Notification and Risk Assessment for Bladder Cancer of a Cohort Exposed to Aromatic Amines

III. Mortality among Workers Exposed to Aromatic Amines in the Last β-Naphthylamine Manufacturing Facility in the United States

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A retrospective cohort mortality study was conducted among workers employed at the last facility in the United States that manufactured β-naphthylamine (BNA), a recognized human bladder carcinogen. This study was conducted in conjunction with a pilot project in which workers were notified of the health risks associated with exposures to carcinogenic amines. Cause-specific mortality for 1,312 male workers employed between 1940 and 1972, and followed through 1979, was compared with the mortality of the general population in the United States. Two deaths from bladder cancer were observed while 0.7 such deaths were expected. Due to the use of these potent carcinogenic amines, it had been anticipated that more bladder cancer deaths would be found in this population. The reasons for the small number of bladder cancer deaths could have been the low percentage of the work force exposed, an inadequate latency period, and/or the high survival rate for bladder cancer. In fact, a notification and medical screening project recently conducted in this same population found an additional 11 bladder cancer cases. This suggests that mortality may not always be an adequate indicator of disease risk.

Aromatic amines, such as β-naphthylamine (BNA) and benzidine, have been shown to be human bladder carcinogens.[1-9] Rehn,[1] in 1895, was the first person to recognize that an excess of urinary bladder tumors occurred among workers in Germany who used aromatic amines in the production of synthetic dyes. Between 1905 and 1946, an international epidemic of cancer of the bladder among dye workers occurred as synthetic dye technology was introduced to other countries (Table 1).[2,3]

In Great Britain, further reports of bladder cancer added evidence of the health risks attributable to the synthetic dye manufacturing industry.[4-6] In a study sponsored by the Association of British Chemical Manufacturers, Case et al[6] found that workers employed six months or longer in the chemical factories of England and Wales producing or using aromatic amines had a 30-fold increased risk of dying of bladder cancer.

In the United States, the manufacture of synthetic dyes began during World War I. In 1931 Gehrmann,[10] then medical director of E.I. duPont de Nemours and Company, Inc., observed three cases of bladder tumors among workers who were exposed to BNA and/or benzidine in the manufacturing of dyes; by 1948, one hundred thirty-nine workers at the facility had developed bladder cancer. In 1955 the DuPont Company ceased production of BNA, stating that it was impossible to control its toxic effects. (*Washington Post*, July 15, 1979, p 21). In 1958 Mancuso and Coulter[11] found six cases of bladder cancer among workers at a midwestern United States synthetic dye facility, where only 0.33 cases were expected. Five years later, Lieben[12] reported the finding of 11 bladder tumors among workers exposed to BNA in two small plants in Pennsylvania. A report by Goldwater et al[13] described 96 cases of bladder carcinoma among 366 workers employed in a synthetic dye facility in New York.

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Animal data have added further evidence of the carcinogenicity of synthetic dyes. Hueper et al[14] reported that commercial BNA fed to 16 dogs for 90 weeks induced two papillomas and six carcinomas of the urinary bladder. Bonser[15] in a similar experiment, induced bladder papillomas or carcinomas in three of four dogs fed BNA in their diet. Conzelman and co-workers[16] demonstrated tumor induction in 24 monkeys fed BNA, 10 of which were found to have carcinoma of the bladder.

Because of the demonstrated carcinogenicity of BNA in both animals and humans, its manufacture and use were banned in Switzerland (1938), in Great Britain (1952), in Italy (1960), and in the state of Pennsylvania in the United States (1961). In 1968 the American Conference of Governmental Industrial Hygienists (ACGIH) recommended the prohibition of BNA manufacturing in the United States.[17] The ACGIH also proposed that no exposure to or contact with BNA be permitted by any route — respiratory, skin, or oral. In 1970 the Occupational Safety and Health Act was passed, and in 1974 federal standards were promulgated for 14 occupational carcinogens by adopting the 1968 ACGIH recommendations for those substances, which included BNA (29CFR 1910.1009).[18]

Background

In 1972 the National Institute for Occupational Safety and Health (NIOSH) conducted surveys of the facilities in the United States manufacturing or using BNA and benzidine in the synthesis of dyes. The purpose of these surveys was to obtain information on current and past industrial hygiene practices, numbers of workers exposed, types of medical surveillance, and history of bladder cancer, if any, among current workers. At a facility manufacturing BNA in Augusta, Ga., several workers were found to have gross hematuria and, therefore, urine cytology tests were recommended for all workers currently employed.[9] A retrospective cohort mortality study of all former workers at the Augusta facility was then initiated to clarify the health risks in this population. In 1977, NIOSH was instructed by the Senate Subcommittee on Labor, Committee on Human Resources, to investigate issues involved in notifying workers of the health risks associated with previous exposures to occupational carcinogens. A pilot project was begun with this cohort of BNA-exposed workers. The pilot project involved locating and providing medical screening and health education for former and current workers at the BNA-manufacturing facility.

The present report describes the results of the retrospective cohort mortality study. In addition, the mortality from bladder cancer in this cohort is contrasted with the cohort's morbidity experience; the morbidity experience has been described in detail in a previous report.[19]

Table 1 — Chronology of the Discovery of Aromatic Amine-Induced Cancers of the Bladder[2]

Year	Country	Investigator
1895	Germany	Rehn
1905	Switzerland	Schedler
1918	Great Britain	Ross
1926	Russia	Rosenbaum & Gottlieb
1932	Austria	Schuller
1934	United States	Gehrmann
1936	Italy	di Maio
1940	Japan	Nagayo & Kinosita
1946	France	Billiard-Duchesne

Materials and Methods

Facility Description — Since the early 1940s, the company under study had been using various aromatic amines as dye intermediates. In 1945 benzidine was first used at the facility and its use continued until the late 1960s. BNA was first manufactured in 1949, and by 1972, 25,000 to 30,000 lb of BNA was being manufactured monthly. At the time of the survey (January, 1972), 60 full-time workers were employed at the company, nine (15%) of whom were directly involved in the manufacture of BNA. Shortly after the completion of the survey, the manufacture of BNA was stopped and tobias acid was used as an alternative feedstock in the manufacture of synthetic dyes.

BNA was prepared by heating β-naphthol with ammonium sulfite and aqueous ammonia at 150 °C. When the reaction was complete, crystallized BNA was discharged into a box filter and the solvent was suctioned off. The remaining moist slurry was shoveled into drums.

Cohort Description — The personnel and work history records of all former and current production workers were microfilmed, coded, and entered into computer storage. Since many of the work history records were not complete as to type of jobs held, it was impossible to classify workers by work assignment. The cohort under study consisted of all workers employed at the company for one day or longer between Jan. 1, 1940, and March 30, 1973. Vital status follow-up for each worker began on his last date

Table 2 — Vital Status of Study Population as of Dec. 31, 1979

	Total		White		Nonwhite	
Vital Status	No.	%	No.	%	No.	%
Traced alive	**964**	73.5	311	75.1	653	72.7
Traced deceased	**262**	20.0	85	20.5	177	19.7
Death certificates:						
Obtained	**229**	87.4	77	90.6	152	85.9
Outstanding	**33**	12.6	8	9.4	25	14.1
Lost to follow-up	**86**	6.5	18	4.4	68	7.6
Total	**1,312**	**100.0**	**414**	**100.0**	**898**	**100.0**

Table 3 — Distribution of Study Population by Year of Initial Hire			
Year of Initial Hire	No.	%	Cumulative %
1940-1944	2	0.2	0.2
1945-1949	487	37.1	37.3
1950-1954	155	11.8	49.1
1955-1959	135	10.3	59.4
1960-1964	138	10.5	69.9
1965-1969	120	9.1	79.0
1970-1972	275	21.0	100.0
Total	**1,312**	**100.0**	**100.0**

Table 4 — Distribution of Study Population by Maximum Possible Length of Observation			
Maximum Observation, yr	No.	%	Cumulative %
<1	10	0.7	0.7
1-4	23	1.7	2.4
5-9	298	22.6	25.0
10-14	141	10.8	35.8
15-19	194	14.8	50.6
20-24	170	13.0	63.6
25-29	154	11.8	75.4
>30	322	24.6	100.0
Total	**1,312**	**100.0**	**100.0**

Table 5 — Distribution of Study Population by Duration of Employment			
Duration of Employment, mo	No.	%	Cumulative %
<2	651	49.7	49.7
2-5	282	21.4	71.1
6-11	136	10.4	81.5
12-59	179	13.6	95.1
60-119	34	2.6	97.7
>120	30	2.3	100.0
Total	**1,312**	**100.0**	**100.0**

employed and continued through Dec. 31, 1979. Follow-up sources included the Social Security Administration, the Internal Revenue Service, the bureaus of motor vehicles of Georgia and South Carolina, and the U.S. Postal Service.

Death certificates were obtained for persons identified as deceased, and their underlying and contributory causes of death were coded by a qualified nosologist according to the rules of the *International Classification of Diseases* (ICD) in effect at the time of death. The codes were subsequently converted to those of the seventh revision for analysis. Those persons known to be deceased, but for whom no death certificates were found, were categorized as deceased, cause unknown. Individuals whose vital status could not be determined were assumed to be alive for the purposes of this study, thereby contributing a maximum number of person-years at risk (PYAR). This approach tended to increase the overall expected number of deaths, thus making the findings somewhat conservative.

Analysis — A modified life-table analysis system developed by NIOSH was used to compute the PYAR.[20] The PYAR were calculated for each worker from either his first day of employment at the plant or from Jan. 1, 1940, whichever came later, until either his date of death or Dec. 31, 1979, the end of the study, whichever came earlier. The PYAR were stratified by sex and race and five-year age groups, five-year calendar time periods, five-year duration of employment periods, and five-year time periods since first employment (latency). These PYAR were multiplied by the appropriate sex-, race-, age-, calendar-year–, and cause-specific death rates from the U.S. population to compute the number of expected deaths for each cause. Standardized mortality ratios (SMRs) were obtained by multiplying the ratio of the observed-to-expected deaths by 100. For each cause of death, an exact two-sided probability and 95% confidence interval (CI) was calculated assuming a Poisson distribution for the number of observed deaths.[21]

Results

Characteristics of Study Population — The study cohort consisted of 1,312 males; females were excluded since they comprised only 5% of the cohort (73 individuals), were not employed in jobs utilizing BNA, and accounted for only eight deaths. The 1,312 male workers accumulated a total of 26,341 PYAR. Vital status follow-up revealed that 73.5% of the cohort were alive, 20.0% were deceased, and 6.5% were lost to follow-up as of the end of the study period, Dec. 31, 1979 (Table 2). Death certificates were not available for 33 of the deceased workers even after extensive follow-up efforts.

Table 2 shows the distribution of the cohort by race. Thirty-two percent of the cohort (414 workers) were white and 68% (898 workers) were nonwhite. (Of this latter group, 26 workers did not have information for race recorded on their employment files and were considered to be nonwhite for purposes of our analysis.)

Dates of birth were unavailable for approximately 1% of the cohort members (11 individuals). These persons were considered to be 20 years of age at date of hire since this was found to be the mean age of hire for all new workers.

The distribution of the study population by year of hire is provided in Table 3. Many of the workers were hired between 1945 and 1949; however, more than 40% of the work force (533 workers) were hired after 1960.

The distribution of the study population by maximum possible length of observation is shown in Table 4. Approximately 50% of the work force had a possible 20 years of observation between their first employment date and the end of the study or date of death.

The distribution of the study population by duration of employment is summarized in Table 5. Approximately 50% of the cohort had worked for less than two months and more than 80% had worked for less than one year, indicating a high employment turnover rate at this plant.

Mortality Experience of Study Population — The observed and expected numbers of deaths by cause of death and

Cause of Death	7th Revision *ICD* Code	No. of Deaths: White Observed	White Expected	Nonwhite Observed	Nonwhite Expected*	Total Observed	Total Expected	SMR†	95% CI
All tuberculosis	(001-019)	0	0.5	1	4.5	1	5.0	20	1-111
All malignant neoplasms	(140-205)	12	12.0	22	25.2	34	37.2	91	63-128
Esophagus	(150)	1	0.3	5	1.7	6	2.0	300‡	110-653
Lung	(162-163)	5	4.0	8	8.6	13	12.6	103	55-176
Bladder	(181)	2	0.3	0	0.4	2	0.7	286	35-1032
Psychoneurotic disorders	(300-326)	3	0.4	4	3.2	7	3.6	194	78-401
Nervous system diseases	(330-334, 345)	4	3.6	17	12.9	21	16.5	127	79-195
Circulatory system diseases	(400-468)	34	26.6	36	49.9	70	76.5	92	71-116
Nonmalignant respiratory	(470-527)	5	3.1	6	9.0	11	12.1	91	45-163
Digestive system diseases	(540-581)	1	2.7	12	8.5	13	11.2	116	62-198
Genitourinary diseases	(590-652)	1	0.7	5	3.4	6	4.1	146	54-319
Accidental deaths	(800-962)	8	6.3	18	21.5	26	27.8	94	61-137
Violent deaths	(963, 970-985)	8	2.7	12	19.2	20	21.9	91	56-141
Unknown causes	(780-793, 795, blank)	7	0.8	26	5.8	33	6.6	500§	344-702
All other causes	. . .	2	3.9	18	14.3	20	18.2	110	67-170
All Deaths	. . .	**85**	**63.3**	**177**	**177.4**	**262**	**240.7**	**109**	96-123

Table 6 — Observed and Expected Number of Deaths by Race and Cause and Their SMR's and 95% CI for the Total Cohort of 1,312 Male Workers

*Assumes persons of unknown race are nonwhite
†SMR equals (observed deaths/expected deaths) ×100
‡*p* = 0.03
§*p* not tested for significance

Table 7 — Demographic Characteristics of Decedents With Bladder and Esophageal Cancer

Cancer	Race	Birth (mo/yr)	1st Employed (mo/yr)	Age (yr) when 1st Employed	Length of Employment (mo)	Latency* (yr)	Death (mo/yr)	Age (yr) at Death
Bladder	W	5/1900	1/1947	47	2	19	7/1966	66
Bladder	W	2/1944	5/1972	28	1	4	7/1976	32
Esophageal	B	9/1930	9/1961	31	5	14	3/1975	45
Esophageal	W	3/1922	12/1957	35	19	18	1/1975	53
Esophageal	B	7/1908	11/1952	44	1	11	6/1963	55
Esophageal	B	2/1899	1/1947	48	13	25	1/1972	73
Esophageal	B	9/1919	9/1971	52	19	5	12/1976	57
Esophageal	B	2/1912	2/1947	35	4	22	10/1969	57

* From first year employed to year of death

race of worker, along with the SMRs and 95% CI are presented in Table 6. There were 262 deaths observed in the cohort compared with 240.7 deaths expected based on U.S. mortality rates, resulting in an overall SMR of 109 for all causes. As stated previously, 33 deaths were placed in the "unknown cause" category since death certificates could not be obtained for them. This resulted in an underestimation of the risks for the other causes of death.

Mortality from cancer of all sites was lower than expected (34 deaths observed vs 37.2 expected; SMR=91). Although a deficit of cancer was observed overall, two deaths were attributed to bladder cancer compared with 0.7 deaths expected (SMR=286; 95% CI = 35 to 1,032). Six deaths were attributed to esophageal cancer compared with 2.0 deaths expected (SMR=300; 95% CI = 110 to 653); this was the only statistically significant excess risk of death found among the workers in this cohort. All other deaths due to malignant neoplasms were approximately equal to or lower than the numbers expected.

There was a nonsignificant excess risk for nonmalignant genitourinary system diseases (six observed vs 4.1 expected, SMR=146); however, none of the death certificates in this group indicated diseases of the bladder as underlying or contributory causes of death. Nonsignificant increases in mortality were also noted for psychoneurotic disorders (seven observed vs 3.6 expected; SMR=194), diseases of the digestive system (13 observed vs 11.2 expected; SMR=116), and diseases of the nervous

Table 8 — Cases of Diagnosed Bladder Cancer (CA) Among the Study Population

Case	Race	Birth (mo/yr)	1st Employed (mo/yr)	Age (yr) When 1st Employed	Length of Employment* (yr)	Latency† (yr)	Diagnosis (yr)	Age (yr) at Diagnosis	Diagnosis
1	W	3/1922	10/1945	23	27	26	1971	49	Transitional papilloma papillary CA
2	B	3/1919	10/1946	27	1	25	1971	52	Infiltrating papillary transitional CA
3	B	10/1933	8/1952	18	19	21	1973	40	Invasive carcinoma, grade III
4	W	12/1911	8/1946	35	1	27	1973	62	Invasive carcinoma
5	B	7/1926	10/1959	33	14	17	1976	50	Carcinoma, grade I
6	B	6/1949	10/1969	20	1	7	1976	27	Transitional cell CA, grade III
7	B	12/1922	5/1946	23	20	31	1977	55	Invasive carcinoma
8	W	1/1910	10/1945	35	22	34	1979	69	Papillary carcinoma, grade I
9	B	12/1940	7/1961	21	7	21	1982	42	Invasive urethral carcinoma
10	B	7/1926	5/1954	27	14	28	1982	56	Carcinoma in situ
11	B	4/1917	6/1957	40	16	25	1982	65	Carcinoma in situ
12‡	W	5/1900	1/1947	47	<1	19	1966	66	Transitional cell CA, grade II or III
13‡	W	2/1944	5/1972	28	<1	4	1976	32	Transitional cell CA, grade IV

* As of March, 1973
† From first year employed to date of diagnosis
‡ Data from Table 7

system (21 observed vs 16.5 expected; SMR = 127). All seven deaths from psychoneurotic disorders were attributed to acute alcoholism, and 11 of the 13 deaths from digestive system diseases were found to be due to cirrhosis of the liver.

Slight deficits in mortality were observed for diseases of the circulatory and respiratory systems, and for accidental and violent deaths. An appreciable deficit of deaths occurred in the tuberculosis category (one observed vs five expected; SMR = 20).

For white workers, analysis of the major causes of death revealed excess risks for diseases of the circulatory system, violent deaths, and total deaths. In contrast, nonwhite workers had deficits of deaths from diseases of the circulatory system and from violence.

The demographic characteristics for members of the cohort who died of either bladder cancer (the *a priori* hypothesis) or esophageal cancer (the only statistically significant excess risk) are presented in Table 7. One of the workers who died of bladder cancer had been employed at the facility for two months in 1947 at age 47; he died at age 66. The other bladder cancer death occurred in a worker who had been employed for less than two months at the facility in 1972 at age 28; he died at age 32. The average duration of employment for the six workers who died of esophageal cancer was 10 months; the mean time between first employment and death was 16 years.

Discussion

The authors' a priori hypothesis in this study of workers employed at a dye manufacturing facility was that there would be an excess risk of deaths due to malignancies of the bladder, because of exposure to BNA or possibly to other dye intermediates. Although only a small excess risk of bladder cancer deaths was found (two observed vs 0.7 expected), only about 15% of the total cohort may have been exposed to BNA (based on the 1972 survey). Given the proportion of workers exposed, the true risk of developing bladder cancer among the BNA-exposed workers may, therefore, be much higher, possibly in the range of observations made in the studies by Case et al[6] and Rubino et al.[8] Furthermore, if the average latency period for bladder cancer is 15 to 20 years, as has been shown in other studies,[4,6] more cases of bladder cancer may yet occur since only 50% of the cohort had been observed for 20 years or more. In fact, in a notification and screening program that is currently being conducted by NIOSH among this population,[19] an additional 11 cohort members have already been diagnosed as having bladder tumors (Table 8).

One interesting feature shown by this mortality investigation and the subsequent notification and screening project is that mortality may not always be an accurate indicator of potential health risks associated with an exposure. This is especially true when the survival rate for a disease is fairly high. Currently, survival rates at five years after detection of bladder cancer can be as high as 90% for persons with well-differentiated tumors. For bladder cancer of all types, the rates during the 1970s were approximately 72% for white males and 49% for nonwhite males.[22,23] Also, it has been shown that bladder tumors may not be recorded on death certificates as underlying or even as contributory causes of death. Case et al[6] found that 18.7% of the patients who had bladder tumors (per hospital records) had no mention of these tumors on their death certificates. Morbidity may, therefore, be a better measurement of bladder cancer risk than mortality in this cohort; this was the subject of a previous report.[19]

It was very difficult to evaluate whether exposure to BNA had contributed significantly to the deaths of the two workers who died of bladder cancer. Both workers had been employed at the facility for less than two months. Furthermore, one of the two workers terminated employment prior to the BNA production period (benzidine and other aromatic amines were being used at this time, however), and the other worker began employment within months after BNA usage had been discontinued at the facility. Although it is possible that there may have been residual BNA in the plant environment, since BNA residue can be found impregnated in wood and bricks,[3] the latter employee, who died at age 32, had also received multiple surgical and radiological procedures on his urinary tract since age 9. While the authors are unaware that prior surgery or diagnostic radiographic procedures have been associated with excess risk of bladder cancer, it is interesting to speculate whether these factors, alone or in combination with possible exposures at the facility, may have increased this individual's bladder cancer risk.

The finding of a significant excess risk for esophageal cancer was not expected, as BNA has not been shown in previous studies to affect organs other than the bladder. A possible explanation for the excess of deaths due to esophageal cancer may be excessive consumption of alcohol.[23,24] If this were the case, one would expect a significant increase in deaths due to alcoholism and cirrhosis of the liver.[25,26] There were, in fact, seven deaths attributed to alcoholism vs 2.7 deaths expected, and 11 deaths attributed to cirrhosis of the liver vs 8.7 deaths expected.

Another possible explanation for the bladder and esophageal cancer excesses is smoking.[24,27,28] As in most historical cohort studies, information regarding smoking history was not available. However, if the bladder or esophageal cancer excess were due to smoking, an increase in lung cancer mortality and nonmalignant respiratory disease among the study population would have been expected as well. In fact, neither of the two respiratory disease categories showed an excess risk of death.

Hueper[2] has described the series of epidemics of bladder cancer that has followed the introduction of synthetic dye manufacturing around the world. This report documents the mortality experience of a cohort employed in the last facility in the United States to manufacture BNA. While the results of this study did not reveal a significant excess risk of bladder cancer deaths, a previous report on the screening project demonstrated an increased risk of bladder cancer for this same population. This medical screening with appropriate therapy may possibly reduce the future number of deaths from bladder cancer. Although this is the last facility manufacturing BNA in the United States, it is not known to what extent BNA is now being manufactured or used in other countries. If BNA exposures are not adequately controlled, the international series of aromatic amine-induced bladder cancers will probably continue.

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