Exhibit 294

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

1984, U.S. Department of Health and Human Services;
Journal of the National Cancer Institute

J Natl Cancer Inst 1984; 72: 973-981

May, 1984

SECTION: INVESTIGATIONS ON MAN

LENGTH: 6087 words

TITLE: Case-Control Study of Bladder Cancer in New Jersey. I. Occupational Exposures in White Males <1,2,3>

AUTHOR: Janet B. Schoenberg, M.P.H., <4> Annette Stemhagen, Dr. P.H., <4> Alexander P. Mogielnicki, M.A., <4> Ronald Altman, M.D., M.P.H., <4> Toshi Abe, M.S.W., <4> and Thomas J. Mason, Ph.D. <5,6>

ABSTRACT: The occupational bladder cancer risk for New Jersey white males was estimated with the use of both industry-job title-based and exposure-based analyses of data from 658 incident cases and 1,258 general population controls. The overall bladder cancer risk attributable to occupational exposures was estimated as 20-22%. A wide variety of employment categories and exposures contributed to this risk. Odds ratios were significantly high for employment as garage and gas station workers and food counter workers and/or cooks and for exposure to leather, rubber, paint, printing ink, and other organic compounds. Odds ratios for textile mill workers, chemical workers, and metal workers for the a priori high-risk employment category and odds ratios for those exposed to dyes, chlorinated compounds, and rubber showed significant differences between younger and older subjects. Bladder cancer risk associated with occupational exposures was not limited to persons with initial exposures before 25 years of age. However, there was significantly decreasing risk for bladder cancer with increasing age at first exposure for chemical workers and metal workers and for the a priori high-risk materials and metals. Drivers and/or deliverymen and miscellaneous laborers had significantly increasing bladder cancer risk with increasing duration of employment.

TEXT:

Occupational exposures have long been recognized as risk factors for bladder cancer [n1-n4]. Industry specific studies have shown high bladder cancer rates among dyestuff workers, rubber workers, electric cable workers, gas workers, and pesticide applicators [n5-n14]. Case-control studies have suggested increased risk in workers exposed to dyes, inks, rubber, leather, paint, petroleum products, plastics, and other chemicals and in textile workers, metal workers, **hairdressers,** truck drivers, and cooks and kitchen and counter workers [n15-n21].

A National Cancer Institute study of the geographic distribution of bladder cancer mortality in the United States for 1950-69 showed that the age-adjusted mortality rate for white males in New Jersey was the highest of all state rates [n22]. Of New Jersey's 21 counties, 18 had bladder cancer mortality rates in the highest 10% of all U.S. counties. The excess mortality was suspected to be related to New Jersey's high density of chemical manufacturing industries. This hypothesis was

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

supported by further national studies that showed a correlation between bladder cancer mortality and concentrations of chemical industries [n23,n24].

The study reported in this paper includes New Jersey white male subjects from a national case-control interview study that assessed the role of artificial sweeteners in relation to incident bladder cancer [n25]. Detailed occupational data also were collected. The major purpose of our analyses was to determine the association of occupational exposures to present-day bladder cancer risk in this state. We also considered various temporal aspects of occupational exposure, including age at first exposure, latency, and duration.

SUBJECTS AND METHODS

Subjects. -- Methods used for selection of New Jersey bladder cancer patients and controls were similar to those previously reported by Hoover et al. [n25] for the entire national study. The New Jersey male patients included residents 21-84 years of age who were newly diagnosed with a histologically confirmed carcinoma of the urinary bladder (or papilloma not specified as benign) in a 1-year period beginning February 1, 1978. Case identification was facilitated by a mechanism whereby incident cases could be reported within 72 hours of diagnosis; hospital pathology records also were searched for additional cases.

Controls 21-64 years old were an age-stratified random sample of males identified by random digit dialing [n26]. Controls 65-84 years old were an age-stratified random sample of males registered with the Health Care Financing Administration for Medicare. Controls were not frequency matched by county within New Jersey or by race, which was determined at the time of the interview. The overall ratio of controls to cases for New Jersey males was 1.7:1. To allow for potential county-specific comparisons, we sampled additional controls by the same methods and stratified them by county so that the control-to-case ratio for each age-county group would be at least 1:1.

Refusal and cooperation rates were similar to those previously reported for the entire national study [n25]. Of the 787 male cases identified and available for interview, 706 (89.7%) were interviewed. Of the 1,608 male controls identified and available, 1,392 (86.6%) were interviewed. Some subjects (20 cases, 38 controls) were excluded from further analysis because their interviews were incomplete or judged unreliable. The small numbers of black males (29 cases, 96 controls) were excluded from these analyses, leaving 658 white male cases and 1,258 white male controls.

Interviews. -- Personal interviews of subjects were conducted in their homes by trained interviewers; there were no next-of-kin respondents. Questionnaire items included demographic data and information on a variety of personal and environmental risk factors. Subjects were questioned about the usual number of filter and/or nonfilter cigarettes smoked per day and the years during which they smoked cigarettes. Information also was obtained for each of the jobs held for 6 months or more since 12 years of age. This included the name and address of employer, type of business, job title, duties performed, materials handled, and time period of employment and whether the job was full-time or part-time. Subjects were then shown lists of industries, employers, and materials to elicit information not initially recalled. All industry and job title information was coded with the use of the 1970 Census Index System [n27]. Materials were coded by use of a classification system designed for the national study.

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

Using the industry and job title codes, we defined 19 employment categories known or suspected to be high risk for bladder cancer or with probable exposure to known or suspect bladder carcinogens. The industry-specific employment categories were carefully designed by persons with expertise in industrial hygience to exclude job titles (e.g., clerical, administrative) that were unlikely to have substantial exposures. We also classified subject-reported exposures to known or suspect carcinogens into 13 groups of materials. The composition of these employment categories and material groups have been summarized in two tables, which are available from the authors upon request.

Employment categories or materials known to be high risk for bladder cancer, on the basis of our assessment of the literature, were combined into either an a priori high-risk employment category or an a priori high-risk material group (*see* footnote *b,* tables 1 and 3). Later, we defined two a posteriori categories as "selected high risk"; they included any employment category or material group found in these analyses to have an overall odds ratio greater than 1.0 (*see* footnote, *c,* tables 1 and 3). Similar analyses were performed for all specific categories and for the four summary categories, except that we considered estimation of significance or confidence limits inappropriate for the two a posteriori categories.

TABLE 1. -- *Odds ratios, with 95% confidence limits (CL), and PAR for association of bladder cancer with employment categories in New Jersey white males* n1

Ever employed as:	No. of cases	No. of controls	Odds ratio	(95% CL)	PAR, %
Leather workers n2,n3	19	19	1.78	(0.91, 3.47)	0.8
Rubber workers n2,n3	14	12	2.15	(0.95, 4.85)	1.2
Textile mill workers n2	12	31	0.61	(0.30, 1.24)	0.4
Fabricated textile workers n2,n3	28	31	1.67	(0.97, 2.87)	1.4
Chemical workers n2,n3	50	91	1.05	(0.73, 1.53)	1.8
Painters and/or artists n2,n3	39	42	1.53	(0.96, 2.44)	1.8
Printing workers n2	20	38	0.87	(0.49, 1.54)	0.2
Boiler workers	24	48	0.94	(0.56, 1.59)	0.2
Petroleum refinery workers n3	13	19	1.34	(0.64, 2.82)	0.4
Garage and/or gas station workers n3	43	36	2.35	(1.47, 3.78)	3.6
Motor vehicle mechanics n3	55	79	1.26	(0.87, 1.84)	1.5
Drivers and/or deliverymen n3	175	284	1.16	(0.93, 1.46)	3.4
Dry cleaning workers n3	7	10	1.33	(0.50, 3.58)	0.4
Agricultural workers n3	93	154	1.16	(0.87, 1.55)	2.4
Metal workers n3	65	99	1.08	(0.77, 1.52)	2.0
Barbers and/or **hairdressers** n3	12	17	1.27	(0.59, 2.73)	0.4
Food counter workers and/or cooks n3	46	50	1.79	(1.17, 2.74)	2.8
Chemists and/or					

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

technicians, miscellaneous n3,n4	18	34	1.42	(0.77, 2.62)	1.2
Laborers, miscellaneous n3,n4	55	80	1.19	(0.82, 1.72)	1.4
A priori high-risk employment	157	245	1.20	(0.95, 1.52)	4.0
Selected high-risk employment	433	704	1.46	-	19.8

n1 Odds ratios from prospective logistic regression model including all 19 employment categories with adjustment for age and duration of cigarette smoking. Model with a priori high-risk employment category included 12 other non a priori employment categories. Model with selected high-risk employment category included 3 other non-high-risk employment categories. -- =CL not calculated for a posteriori category (*see* text).

n2 Employment categories included in the a priori high-risk employment category.

n3 Employment categories included in the selected high-risk employment category.

n4 Miscellaneous chemists and technicians, or laborers, do not include those chemists or laborers already included in specific industry categories, such as chemical workers.

TABLE 3. -- *Odds ratios, with 95% confidence limits (CL), and PAR for association of bladder cancer with material exposure groups in New Jersey white males* n1

Ever exposed to:	No. of cases	No. of controls	Odds ratio	(95% CL)	PAR, %
Leather materials n2,n3	34	31	1.88	(1.11, 3.16)	2.1
Rubber n2,n3	32	37	1.69	(1.02, 2.81)	2.8
Dyes n2,n3	40	57	1.10	(0.70, 1.72)	1.4
Known bladder carcinogens n2,n3	18	22	1.55	(0.76, 3.16)	1.4
Paint n2,n3	111	144	1.56	(1.15, 2.12)	5.9
Printing ink n2,n3	42	53	1.59	(1.03, 2.47)	2.6
Coal materials n3	88	116	1.36	(0.99, 1.85)	3.3
Petroleum materials n3	236	405	1.13	(0.91, 1.42)	3.6
Chlorinated compounds	61	93	1.32	(0.91, 1.92)	2.8
Pesticides n3	40	61	1.12	(0.72, 1.74)	0.5
Organic solvents	48	74	0.76	(0.57, 1.02)	- n4
Other organic compounds n3	90	126	1.38	(1.00, 1.89)	3.7
Metal	209	446	0.75	(0.61, 0.94)	- n4
A priori high-risk materials	217	286	1.70	(1.34, 2.15)	13.6
Selected high-risk materials	411	676	1.52	- n5	22.3

n1 Odds ratios from prospective logistic regression model including all 13 material groups, with adjustment for age and duration of cigarette smoking. Model with a priori high-risk materials group included 7 other non a priori materials. Model with selected high-risk materials group included 2 other non high-risk materials.

n2 Materials groups included in the a priori-high-risk materials group.

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

n3 Materials groups included in the selected high-risk materials group.

n4 PAR calculation results in a negative value.

n5 Confidence limits not calculated for a posteriori category (*see* text.)

Data analysis. -- We calculated odds ratios and 95% confidence limits by multiple logistic regression analysis [n28,n29]. Our basic model included either 19 exposure terms, one for each employment category, or 13 exposure terms, one for each group of materials. We also estimated age-specific odds ratios (ages <65, >=65 yr) and age-specific PAR percents. These were used to calculate the overall age-adjusted PAR percent [n30].

After analyses that included all subjects ever employed or exposed, we also considered temporal aspects of exposure: 1) first exposure before 25, between 26 and 40, and after 41 years of age; 2) latency of <20, 20-39, 40-59, and >=60 years; and 3) duration of <2, 2-4.9, 5-9.9, 10-19.9, and >=20 years. We also tested the trend in odds ratios for the temporal subgroups. One control with unknown age at first exposure and latency was excluded from these analyses. The few exposure periods of unknown duration were assigned the minimum duration of 6 months.

In all models, we included duration of cigarette smoking (never, <=30 yr, >30 yr, unknown yr) as well as age. Duration provided slightly better control than did intensity for confounding by smoking. Adding the variables previous bladder or kidney infection, family history of urinary tract cancer, coffee consumption, education, and use of artificial sweeteners did not change any of the elevated odds ratios by more than 10%; therefore, these variables were not included in the final models as confounders.

RESULTS

The odds ratios and PAR (%) estimates for all employment categories in white males are shown in table 1. Garage and gas station workers and food counter workers and/or cooks had significantly high odds ratios. Leather workers, rubber workers, fabricated textile workers, and painters and/or artists also had odds ratios greater than 1.5.

To further define occupational bladder cancer risk, we divided some of the 19 employment categories into two or more subcategories (table 2). The odds ratio for food counter and fountain workers was significantly high, while those for leather tanning and finishing workers, shoe repairmen and bootblacks, and artists were greater than 1.5. Although these results suggested some interesting differences within employment categories, most of the subsequent analyses were done with only the original 19 categories to limit the size of the logistic models.

TABLE 2. -- *Odds ratios, with 95% confidence limits (CL), and PAR for association of bladder cancer with employment subcategories in New Jersey white males* n1

Ever employed as:	No. of cases	No. of controls	Odds ratio	(95% CL)	PAR, %
Leather workers					
Leather tanning and finishing workers	4	3	2.74	(0.59, 12.69)	0.3
Leather products workers	6	9	1.22	(0.42, 3.60)	0.1

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

Shoe repairmen and/or boot blacks	9	8	1.87 (0.68, 5.11)	0.5
Chemical workers				
Plastics workers	12	18	1.42 (0.65, 3.06)	1.3
Paint manufacturing workers	7	10	1.10 (0.40, 3.04)	0.2
Miscellaneous chemical workers	28	52	1.01 (0.62, 1.66)	0.9
Other chemical (e.g., drug and soap) workers	7	16	0.79 (0.32, 1.96)	-
Painters and/or artists				
Painters	34	39	1.39 (0.85, 2.28)	1.3
Artists	5	3	4.01 (0.92, 17.44)	0.5
Drivers and/or deliverymen				
Bus drivers and/or conductors	20	27	1.17 (0.63, 2.17)	0.4
Deliverymen, routemen	95	146	1.23 (0.92, 1.64)	2.9
Taxicab drivers	25	35	1.36 (0.79, 2.34)	0.7
Truck drivers	70	114	1.06 (0.76, 1.48)	0.8
Metal workers				
Primary metal workers	37	54	1.12 (0.71, 1.76)	1.1
Fabricated metal workers	29	53	0.85 (0.53, 1.39)	0.7
Food counter workers and/or cooks				
Food counter workers, fountain workers	23	18	2.64 (1.38, 5.05)	2.1
Cooks	24	33	1.34 (0.77, 2.34)	0.8

n1 Odds ratios from prospective logistic regression model, including 13 original employment categories (as in table 1) and 17 subcategories defined from the remaining 6 employment categories. -- =PAR calculation results in a negative value.

The odds ratios and PAR (%) estimates for all materials groups in white males are shown in table 3. The odds ratios for exposure to leather, rubber, paint, printing ink, and other organic compounds and for a priori high-risk materials were significantly high, while the odds ratio for exposure to metals was significantly low.

To determine if the addition of extra controls selected by county-specific sampling methods had affected any of the results shown in tables 1 and 3, we reestimated all odds ratios and PAR (%) values using only the original control sample. Only the odds ratio for agricultural workers changed by more than 10% of the initial estimate, increasing to 1.30 (0.97, 1.75), while the PAR estimate increased to 3.3%. These increased values reflected a higher proportion of rural residents among the additional controls than in the original control sample. The PAR estimates also increased for several other categories: motor vehicle mechanics, to 1.9%; petroleum materials, to 4.7%; and other

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

organic compounds, to 4.1%. All of these changes were relatively minor; therefore, the total control sample was included in all subsequent analyses.Isee text.)

Table 4 shows age-specific odds ratios for all four summary categories and for those individual categories with significant differences in occupational risks for bladder cancer between young and old subjects. Textile mill workers, chemical workers, and metal workers, the a priori high-risk employment category, and exposure to dyes and chlorinated compounds had odds ratios significantly higher among younger than older subjects. The odds ratio was significantly higher among older than younger subjects for exposure to rubber.

TABLE 4. -- *Age-specific odds ratios and PAR for association of bladder cancer with employment categories or with material exposure groups in New Jersey white males* n1

Exposure category	Age, yr	No. of cases	No. of controls	Odds ratio	PAR, % n1	*X*<2> (*P*) n3
Ever employed as:						
Textile mill workers	<65	8	7	1.86	1.0	6.46 (.01)
	>=65	4	24	n4 0.25	-	
Chemical workers	<65	33	44	1.60	4.2	5.37 (.02)
	>=65	17	47	0.64	-	
Metal workers	<65	30	35	n4 1.81	4.5	5.09 (.02)
	>=65	35	64	0.80	-	
A priori high-risk employment	<65	81	110	n4 1.55	9.1	4.66 (.03)
	>=65	76	135	0.92	-	
Selected high-risk employment	<65	201	333	1.79	30.3	-
	>=65	232	371	İ.23	11.6	
Ever esposed to:						
Rubber	<65	11	25	0.82	-	7.73 (.005)
	>=65	21	12	n4 3.81	4.9	
Dyes	<65	29	32	1.60	3.1	4.39 (.04)
	>=65	11	25	0.57	-	
Chlorinated compounds	<65	46	54	n4 1.77	6.4	4.93 (.03)
	>=65	15	39	0.70	-	
A priori high-risk materials	<65	120	155	n4 1.83	17.5	0.35 (.56)

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

	>=65	97	131	n4 1.59	10.6
Selected high-risk materials	<65	209	351	1.80	31.5
	>=65	202	325	1.35	15.0

n1 *See* footnote a, tables 1 and 3. Logistic models included an age X exposure interaction term for each employment category or material group. *X*<2> of interaction term reflects significance of difference in occupational risks between young and old subjects. n4, *P*<.05.

n2 -- =*See footnote* d, table 3.

n3 -- =significance test not conducted for a posteriori categories (*see* text).

Tables 5-7 show the results of analyses considering temporal factors of employment or exposure. Results are shown for all four summary categories and for those specific categories either with significant trends in odds ratios or with significantly high odds ratios in any subgroup with at least 5 cases and 5 controls.

TABLE 5. -- *Odds ratio for bladder cancer association with employment categories or with material exposure groups, by age at first exposure, in New Jersey white males* n1

Exposure category	Exposed age, yr <=25	26-40	>=41	*X*<2> trend (*P*) n2
Employment				
Chemical workers	1.45	0.98	n3 0.24	5.95 (.01)
Painters and/or artists	n4 1.89	0.67	n3 2.49	0.13 (.72)
Garage and/or gas station workers	n4 2.15	n3 5.44	n3 4.75	1.31 (.25)
Metal workers	1.44	1.01	n3 0.16	10.19 (.001)
Food counter workers and/or cooks	n4 1.89	1.59		0.02 (.90)
A priori high-risk employment	n4 1.37	0.92	0.79	2.75 (.10)
Selected high-risk employment	1.49	1.46	1.02	-
Materials				
Leather materials	n4 1.90	n4 3.35	n3 0.46	0.45 (.50)
Paint	n4 1.67	n4 1.71	0.82	2.22 (.14)
Printing ink	n4 1.73	1.18	2.12	0.01 (.91)
Coal materials	n4 1.48	1.21	0.91	0.64 (.42)
Petroleum materials	1.00	n4 1.92	0.57	0.02 (.90)
Other organic				

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

compounds	1.46	n4 2.17	1.01	0.25 (.61)
Metal	0.88	n4 0.49	n4 0.40	6.47 (.01)
A priori high-risk materials	n4 1.99	n4 1.65	0.75	7.27 (.007)
Selected high risk materials	1.63	1.49	0.76	-

n1 *See* footnote a, tables 1 and 3. Logistic models included three terms (exposed age <=25, age 26-40, age >=41 yr) for each exposure.

n2 *X*<2> for linear trend in the logarithm of the relative risks.

n3 <5 cases or 5 controls in this subgroup. *Number between columns* indicates odds ratio for exposed ages 26-40 and >=41 yr old combined -- =*see footnote* c, table 4.

n4 *P*<.05.

TABLE 6. -- *Odds ratios for bladder cancer association with employment categories or with material exposure groups, by latency since first exposure, in New Jersey white males* n1

Exposure category	Latency, yr				*X*<2> trend (*P*) n2
	<20	20-39	40-59	>=60	
Employment					
Garage and/or gas station workers	n3 3.06	n3 3.16	1.66		1.14 (0.29)
Food counter workers and/or cooks	n4 5.18	0.85	n3 3.33	n4 1.34	0.21 (0.65)
A priori high-risk employment	0.94	n3 1.57	1.01	1.22	0.23 (0.63)
Selected high-risk employment	1.82	1.36	1.49	1.39	-
Materials					
Rubber	n4 0.66	1.26	n3 2.50	n4 8.03	4.55 (0.03)
Leather materials	n4 3.52	n3 3.02	1.38	1.34	1.42 (0.23)
Printing ink	1.21	n3 2.92	1.16		0.23 (0.63)
Chlorinated compounds	1.83	n3 1.93	0.69	n4 0.56	3.38 (0.07)

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

A priori high-risk materials	1.16	n3 1.78	n3 1.76	n3 2.26	1.88 (0.17)
Selected high-risk materials	1.22	1.57	1.56	1.37	-

n1 *See footnote* a, tables 1 and 3. Logistic models included four terms (latency 20, 20-39, 40-59, >=60 yr) for each exposure.

n2 *See footnote* b, table 5.

n3 *P*<.05. *Numbers between columns* indicate odds ratio for latency 40-59 and >=60 yr combined.

n4 odds ratios indicate <5 cases or 5 controls in this subgroup. -- =*see footnote* c, table 4.

TABLE 7. -- *Odds ratios for bladder cancer association with employment categories or with material exposure groups, by duration of exposure, in New Jersey white males* n1

Exposure category	Duration, yr					*X*<2> trend (*P*) n2
	<2	2-4.9	5-9.9	10-19.9	>=20	
Employment						
Painters and/or artists	1.65	0.97	1.71	1.87	n3 3.23	2.81 (0.09)
Garage and/or gas station workers	1.58	n3 5.02	n4 4.08		0.63	0.56 (0.45)
Motor vehicle mechanics	n3 2.96	0.82	1.34	0.77	2.31	0.23 (0.63)
Drivers and/or deliverymen	0.88	0.96	0.94	n3 1.81	n3 1.65	4.83 (0.03)
Agricultural workers	1.61	1.18	0.85	1.01	n3 2.30	1.17 (0.28)
Food counter workers and/or cooks	n3 2.14	1.51	n4 3.24		0.93	1.99 (0.16)
Laborers, miscellaneous	0.77	1.11	1.54		6.80	4.56 (0.03)
A priori high-risk employment	1.33	1.12	1.33	1.21	1.34	0.02 (0.88)
Selected						

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

high-risk employment	1.04	1.14	1.42	1.78	1.85	-
Materials						
Paint	n3 2.53	1.26	1.71	1.37	1.66	0.89 (0.35)
Coal materials	0.90	1.18	n3 2.14	1.51	1.65	0.86 (0.35)
Chlorinated compounds	0.63	1.61	1.34	1.44	n3 2.01	1.85 (0.17)
Other organic compounds	n3 3.34	1.12	0.84	1.57	1.37	0.02 (0.90)
A priori high-risk materials	n3 3.19	n3 1.57	1.65	1.33	n3 1.51	1.31 (0.25)
Selected high-risk materials	1.35	1.53	1.58	1.73	1.45	-

n1 *See footnote* a, tables 1 and 3. Logistic models included five terms (duration <2, 2-4.9, 5-9.9, 10-19.9, >=20 yr) for each occupational exposure category.

n2 *see footnote* b, table 5.

n3 $P<.05$.

n4 odds ratios indicate <5 cases or 5 controls in this subgroup. *Numbers between columns* indicate odds ratio for durations 10-19 and >=20 yr combined. -- =*see footnote* c, table 4.

Table 5 shows results of the analyses by age at first exposure. There were several significantly high odds ratios for employment or material exposure before 25 years of age and for material exposure for those between 26 and 40 years of age. Exposure to metal for those between 26 and 40 years old and for those over 40 years old had significantly low odds ratios. Significantly decreasing trends in bladder cancer risk by age at first exposure were found for employment as chemical workers and metal workers and for exposure to metal and to a priori high-risk materials.

Table 6 shows the results of the analyses by latency. Garage and gas station workers had significantly high odds ratios for both latent periods less than 20 and 20-39 years. Other employment categories and materials had significantly high odds ratios for latent periods 20-39 or 40-59 years. The a priori high-risk material group had significant odds ratios for all but the shortest latent period. Only exposure to rubber had a significant increasing trend in bladder cancer risk with latency.

Table 7 presents results of analyses by duration of exposure. There were significantly high odds ratios for duration of more than 20 years for painters and/or artists, agricultural workers, drivers and/or deliverymen, and those exposed to chlorinated compounds and to a priori high-risk materials. Significantly high odds ratios were found also in each of the other duration periods. Notably, garage and gas station workers had a significantly high odds ratio for duration 2-4.9 years; few cases or controls were employed in this category for more than 5 years. Both drivers and/or

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

deliverymen and miscellaneous laborers had a significant increasing linear trend in bladder cancer risk by duration. The selected high-risk employment category also had odds ratios increasing consistently with duration.

We also conducted simultaneous analyses by latency and duration. There were no consistent patterns in odds ratios other than those shown for latency and duration separately. We found no evidence for an inverse association between latency and duration.

DISCUSSION

We used both industry-job title-based and exposure-based analyses of our case-control data to estimate occupational bladder cancer risk. We found PAR of 4.0% based on a priori high-risk employment, of 13.6% based on reported exposure to a priori high-risk materials, of 19.8% based on selected high-risk employment, and of 22.3% based on reported exposure to selected high-risk materials. Both of the a priori categories exclude several suspect employment categories or materials that had elevated odds ratios in our study. Therefore, the two a posteriori values of 20-22% may better estimate the overall white male bladder cancer risk attributable to occupational exposures in New Jersey in 1978.

The PAR estimate of 20% means that the ageadjusted bladder cancer incidence rate of 46/100,000 white males at risk between 21 and 84 years of age would be reduced to 37/100,000 if all of these occupational exposures could be eliminated. The estimates of 20-22% are slightly higher than the estimate of Cole et al. [n17] of 18% for bladder cancer risk attributable to occupational exposure in eastern Massachusetts. They cannot be directly compared with results from the Canadian study by Howe et al. [n18], which reported separate, not additive, PAR estimates of 8% for exposure to a priori high-risk industries (defined differently from ours) and of 19% for exposure to dust or fumes other than in the a priori suspect industries.

Contrary to our expectations based on earlier studies [n1-n2,n5-n8,n23-n24], this study of incident bladder cancer cases in 1978 did not show a strong overall association between bladder cancer risk and chemical industry employment. We did find a significantly higher risk in younger than in older chemical workers and a significantly decreasing trend in risk with increasing age at first employment. The subcategories plastics workers and "miscellaneous chemical workers," including both inorganic and organic chemical workers, contributed most to these findings. Review of the occupational histories of the miscellaneous chemical workers did not suggest that we missed a very high risk concentrated only in the organic chemical workers.

The other individual employment categories and materials that contributed to the overall occupational bladder cancer risk in New Jersey white males in 1978 were quite diverse, and no single category predominated. The significantly high odds ratios for garage and gas station workers and for drivers and/or deliverymen employed more than 10 years are especially worth noting in view of the Detroit study findings on truck drivers [n21]. Because of multiple comparisons, the statistical significance of some of our risk estimates may be due to chance. This occurrence is less likely with findings that are consistent with results of several previous studies, for example, the significant odds ratios for leather, rubber, and paint exposures. The significantly high odds ratio for food counter and fountain workers (table 2) is consistent with that of one previous study [n17]; however, the etiologic exposure associated with this employment category is unknown, so the possibility of a chance finding still cannot be ruled out. Furthermore, the inclusion of chance

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

associations in the calculation of the a posteriori PAR values of 20-22% may have led to an overestimate of the PAR.

We used logistic regression analysis to control not only for confounding by age and by cigarette smoking but also for confounding of one occupational risk factor by another. For example, confounding by exposures to leather and to other organic compounds appreciably reduced the odds ratios for dyes and for known bladder carcinogens (from 1.4 and 2.0, respectively).

As with all retrospective case-control data, misclassification may affect our findings, particularly from the exposure-based analyses [n31]. Recall bias may be a factor in the apparent inconsistency between the low odds ratio for printing workers and the high odds ratio for printing ink. Among printing workers, most of the cases reported exposure to printing ink, whereas many controls did not report such exposure although it might be inferred from their description of job duties.

Our concerns about the validity of self-reported material exposure might lead us to put more weight on the results of the employment analysis. However, exposure-based analyses have some advantages over industry-job title-based analyses [n32]. The combination of subjects from several occupational groups according to their actual exposures may increase the power and precision of the analysis. This point is particularly illustrated by comparison of our findings for leather materials versus leather workers and for paint versus painters (tables 1, 3). Another example is the significantly high odds ratio for initial petroleum exposure for those between 26 and 40 years old, a pattern seen to a lesser extent in each of the petroleum-related job categories.

However, some materials may be associated with greater risk in a specific job. Pooling material exposures from different jobs may dilute a high risk. The low overall odds ratio for petroleum materials does not reflect the high odds ratio for employment as garage and gas station workers. Furthermore, petroleum materials showed no pattern of risk by duration while garage and gas station workers had a high odds ratio for 2-4.9 years of employment and drivers and/or deliverymen showed high odds ratios for employment longer than 10 years. Therefore, it seems that neither exposure- nor employment-based analysis completely describes the complex risk patterns.

The analysis of risk by duration, latency, and age at first employment showed a variety of patterns, and it is difficult to form a consistent picture of the overall nature of occupational bladder carcinogenesis. For example, risk often peaked in the intermediate latent period of 20-39 years, but there were also patterns suggesting earlier or later peaks.

Prospective studies of bladder cancer associated with dye exposure have shown mean induction times of 16 or 18 years and ranges of 4-45 years [n5,n6]. The latent periods reflected in our study and by Hoover and Cole [n33] were usually longer. Matanoski and Elliott [n34] suggested that case-control studies would show longer latent periods than would prospective studies. Persons with long latencies might not be detected by a prospective study if the follow-up time was relatively short. Also, persons with intense exposures in the past who were susceptible to short latency disease would no longer be present in the population for a case-control study. Such selection factors operating on an evolving population at risk in a changing occupational environment might also partially explain our findings of significant differences in occupational risk between young and old subjects.

The significant decreasing trends in risk with increasing age at first exposure differ from the results of Case et al. [n6] who found higher bladder cancer risk for men who were older when they

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

were first employed in the dyestuffs industry. Our findings could reflect the systematic placement of young workers in jobs with the heaviest exposures. For example, in the 1930's it was recommended that eligibility for work in the dye operations at organic chemical plants be restricted to applicants between 20 and 45 years old [n2]. These findings might also reflect age differences in biologic susceptibility to some carcinogens, which would occur if these chemicals were to act only at an early age of carcinogenesis [n35].

However, our results did not reproduce Hoover and Cole's [n33] finding of no excess bladder cancer risk for men first employed after 25 years of age. We found significant odds ratios for subjects first exposed between 26 and 40 years old as well as before 25 years old; some specific materials, e.g., petroleum materials, had significantly high odds ratios only for those first exposed between 26 and 40 years of age.

Hoover and Cole [n33] did not find any overall association between bladder cancer risk and duration of occupational exposure but found an inverse association between latency and duration. In our data, the patterns of risk by duration of exposure were mixed. We found some significantly high odds ratios for long exposures but also some for shorter exposures. We found only two significant linear trends in risk with duration. Several factors in addition to chance statistical fluctuation may contribute to these varying patterns of risk with duration. For example, persons exposed to a very dirty environment may leave after short periods of time. If intensity of exposure affects risk more than duration, this may partially explain why we saw no inverse association between duration and latency. Also, response bias may have resulted in cases reporting short exposures to materials that controls omitted from their histories.

Finally, persons briefly employed in one high-risk job may be more likely to be employed in other highrisk jobs. Within the selected high-risk employment category, the odds ratios for persons with 1, 2, 3, 4, and 5 or 6 different job categories were 1.2, 1.8, 2.2, 1.1, and 23.1, respectively. Such interaction between multiple employment categories may explain why the sum of all years of selected high-risk employment showed the most consistent pattern of increasing bladder cancer risk with increasing duration of employment. These results support our impression that many diverse exposures are acting together to produce the substantial occupational bladder cancer risk that still exists in New Jersey.

ABBREVIATION USED: PAR=population attributable risk(s).

SUPPLEMENTARY INFORMATION: <1> Received April 22, 1982; revised December 27, 1983; accepted January 6, 1984.

<2> Supported by Public Health Service contract N01CP-61031 from the Division of Cancer Cause and Prevention (Division of Cancer Etiology), National Cancer Institute.

<3> Most of the data were collected as part of the National Survey of Environment and Health.

<4> Division of Epidemiology and Disease Control, New Jersey State Department of Health, CN 360, Trenton, N.J. 08625.

<5> Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Bethesda, Md. 20205.

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

<6> We thank Dr. Patricia Hartge and Dr. Linda Pickle (Environmental Epidemiology Branch, National Cancer Institute), Dr. Debra Silverman (Biostatistics Branch, National Cancer Institute), and Ms. Betsy Kohler (Cancer Epidemiology Program, New Jersey State Department of Health) for advice on data analysis and for review of earlier drafts of this manuscript. We thank Dr. Kenneth Rosenman and Ms. Kathleen O'Leary (Occupational Health Program, New Jersey State Department of Health) for advice on the classification of employment categories. We also thank all New Jersey pathologists and urologists for their cooperation in rapid case ascertainment and for their overall support for our study.

REFERENCES:

[n1.] REHN L. Blasengeschwulste bei Anilinarbeitern. Arch Klin Chir 1895; 50: 588-600.

[n2.] GEHRMANN GH. The carcinogenetic agent-chemistry and industrial aspects. J Urol 1934; 31: 126-137.

[n3.] HENRY SA, KENNAWAY NM, KENNAWAY EL. The incidence of cancer of the bladder and prostate in certain occupations. J Hyg (Lond) 1931; 31: 125-137.

[n4.] HUEPER WC. Occupational and environmental cancers of the urinary system. New Haven: Yale Univ Press, 1969.

[n5.] SCOTT TS. The incidence of bladder tumours in a dyestuffs factory. Br J Ind Med 1952; 9: 127-132.

[n6.] CASE RA, HOSKER ME, McDONALD DB, PEARSON JT. Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. Part I. The role of aniline, benzidine, alpha-naphthylamine, and beta-naphthylamine. Br J Ind Med 1954; 11: 75-104.

[n7.] CASE RA, PEARSON JT. Tumours of the urinary bladder in the manufacture and use of certain dyestuff intermediates in the British chemical industry. Part II. Further consideration of the role of aniline and of the manufacture of auramine and magenta (fuchsine) as possible causative agents. Br J Ind Med 1954; 11: 213-216.

[n8.] ZAVON MR, HOEGG U, BINGHAM E. Benzidine exposures as a cause of bladder tumors. Arch Environ Health 1973; 27: 1-7.

[n9.] CASE RM, HOSKER ME. Tumours of the urinary bladder as an occupational disease in the rubber industry in England and Wales. Br J Prev Soc Med 1954; 8: 39-50.

[n10.] DELZELL E, MONSON R. Mortality among rubber workers. III. Cause-specific mortality 1940-1978. J Occup Med 1981; 23: 677-684.

[n11.] McMICHAEL AJ, SPIRTAS R, GAMBLE JF, et al. Mortality among rubber workers: Relationship to specific jobs. J Occup Med 1976; 18: 178-185.

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

[n12.] DAVIES JM. Bladder tumours in the electric cable industry. Lancet 1965; 2: 143-146.

[n13.] DOLL R, VESSEY MP, BEASLEY RW. Mortality of gasworkers -- final report of a prospective study. Br J Ind Med 1972; 29: 394-406.

[n14.] WANG HH, MACMAHON B. Mortality among pesticide applicators. J Occup Med 1979; 21: 741-744.

[n15.] ANTHONY HM, THOMAS GM. Tumors of the urinary bladder: An analysis of the occupations of 1,030 patients in Leeds, England. J Natl Cancer Inst 1970; 45: 879-895.

[n16.] WYNDER EL, ONDERDONK J, MANTEL N. An epidemiological investigation of cancer of the bladder. Cancer 1963; 16: 1388-1407.

[n17.] COLE P, HOOVER R, FRIEDELL GH. Occupation and cancer of the lower urinary tract. Cancer 1972; 29: 1250-1260.

[n18.] HOWE GR, BURCH JD, MILLER AB, et al. Tobacco use, occupation, coffee, various nutrients, and bladder cancer. JNCI 1980; 64: 701-713.

[n19.] DECOUFLE P, STANISLAWCZYK K, HOUTEN L, BROSS ID, VIADANA E. A retrospective survey of cancer in relation to occupation. Washington, D.C.: U.S. Govt Print Off, 1977 [DHEW publication No. (NIOSH)77-178].

[n20.] NAJEM GR, LOURIA DB, SEEBODE JJ, et al. Lifetime occupation, smoking, caffeine, saccharine, hair dyes and bladder carcinogenesis. Int J Epidemiol 1982; 11: 212-217.

[n21.] SILVERMAN DT, HOOVER RN, ALBERT S, GRAFF KM. Occupation and cancer of the lower urinary tract in Detroit. JNCI 1983; 70: 237-245.

[n22.] MASON TJ, McKAY FW. U.S. Cancer mortality by county 1950-69. Washington, D.C.: U.S. Govt Print Off, 1973 [DHEW publication No. (NIH) 74-615].

[n23.] HOOVER R. FRAUMENI JF JR. Cancer mortality in U.S. counties with chemical industries. Environ Res 1975; 9: 196-207.

[n24.] BLOT WJ, FRAUMENI JF JR. Geographic patterns of bladder cancer in the United States. JNCI 1978; 61: 1017-1023.

[n25.] HOOVER RN, STRASSER PH, CHILD M, et al. Artificial sweeteners and human bladder cancer. Preliminary results. Lancet 1980; 1: 837-840.

[n26.] WAKSBERG J. Sampling methods for random digit dialing. J Am Stat Assoc 1978; 73: 40-46.

This Electronic Copy of Copyrighted Material Was Made and Delivered for Governmental Regulatory/Judicial Purposes Only - No Further Reproduction is Permitted without Permission from the Rightsholder.

[n27.] U.S. Bureau of Census. 1970 Census of population: Alphabetical index of industries and occupations. Washington, D.C.: U.S. Govt Print Off, 1971.

[n28.] BRESLOW NE, DAY NE. Statistical methods in cancer research: Vol I. The analysis of case-control studies. Lyon: IARC, 1980.

[n29.] SAS Institute. SAS supplemental library user's guide. Cary, N.C.: SAS Institute, 1980: 83-102.

[n30.] COLE P, MACMAHON B. Attributable risk percent in case-control studies. Br J Prev Soc Med 1971; 25: 242-244.

[n31.] GREENLAND S. The effect of misclassification in the presence of covariates. Am J Epidemiol 1980; 112: 564-569.

[n32.] SIEMIATYCKI J, DAY NE, FABBY J, COOPER JA. Guest editorial. Discovering carcinogens in the occupational environment: A novel epidemiologic approach. JNCI 1981; 66: 217-225.

[n33.] HOOVER R, COLE P. Temporal aspects of occupational bladder carcinogenesis. N Engl J Med 1973; 288: 1040-1043.

[n34.] MATANOSKI GM, ELLIOTT EA. Bladder cancer epidemiology. Epidemiol Rev 1981; 3: 203-229.

[n35.] DAY NE, BROWN CC. Multistage models and primary prevention of cancer. JNCI 1980; 64: 977-989.