.2) were much greater than for the total cohort.

Incidence Density Rates and Cox's Proportional Hazard Model

Annual incidence density rates were calculated for this population. When all men were considered, there was a significant linear trend for increasing bladder cancer incidence with increasing exposure (P = 0.015). Whereas the annual incidence for the non-exposed was zero, it was 0.47 (per 1000 person-years follow-up) for those with a cumulative exposure score of less than 2.5, and 2.05 per 1000 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 that for all men combined (smokers and nonsmokers). Again, among the non-exposed. the incidence was zero, but it was 0.64 in the lower exposure group, and 4.50 for those in the higher exposure group, with a significant linear trend (P = 0.015). The limited data restrict

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

The data submitted to Cox's proportional hazard regression showed similar results for total cancer. The model failed, however, when bladder cancer and smoking was considered because there were no bladder cancer cases among nonsmokers, which made the hazard ratio approach infinity among smokers.

Discussion

This study was undertaken to determine the incidence of cancer, particularly with respect to the bladder, 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 the US Environmental Protection Agency as a probable human carcinogen and by the National Toxicology Program as a substance that "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 after exposures by the oral route[12–14]; however, evidence of carcinogenicity in humans is considered to be inadequate.

Although occupational advisories have been issued concerning the potential carcinogenicity of nonbenzidine arylamines, the evidence on the carcinogenicity of arylamines such as DCB, o-dianisidine, or o-tolidine is inadequate, in part because cohorts exposed to these substances alone and not benzidine, are difficult to find in sufficiently large numbers. Three epidemiologic studies[15–17] 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. The study reported here is relevant to the question of the carcinogenicity of arylamines other than benzidine.

An association between jobs with arylamine exposure and bladder cancer was observed in this study. 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 workers were exposed 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 7 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 the company's urinary amine monitoring program over this time period. We observed that five of the seven cancer case subjects 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 follow-up period. SIRs were not developed separately for these time periods because of the limited number of person-years of observation and the shorter latency period in the cohort employed after 1971.

Several factors 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 ongoing 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 being accrued. 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 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. It is not believed 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 follow-up of a substantial portion of the cohort, and categorization of workers by exposure to arylamines. The results support an association between bladder cancer and arylamine exposure. First, the bladder cancer risk among all men in the cohort was substantial and statistically significant, with risks being over 700% greater than expected (SIR = **8.3;** 95% CI, **3.3** to 17.1). Data from a biological monitoring program could not be used for quantifying exposures in this study. 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. We also note the relatively young average age at time of diagnosis (52 years) among the bladder cancer case subjects, an occurrence frequently observed when an occupational association between disease and exposure is shown. The fact that we observe a younger age at diagnosis in this study argues in favor of an occupational association. Also, the excess bladder cancer risks were found among those workers in which an adequate latency period (more than 5 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 have been 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.[17] *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. 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.[18] 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 among the plant's bladder cancer case subjects 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.

All of the bladder cancer case subjects are current or ex-smokers. Smoking is known to be related to bladder cancer and increases the risk by approximately a factor of two.[17] It is unlikely that smoking alone explains the high eightfold increase in bladder cancer risks seen in this study. The magnitude of the contribution of arylamine exposure can be assessed by comparing the incidence rates observed in the high exposure group to that of the lower exposure group among smokers only. The incidence density ratio is 7.0. In addition, if one assumes that one of the bladder cancer case subjects is a non-smoker in an effort to assess the magnitude of smoking as a confounder, the incidence density ratio for any arylamine exposure in smokers compared with that of nonsmokers is 10.4. Creative rearranging of the data, however, can be misleading. It is possible that smoking and arylamine exposures are additive or synergistic. A final analysis can only be completed when the cohort is older and has accrued more years of follow-up, and bladder cancer has developed among nonexposed individuals.

Epilogue

After the study cutoff date of August 31, 1994, the company surveillance program identified an additional bladder cancer case subject. The worker was employed between 1965 and **1966** in a position that involved contact with arylamines. This worker had been a heavy smoker.

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SPRINGTIME COMESTOTHE COLDWAR

It has been a long time since the air-raid siren went off at the comer of Olympic and Figueroa. Or anywhere in Los Angeles, for that matter. But LA officials have decided it would cost too much to dismantle all 200 abandoned sirens that went up in the 1950s and finally were disconnected in 1985. Instead, the City's Community Redevelopment Agency has offered $20,000 grants to local artists with ideas for using the sirens to brighten the streets. Sculptor Michael Tansey redesigned the first one last **week** he mounted bright yellow petals atop the 30-foot-high wailer at Olympic and Figueroa to create a 10-foot-wide manmade daffodil. If the bud is a hit, officials will consider citywide distribution. Ah, springtime in Hollywood.

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