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Excess Number of Bladder Cancers in Workers Exposed to Ortho-Toluidine and Aniline

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A retrospective cohort study of the incidence of bladder cancer was conducted in response to a union request for an evaluation of a possible excess number of cases of bladder cancer at a chemical plant in western New York State. Workers at the plant were exposed to two potential bladder carcinogens—ortho-toluidine (*o*-toluidine) and aniline. Incidence rates of bladder cancer among workers at the plant were compared with those of the population of New York State (excluding New York City). Among all 1749 workers at the plant, 13 cases of bladder cancer were observed versus 3.61 expected [standardized incidence ratio (SIR) = 3.60; 90% confidence interval (CI) = 2.13-5.731. Among the 708 workers who worked in areas in which o-toluidine and aniline were used, 7 cases were observed versus 1.08 expected (SIR = 6.48; 90% CI = 3.04-12.2). Among the 288 maintenance, shipping, and janitorial workers thought to have been possibly exposed, 4 cases were observed versus 1.09 expected (SIR = 3.66; 90% CI = 1.25-8.37). Among the remaining 753 workers who were probably not exposed, 2 bladder cancers were observed versus 1.43 expected (SIR = 1.39; 90% CI = 0.25-4.39). Increased risk of bladder cancer was strongly associated with increased duration of employment in the department where o-toluidine and aniline were used (*P*<.001). Among workers with 10 or more years of employment in the department, the SIR was 27.2 (90% CI = 11.8-53.7). o-Toluidine is an animal carcinogen more potent than aniline and is known to produce bladder tumors in rats; hence, it is more likely that o-toluidine is responsible for the observed excess number of cases of bladder cancer, although aniline may have played a role. [J Natl Cancer Inst 83501–506,19911

Aniline-based dyes such as benzidine and beta-naphthylamine have long been

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known to be human bladder carcinogens (*1*). However, the carcinogenicity of aniline itself and of a related compound, ortho-toluidine (o-toluidine), has remained in question. In animal experiments in which the carcinogenicity of aniline and o-toluidine has been tested under similar conditions (*2,3*), aniline has been only weakly carcinogenic, whereas o-toluidine has been a more potent carcinogen. In addition, o-toluidine produced bladder tumors, whereas aniline did not.

In the only epidemiologic study of aniline, Case et al *(1)* found no evidence that workers exposed to aniline alone had an increased risk of developing bladder tumors. However, this study had only 1 case observed and 0.54 expected among workers exposed only to aniline. There are no epidemiologic studies of workers exposed to o-toluidine in the absence of other potentially carcinogenic aromatic amines. In one department of an Italian dyestuff factory, Rubino et al *(4)* reported a 62-fold increase (five incident cases observed versus 0.08 expected) in bladder cancer mortality among a group of workers exposed to o-toluidine and 4,4′-methylene-bis(2-methylaniline), a carcinogen in rats (5). One recent study *(6)* reported a 72-fold increase (eight cases observed versus 0.11 expected) in the incidence of bladder cancer among 116 workers exposed to o-toluidine in the manufacture of 4-chloro-*o*-toluidine between 1929 and 1970. The observed excess number of bladder cancer cases in this cohort was attributed to 4-chloro-*o*-toluidine, a carcinogen in mice (*7,8*), rather than to o-toluidine, because exposure to 4-chloro-*o*-toluidine was more extensive.

The International Agency for Research on Cancer (IARC) (*9,10*) has concluded, ". . . there is sufficient evidence for the carcinogenicity of o-toluidine hydrochloride in experimental animals. An increased incidence of bladder cancer has been observed in workers exposed to *o*-toluidine, but as all were exposed to other possibly carcinogenic chemicals, o-toluidine cannot be identified specifically as the responsible agent. *o*-Toluidine should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans." Regarding aniline, the IARC concluded, ". . . there is limited evidence for the carcinogenicity of aniline hydrochloride in experimental animals. The available epidemiologic data are insufficient to allow a conclusion as to the carcinogenicity of aniline."

o-Toluidine and aniline are of special interest because they are present both in mainstream cigarette smoke and, at much higher levels, in sidestream smoke *(11)*. The levels of o-toluidine and aniline in both sidestream and mainstream smoke are substantially higher than levels of the known bladder carcinogens beta-naphthylamine and 4-aminobiphenyl. For example, mainstream smoke from a commercial nonfilter cigarette has been found to contain 364 ng of aniline, 162 ng of o-toluidine, 1.7 ng of beta-naphthylamine, and 4.6 ng of 4-aminobiphenyl per cigarette *(11)*. Hence, o-toluidine and aniline may play a role in the twofold to threefold excess risk of bladder cancer observed among smokers (12) and may conceivably be a danger for passive smokers as well. To date, however, epidemiologic studies have not demonstrated an increased risk of bladder cancer among passive smokers (*13,14*).

To investigate the risk of bladder cancer among workers exposed to 0-toluidine and aniline, we have conducted a retrospective cohort study of the incidence of bladder cancer among workers exposed to these chemicals at a chemical plant in western New York State. The impetus for this study was an initial report to the National Institute for Occupational Safety and Health (NIOSH) from the union at the plant that had an apparent cluster of bladder cancers among the workers (*15*).

Plant, Processes, and Substances

The chemical plant was opened in 1946 for the production of polyvinyl chloride. Production of an antioxidant for use in tire manufacturing began in 1957 in a new building. In 1970 an expansion of the new building was completed, and production of a new rubber accelerator was begun. The antioxidant is produced by the mixing of o-toluidine, aniline, hydroquinone, and toluene. The rubber accelerator is produced by the mixing of carbon disulfide, sulfur, aniline, benzothiazole, and a proprietary chemical. Few changes have occurred in these processes over time (15).

Among the major chemicals used or formed in the two processes, only o-toluidine, aniline, and hydroquinone have been evaluated as potential carcinogens by the IARC, and only o-toluidine was classified as demonstrating sufficient evidence of carcinogenicity in animals *(10)*. Recent testing of hydroquinone in the National Toxicology Program found "some evidence of carcinogenicity" in male and female rats *(16)*. It is thought that on the basis of the reactants present, 4-aminobiphenyl, a known human bladder carcinogen (*17*), is a possible contaminant of the process. However, in bulk samples of process chemicals obtained by NIOSH in 1990, only trace amounts of 4-aminobiphenyl were found.

No exposure data were collected by the company before 1975. NIOSH conducted its own air monitoring in 1988. Both company air monitoring and monitoring conducted by NIOSH show o-toluidine and aniline levels below 1 ppm. It was not possible to separate workers exposed to o-toluidine and aniline from those exposed to aniline alone on the basis of work history records.

Study Design and Methods

We divided the study population into the following three groups for epidemiologic analysis: 1) workers ever employed in the department where o-toluidine and aniline were used, who were assumed to be definitely exposed, 2) workers in maintenance, janitorial or yard work, and shipping, who were assumed to have experienced possible exposure to *o*-toluidine and aniline, and 3) all other workers, who were not likely to have been exposed to o-toluidine and aniline.

In a study of the incidence of bladder cancer, the rate of bladder cancer among workers in the total cohort and the three exposure groups was compared with the rate in the population of New York State (excluding New York City). Personnel records were microfilmed for all workers employed at the plant since 1946, including those of office and salaried personnel. In addition, vital status information was obtained by means of review of death certificates from the company pension program, records of deaths reported to the Social Security Administration from 1962 through 1988, and current addresses ob-

tained from the Internal Revenue Service and the US Postal Service. Confirmation of bladder cancer cases identified by the company and the union was obtained through review of medical records. Additional cases were identified when the computer file of workers was matched with the New York State Cancer Registry. Medical records of individuals identified only from the registry were not requested because acceptance of a case by the registry was considered adequate documentation of the diagnosis.

The comparison group in this study is the population of New York State (excluding New York City). Bladder cancer incidence rates for males and females were obtained from the New York State Cancer Registry. A standard life-table program was used to calculate the number of observed versus expected bladder cancer cases (18). Although rates of bladder cancer in the United States are higher for white than for nonwhite males (*19*), we have combined whites and nonwhites in our analysis because the New York State Cancer Registry rates are not stratified by race. Of the 670 individuals in the cohort whose race was known, 91% were white, a percentage similar to that of whites (94%) in New York State (excluding New York City).

The New York State Cancer Registry began calculating incidence rates in 1973. Before 1973, the registry did not code *So*cial Security number, making it difficult to identify cases through computer matching. Consequently, in the analysis, person-years at risk began on January 1, 1973, or on date of starting employment, whichever occurred later. Bladder cancer cases (n = 1) occurring before that date were excluded from the analysis. Person-years at risk were accumulated to the date of diagnosis for bladder cancer case subjects, to the date of death for individuals who died of causes other than bladder cancer, and to the end date of the study for all other individuals (January 1, 1989). This end date was chosen because workers at the New York State Cancer Registry had searched its files for cases occurring through December 1988. Although the registry was able to provide incidence rates only through 1985, bladder cancer incidence rates did not change markedly during the period of 1980 through 1985. The age-specific incidence rates for 1980 through 1984 were therefore used to estimate the rates during the years 1985 through 1988.

Under the assumption of a Poisson distribution test, statistics and confidence intervals (CIs) were calculated according to the methods of Rothman and Boice ***(20)***. Ninety percent CIs were used because of the one-sided nature of the alternative hypothesis (the number of bladder cancer cases will be elevated).

For workers ever employed in the exposed department, we also calculated the standardized incidence ratio (SIR) for bladder cancer by duration of exposure and by time since first exposure (potential latency). Three categories were chosen for duration of exposure (<5 years, 5 through 10 years, and 10+ years) and time since first exposure (<10 years, 10 through 20 years, and 20+ years). Directly standardized rate ratios and tests for trend were calculated for duration of exposure by use of the NIOSH life-table program based on methods described by Rothman ***(21)***. This program used the age distribution of the entire cohort and the incidence rates in the least exposed group to generate the numbers of expected cases in the possibly and definitely exposed groups.

Cigarette smoking is the major nonoccupational risk factor for bladder cancer ***(22)***. Medical records at the company contained information about employee smoking habits, which has been collected systematically as part of the annual physical examination since the early 1980s. A 5% sample of the most recent smoking histories of current and former workers was collected.

Results

Of 1749 individuals identified from personnel records at the plant, 1643 were male and 106 were female. Members of the cohort were, in general, quite young, with 72% born after January 1, 1939, and therefore younger than the age groups (50 years and older) in which 80% of bladder cancers are diagnosed in the general population ***(23)***. As of August 1, 1988, the date the personnel records were obtained, 293 of the 1749 workers were still actively employed at the plant.

A total of 13 subjects in the cohort were identified as having had bladder cancer during the study period (1973 through 1988). Two additional cases were excluded from the analysis because they occurred in 1972 and 1989. Of the 13 case subjects included in the statistical analysis, 7 had worked in the exposed department, 4 had worked in departments considered to have possible exposure (maintenance, janitorial/yard, or shipping), and 2 had worked only in other areas probably not exposed. Both case subjects who were excluded from the analysis had worked in departments considered to have possible exposure. The characteristics of the 15 cases are summarized in Table 1.

Table 2 presents the number of observed and expected bladder cancer cases for the total cohort and for each of the exposure groups. Tables 3 and 4 examine the trends in bladder cancer risk among workers in the exposed department by duration of exposure and time since first employment in the exposed department, respectively. A test for trend indicates that the positive relationship between risk and duration of exposure is highly statistically significant. In Table 4, the highest SIR occurs in the category 20+ years since first employment in the exposed department. The mean latency period for all seven case subjects in the department is 23 years, consistent with the mean or median latent period of 20 years for occupational bladder cancer ***(24)***.

Among the 143 workers whose smoking histories were obtained, 41 (28.7%) had never smoked, 62 (43.4%) were current smokers, and 40 (28.0%) were former smokers. The average year to which the smoking histories applied was 1984, so the smoking habits of white males in the United States in 1983 were used for comparison ***(25)***. Comparable smoking prevalence rates in the US population, when directly standardized to the age distribution of the cohort, were 32.2% for those who had never smoked, 36.8% for current smokers, and 31.0% for former smokers. Thus, cohort members were slightly more likely to be current or former smokers than was the general US population. This characteristic is frequently associated with occupational cohorts ***(26)***. The excess risk of bladder cancer based on this difference in smoking habits alone (assuming no occupational risks) was estimated by the method

Table 1. Characteristics of bladder cancer cases among chemical workers by exposure group

Exposure group	Case No.	Year of first exposure	Duration of exposure.* y	Latency. y	Year of diagnosis	Age at diagnosis	Stage	Source of case?	Pathology	Vital statistics/y
Definitely exposed	1	1970	1t	16	1986	71	1	R	Unknown	Alive/1989
	2	1957	18	23	1980	61	I	P, R	Grade 1 papillary tumor	Alive/1989
	3	1957	25	25	1982	57	3	P, R	Adenocarcinoma	Died/1983
	4	I957	21	21	1978	43	I	P, R	Grade 2 papillary transitional cell carcinoma	Died/1982
	5	1961	10	25	I986	53	I	P, R	Grade 2 papillary transitional cell carcinoma	Alive/1989
	6	1957	13	23	1980	56	2	P. R	Grade 2 papillary transitional cell carcinoma	Alive/1989
	7	1957	7	31	1988	64		P	Multiple grade 2 or 3 papillary transitional cell carcinoma	Alive/1989
Possibly exposed: worked in maintenance, janitorial/yard. shipping	8	1957	11	25	1986	60	3	R	Grade 2 papillary transitional cell carcinoma	Alive/1989
	9	1963	9	10	1973	56	I	P, R	Unknown	Died/1989
	10	1979	5	5	1984	52	I	P, R	Grade 1 or 2 papillay transitional cell carcinoma	Alive/1989
	11	I968	I	9	1978	64	1	R	Unknown	Alive/1989
Probably not exposed	12				1975	46		R	Unknown	Alive/1989
	13				1983	64	3	R	Unknown	Alive/1988
Not included in analysis	14	1957	15	15	1972	44		P, R	Grade 3 transitional cell carcinoma	Died/1986
	15	1979	8	9	I989	60	I	P	Grade 2 papillary transitional cell carcinoma	Alive/1989

*Duration of exposure includes only the period before diagnosis. For individuals who worked in the exposed department, duration of exposure includes only time in that department. For workers in "possibly exposed" jobs, duration of exposure includes only time spent in those jobs.

†R = case identified from the New York State Cancer Registry; P = case reported by company or union.

Table 2. Observed and expected numbers of bladder cancers among chemical workers by exposure group

Probability of exposure to o-toluidine and aniline	No. of persons	Bladder cancers		SIR	90% CI
		Observed	Expected		
Definitely exposed	708	7	1.08	6.48	3.04-12.2
Possibly exposed	288	4	1.09	3.66	1.25-8.37
Probably unexposed	753	2	1.43	1.39	0.25-4.39
Total	1749	13	3.61	3.60	2.13-5.73

Table 3. Trends in bladder cancer risk by duration of employment in exposed department

Duration of exposure, y	No. of persons)	Bladder cancers		SIR†	90% CI
		Observed	Expected		
<5	584	0	0.75	—	—
5-9.99	51	1	0.11	8.8	0.45-41.7
10+	73	6	0.22	27.2	11 8-51 7

*No. of persons whose duration of employment (as of the study end date. the date of diagnosis. or date of death) was in the category stated.

†Directly standardized rate ratios were 1.00. 3.31. and 16.0 (with low exposure group as referent). Test for linear trend was highly significant ($P < .001$).

described by Axelson and Steenland **(27).** Risk ratios for bladder cancer of 1.0 for those who had never smoked. 1.7 for former smokers, and 2.9 for current smokers were taken from a recent case-control study (*12*). We found that the differences in smoking habits between the cohort and the US population would account for an SIR of 1.05 for bladder cancer.

Discussion

This investigation found a significant risk of bladder cancer among workers who were ever employed at the study plant. Of the 13 bladder cancer cases, 8 were initially reported to **NIOSH** by the union; 7 of the 8 original cases were independently identified by the New York State Cancer Registry. **An** additional 5 cases were identified from the cancer registry. The toxicologic literature clearly implicates o-toluidine and aniline as potential bladder carcinogens. The risk of bladder cancer was highest among workers considered to have definite exposure to o-toluidine and aniline. intermediate among workers considered to have possible exposure, and lowest among workers considered unexposed. The risks among those definitely exposed increased with duration of exposure and time since first exposure. strengthening the observed association.

There are several methodological reasons that our study would tend to under-

Table 4. Trends in bladder cancer risk by time since first employment in exposed department

Time since first employment in exposed department, y	No. of persons*	Bladder cancers		SIR	90% CI
		Observed	Expected		
<10	196	0	0.22	—	—
10-20	364	1	0.49	2.03	0.10-9.64
20+	148	6	0.37	16.4	7.13-32.3

*No. of persons whose time since first employment (as of the study end date. the date of diagnosis, or date of death) was in the category stated.

estimate the risk of bladder cancer. First, we may have missed cases that occurred among former workers who have moved out of New York State. Records of the Internal Revenue Service indicate that currently approximately 28% of cohort members have addresses outside New York State. Although bladder cancer cases could have been identified from death certificates for individuals who had moved outside New York State, no such cases were found. Second, we assumed that all cohort members not known to have died or to have developed bladder cancer were alive and free of disease until the end of the study. Moreover, the age structure of the plant population and the relatively brief history of the use of *o*-toluidine and aniline at the plant suggest that the full expression of the bladder cancer risk may not yet be realized.

Because o-toluidine appears to be a more potent carcinogen than aniline in animals (*2,3*), it appears more likely that the bladder carcinogen in this plant is *o*-toluidine, but the possibility that aniline also contributed to the excess number of cases cannot be excluded. Contamination by 4-aminobiphenyl is an unlikely cause of the excess number of bladder cancer cases because 4-aminobiphenyl levels were so low in the bulk samples analyzed by NIOSH. Historical air-monitoring data for o-toluidine and aniline do not exist for the years before 1975, making it difficult to estimate past exposure. In addition, air monitoring does not reflect dermal absorption, probably an important route of exposure for both chemicals (28). Preliminary results from a NIOSH exposure survey conducted at the study Plant in March 1990 show elevated levels of o-toluidine and aniline in the urine of exposed workers compared with those in control subjects, suggesting that workers are exposed to these chemicals despite low air concentrations.

It is reasonable to consider the link between o-toluidine and human bladder cancer considerably strengthened by this study and sufficient to warrant the recommendation that exposure to o-toluidine be minimized. Since aniline may have contributed to the excess number of bladder cancers, it would be prudent to reduce exposure to aniline as well. NIOSH (unpublished provisional data as of January 1, 1990) estimates that during the period 1981 through 1983, 28 500 workers were potentially exposed to o-toluidine and 35 800 workers were potentially exposed to aniline. The potential carcinogenicity of *o*-toluidine and aniline is of broader significance than the occupational setting, since both compounds are present in significant amounts in cigarette smoke (*11*) and have been found in the urine of both smokers and nonsmokers in the general population ***(29)***.

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