American Journal of Industrial Medicine 19:291–301 (1991)

Drake Chemical Workers' Health Registry Study: I. Notification and Medical Surveillance of a Group of Workers at High Risk of Developing Bladder Cancer

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A medical surveillance program and epidemiologic study of 408 former workers of the Drake Chemical Company (now a Superfund waste site) was established in 1986. The Drake Health Registry Study was initiated because these workers had probable past exposures to beta-naphthylamine (BNA), a potent bladder carcinogen. The registry is widely viewed as a model for notification of workers at high risk of disease due to past occupational exposures. By the 40th month, 90% of the 366 living workers had been notified of the existence of the registry; 262 had been enrolled in the annual or semi-annual screening for bladder cancer. Among these, 27 persons have had abnormal screening results indicating moderate to high risk of bladder cancer and have been made eligible for further diagnostic tests. While no invasive bladder tumors were found among 18 persons completing the extended diagnostic evaluation, two diagnoses of moderate to severe dysplasia have been made. The registry has also identified three living and three deceased cases of bladder cancer in the cohort; a mortality analysis showed a 20- to 30-fold excess of bladder cancer. An incidence projection, based on the six identified cases, reveals that between six and ten new bladder cancer cases are likely to occur among the Drake cohort over the next 20 year period.

Key words: beta-naphthylamine, aromatic amines, cohort study, high risk notification, chemical manufacture, occupational mortality risks

INTRODUCTION

This report describes a medical surveillance program and epidemiologic study of 408 former employees of a small chemical manufacturing plant in north-central

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Accepted for publication June 29, 1990.

Pennsylvania. These workers are at increased risk of developing bladder cancer because of possible past exposures to aromatic amines, primarily beta-naphthylamine (BNA). The registry provides free screening and diagnostic services to detect early signs of bladder cancer for all former employees. The registry also maintains a database that provides information for epidemiologic analysis of morbidity and mortality among the cohort. This report reviews the background, objectives, and operational protocol of the registry and presents a descriptive overview of findings through 40 months of operation.

BACKGROUND

The Drake Chemical Company and its predecessor, the Kilsdonk Chemical Company, occupied the same site in Lock Haven, Pennsylvania, from 1948 until 1981. Both were small chemical manufacturing operations, generally employing from 20 to 50 persons. Lock Haven itself has a population of 12,000 and is located in largely rural Clinton County.

During their 33 years of operation, Drake and Kilsdonk were involved in the manufacture of a wide variety of speciality chemicals for producers of dyes, pharmaceuticals, cosmetics, and pesticides, disposing of many of the waste products on site. In 1982, the area was declared a hazardous waste site, eligible for emergency clean-up under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), popularly known as the "Superfund."

PRIMARY CHEMICAL EXPOSURES

Most of the concern about the Drake site focuses on potential exposure to BNA, an aromatic amine used as an intermediate in the manufacture of dyes and antioxidants. Studies in both Europe and the United States have established that long-term exposure to BNA is associated with an increased incidence of inflammation of the bladder and/or bladder cancer [Case et al., 1954; Matanoski and Elliot, 1981; Stern et al., 1985]. Major findings include a relative risk as high as 87 for bladder cancer associated with occupational exposure to BNA [Case et al., 1954].

BNA was manufactured at Kilsdonk as one of the firm's leading products between 1948 and 1962, at which time it constituted 30–40% of the plant's output [Lock Haven Express, 1961, 1962]. Because of increasing evidence of the hazards associated with its use, BNA was banned in Pennsylvania in 1962. It is suspected, however, that even after the ban, BNA may have been synthesized by Drake as a residual contaminant in the manufacture of Broenner's acid, which was produced in large quantities until the plant's closure [U.S.D.H.H.S., 1981].

Documentation concerning the processes and potential exposures at the plant is sparse; in fact, virtually no plant records have been found from the Kilsdonk years. Thus, much industrial hygiene information must be reconstructed based on reports from former employees.

PREVIOUS HEALTH STUDIES

In 1963, Lieben reported that 11 of 77 cases of bladder cancer reported by Lock Haven area hospitals occurred in persons with a history of working at Kilsdonk or the

neighboring American Color and Chemical Company (which also utilized BNA in processing). An ecologic study of local county-wide mortality rates between 1950 and 1979 [Budnick et al., 1984] showed a significantly increased number of bladder cancer deaths occurring among white males in Clinton County.

In 1983, the Pennsylvania DOH developed a comprehensive health surveillance program for both community members and for former Drake employees in the Lock Haven area. While there was no evidence of morbidity related to exposure among the community at large [Logue and Fox, 1986], there was evidence of higher than expected prevalence rates for total cancers, as well as skin and eye irritation among former employees exposed to BNA, herbicides, or pesticides [Marsh et al., 1988]. The employee study also included a bladder cancer screening program which served as an important source of data for the current study.

MATERIALS AND METHODS

Objectives of the Registry Program

The Drake Health Registry Study (DHRS) was implemented in August 1986. The primary objectives of the registry program are to: 1) identify all former Drake and Kilsdonk workers and determine their vital status; 2) determine current addresses for all living cohort members and notify, enroll, and maintain compliance among as many persons as possible; 3) establish and maintain an ongoing program of medical surveillance for bladder cancer; 4) evaluate the notification and surveillance programs; and 5) evaluate bladder cancer risk as well as total and cause-specific mortality risks in the cohort.

The clinical and laboratory operations of the DHRS are based at the Lock Haven Hospital (LHH). The University of Pittsburgh (PITT) provides administrative and technical support including data management, statistical analysis, and program evaluation. The registry was adapted from the surveillance program established for BNA-exposed workers in Augusta, Georgia [Schulte et al., 1985a].

Development of Study Roster and Follow-up

All former employees of the Drake and Kilsdonk companies are eligible for the screening program. The study roster was based on the list of former employees constructed for the Pennsylvania DOH registry [Marsh et al., 1988] from available company records plus lists supplied by a local environmental advocacy group, key employees, and phone-ins following a publicity campaign. The DOH list was revised and supplemented, based on a work record review by the PITT investigators, further telephone tracing, and cohort verification based on employer's quarterly IRS reports [Marsh and Enterline, 1979]. The vital status of the cohort was determined via the Social Security Administration and National Death Index, as well as drivers' license bureaus and post-office forwarding services. The addresses obtained through the forwarding services formed the basis for the initial notification effort.

Notification and Enrollment

Prior to the actual notification process an advisory committee of community representatives was established, along with a separate committee of former employees. Both of these groups were consulted on the general strategy of recruitment as well as on the actual content of notification materials. A three-part notification and

enrollment system was formulated, beginning with media coverage followed by two notification letters and finally, personal contact. All notification materials were developed and pretested in conjunction with the workers' committee and were designed to contain three key messages: 1) persons who worked at Drake or Kilsdonk are at greater risk of bladder cancer because of possible exposure to BNA; 2) bladder cancer is easily treated if detected at an early stage; and 3) free bladder cancer screening diagnostic services are available. The initial notification was directed toward 200 persons with addresses obtained through the post-office forwarding service. Once these persons were notified, the LHH assumed responsibility for telephone tracing of the remaining cohort members.

Medical Surveillance Program

Clinical and health promotion operations began at the LHH in November of 1986. The DHRS provides three screening tests free of charge to participants: a standard urinalysis, a Papanicolaou (PAP) urine cytology, and a Quantitative Fluorescence Image Analysis (QFIA). The QFIA test, developed by Hemstreet and associates [Hemstreet et al., 1983, 1986; Bass et al., 1987], is a relatively new screening modality that detects early, pre-cancerous changes by measuring the amount of DNA present in bladder cells. All QFIAs are performed by the University of Oklahoma. In addition to providing a urine sample, the participants are asked to complete a detailed questionnaire concerning both occupational and medical history, including tobacco and alcohol consumption. A positive screening test qualifies the participant for a free diagnostic evaluation which includes an intravenous pyelogram (IVP), physical examination, and cystoscopy with random biopsy. These clinic services are offered at Lock Haven Hospital for participants residing within a 50-mile radius of Lock Haven. Persons living outside this 50-mile area are sent home catch kits to be mailed back to the clinic and are referred to a local hospital if a diagnostic evaluation is warranted. If a tumor is found during the diagnostic evaluation, the patient is counselled and referred for treatment outside the program.

The protocol for the clinical management of registrants has undergone several changes over the history of the DHRS. The most recent major change has been the elimination of occupational risk group (based on year of hire and duration of employment) as a criterion for rescreening eligibility. This modification was based on concerns about exposure misclassification and the occurrence of non-negative results among persons initially classified as low risk (hired after 1965 and duration of employment less than 5 years). Currently, all cohort members are eligible for at least annual screening. The developmental history of the clinical protocol is described elsewhere [Marsh et al., in press].

The current bladder cancer screening/diagnostic protocol has three clinical categories: 1) negative—all test results are normal and the registrant is advised to return for an annual rescreen; 2) monitor—one or more of the tests is non-negative (depending on the specific test results some registrants are advised to confirm the test in 1 month and others to return for a semi-annual rescreen); and 3) positive—the results of one or more tests warrant an immediate diagnostic evaluation. The criteria for a positive screening test include: evidence of hematuria (gross visual hematuria or microscopic levels above 15 cells per high power field with follow-up for lower levels of hematuria above five cells per hpf being referred to a physician); abnormal PAP cytology (Class 3 or above-Class 2 PAPs are repeated within 1 month with a repeat

Class 2 result qualifying for cystoscopy); a highly abnormal QFIA result (Risk Group 1 or 2); and/or untoward symptomatology (e.g., frequency, urgency, or pain during urination). Latitude is allowed for physician discretion in following persons whose medical histories overlap the protocol's categories. Further definitions of the screening test outcomes and decision-making criteria are described in a separate report [Marsh et al., in press].

The results of the bladder cancer screening tests are conveyed to study members by the Lock Haven Hospital clinical staff according to a strict protocol developed by the PITT investigators. The protocol emphasizes the prompt notification of results by using phrasing that clearly directs attention to the possibilities of health risks without arousing unnecessary fear. Persons with an overall negative screening test are simply notified by a letter that indicates their tests were within normal ranges and encourages them to undergo annual rescreening. Persons with screening test results in the monitor or positive categories are initially notified by telephone with a follow-up letter that describes the test results and encourages them to undergo semi-annual rescreening (monitor) or to undergo a free diagnostic evaluation (positive). The personal telephone contact used for the monitor and positive results has been found to be effective in reducing fear and anxiety and in permitting an opportunity for the clinical staff to respond directly to any questions that the study members may have concerning their test results.

RESULTS

As of September 30, 1989, or Month 40 of the study, the cohort totals 408 and is comprised chiefly of white males with only 26 (6%) females and two non-whites.

Of the 408 study members, 42 persons were presumed deceased at the time of notification, leaving 366 potential registry members. By the end of Month 40, 334 or 91% of those persons were considered to have been notified; i.e., current addresses had been determined and notification letters sent. Over 45 persons were located in 20 states outside of Pennsylvania and at least one person overseas. Of the 334 notified, 271 agreed to participate or to seriously consider participating in the screening program. Refusals were received from 24 persons and a definitive response is pending for 39. Notification was confirmed for 21 of the 39 by personal contact with a household member. Thus, the current participation rate of the DHRS (defined as the number of persons agreeing to participate of those considered notified) stands at 271/334 or 81%. This rate compares favorably with enrollment rates of similar registries such as that established for BNA-exposed workers in Augusta, Georgia [Schulte et al., 1985b].

The number of persons actually registered (completing the questionnaire and/or screening tests) totals 262. This number represents 78% of the 334 persons notified and 71% of the total eligible cohort. Fifty-eight or 22% of the 262 registrants live outside the Lock Haven area and were screened in a nearby hospital or utilized catch kits sent to their homes, completing the questionnaires by telephone.

Table I shows selected demographic and work history characteristics for the current cohort and registrant groups. Generally, the registrants are representative of the cohort as a whole with regard to sex, age, year of hire, duration of employment, and risk group. Registrants are typically young to middle-aged males (median age 36) who worked for short terms (median duration of employment 12 months) in fairly

TABLE I. Demographic and Work History Characteristics of Current Drake Cohort and Registrant Group (as of 09/15/89)

Characteristic	Cohort (n = 408)		Registrants (n = 262)	
	No.	%	No.	%
Sex				
Male	382	93.4	244	93.1
Female	26	6.6	18	6.9
Year of birth				
Prior to 1930	61	15.0	27	10.4
1930–1949	131	32.0	95	36.2
1950+	203	49.8	140	53.4
Unknown	13	3.2	0	0.0
Year of hire				
1948–1960	33	8.1	28	10.7
1961–1970	88	21.5	57	21.7
1971–1981	259	63.5	174	66.4
Unknown	28	6.9	3	1.2
Duration of employment (years)				
Under 1	235	57.6	145	55.5
1–5	97	23.8	80	30.5
5+	48	11.8	34	12.9
Unknown	28	6.8	3	1.1
Risk group[a]				
Low	287	70.3	189	72.1
Medium	28	6.9	19	7.3
High	83	20.3	54	20.6
Unknown	10	2.5	0	0.0

[a]Low = less than 5 years employment 1966–1981; Medium = 5 or more years employment 1966–1981; High = hired prior to 1966.

recent time periods (i.e., after 1970). Thus, as reflected in the risk group distribution, the majority of registrants presumably would have a low probability of being exposed to BNA and developing a related bladder cancer. However, at least 43% worked 1 year or longer and 21% were hired prior to 1966, when BNA exposures were most likely. Of those hired prior to 1966, 39 or 72% worked for 1 year or longer.

Table II presents a summary of the notification effort and test results seen to date across three screening sessions. A total of 254 persons have complete initial screening results. Of these, 216 had become eligible for a second screening session and 82 for a third session as of Month 40. (Eleven persons have been dropped from the re-screening cycle because of death, refusal, or previous cancer diagnosis.) Of the 216, 174 persons (or 80%) actually completed the second round of screening tests, and 57 of the 82 (69%) eligible completed the third screening cycle as of this time. One hundred sixty-six persons are currently assigned to an annual screening cycle because test results to date have been negative across all screens and 52 to semi-annual screening because of a history of a monitor level result at any one screening session. A total of 27 persons (roughly 10% of the total group) have been considered eligible for diagnostic evaluation based on first, second, or third screening sessions (for a total of 31 positive screening results). Three of these had repeat positives in their first and in subsequent sessions. One individual was found positive for untoward symptomatology, one for gross hematuria, and the remaining 25 based on PAP cytology or

TABLE II. Drake Health Registry Study: Summary of Notification and Clinical Outcomes Across Three Screening Cycles (as of 09/15/89)

	Screen 1		Screen 2		Screen 3	
	No.	%	No.	%	No.	%
Total eligible	366	100.0	216	100.0	84	100.0
Notified	334	91.3	215	99.4	82	97.6
Not Located	32	8.7	1	0.6	2	2.4
Total notified	334	100.0	215	100.0	82	100.0
Refused	24	7.2	4	1.9	0	0.0
Response pending	39	11.7	32	14.9	24	29.3
Consented to participate	271	81.1	179	83.2	58	70.7
Registered	262	78.4	174	80.9	57	69.5
Total registered	262	100.0	174	100.0	57	100.0
Screening pending	8	3.1	9	5.2	4	7.0
Results outstanding	0	0.0	1	0.6	3	5.3
Results complete	254	96.9	164	94.2	50	87.7
Test results complete	254	100.0	164	100.0	50	100.0
Negative	123	48.4	111	67.7	31	62.0
Monitor	35	13.8	23	14.0	9	18.0
Positive	21	8.3	6	3.7	4	8.0
Inadequate sample/ repeat test required[a]	75	29.5	24	14.6	6	12.0

[a]QFIA requires 500 cells per sample.

QFIA results. Only three individuals were found positive based solely on an abnormal PAP. Another eight were based on abnormal PAP plus a positive QFIA result, and 14 on QFIA only. There have only been four instances of PAP scores above Class II.

Of the 27 persons with positive screens, 18 completed the diagnostic evaluation and are now assigned to semi-annual screening. The other nine persons have appointments pending, refused, or were too ill to undergo the cystoscopy (two have since died from other causes), and are also being monitored semi-annually. While no invasive bladder tumors were found at the time of cystoscopy, two diagnoses of moderate to severe dysplasia have been made, both of which were found on the third screening cycle. In most of the remaining cases, some type of bladder abnormality was cited, including chronic cystitis, inflammation, and hyperplasia. Cytologies (PAP or QFIA) performed on bladder washings remained abnormal in eight cases.

Prevalence and Incidence of Bladder Cancer in the Cohort

Currently, six male cohort members have been identified as having been diagnosed with bladder cancer, three according to the cause of death listed on the death certificate and the remaining three according to diagnosis by their personal physicians. The age at diagnosis ranged from 38 to 62 years, with four men being diagnosed sometime during their forties. The average latency period between date of hire and date of diagnosis was 19 years, ranging from 9 to 26 years. All six men were hired prior to 1970. For the five persons with available employment dates, the duration of employment ranged from 2 months (two persons were known to have been employed less than 6 months) to 26 years, with an average of 15 years. Two were known to have worked directly in BNA processing. These characteristics are consistent with what has been observed among other cohorts experiencing occupationally

TABLE III. Observed and Expected Number of Deaths and Standardized Mortality Ratios (SMR) by Cause Among White Male Drake/Kilsdonk Chemical Workers—No. at Risk 362 (1950–1986); Person-Years at Risk 5,038.3

Cause of death	ICD 8th revision codes	SMR			
		OBS	U.S.[a]	PA[b]	Counties[b]
All causes	0–999	35	164.9[c]	165.1[c]	184.0[c]
All cancers	140–209	10	233.6[d]	224.9[d]	243.7[d]
Digestive system	150–159	1	97.0	87.9	94.5
Respiratory system	160–163	4	268.9	274.8	309.3
Bladder and other urinary organs	188,189.9	3	3259.8[c]	2908.3[c]	2391.8[c]
All other cancer	Residual	1	59.9	57.1	61.7
All heart disease	390–398,400.1,400.9 402,404,410–414	12	182.2	165.8	170.0
Cirrhosis of liver	571	3	482.1	536.5[d]	866.2[d]
Accidents	800–949	6	164.8	196.4	214.9
Motor vehicles	810–823	2	91.7	104.6	108.5
Other accidents	Residual	4	273.9	347.8	421.1
Unknown causes		2 (not included in "All causes" category)			

[a]Represents 1950–1986 study period.
[b]Represents 1960–1986 study period for nonmalignant causes only.
[c]p less than 0.01.
[d]p less than 0.05.

induced bladder cancer [Case et al., 1954; Matanoski and Elliot, 1981; Lieben, 1963; Schulte et al., 1985b].

Mortality Experience of the Cohort

Currently, a total of 47 deaths have been identified. (Five of these deaths occurred among registry members.) Death certificates have been obtained for all but three. Underlying causes of death were coded by an independent nosologist according to the International Classification of Diseases (ICD) revision in effect at time of death. To assess overall and cause-specific disease risks, the mortality experience of the Drake cohort was examined during the time interval January 1, 1950, to December 31, 1986. The analysis was limited to 35 deaths that occurred among 362 white male study members through 1986 and was performed by utilizing the Occupational Cohort Mortality Analysis Program (OCMAP) [Marsh and Preininger, 1980; Marsh et al., 1986]. Seventeen males were excluded from the analysis (including two presumed deaths) because of incomplete data. By using a modified life table technique, age and time period standardized mortality ratios (SMRs) were calculated by taking the ratio of the sum of observed to expected numbers of deaths ($\times 100$). Expected numbers of deaths were based on white male general population rates for the U.S., the state of Pennsylvania, and the three-county local area (Clinton, Lycoming, and Centre counties). Due to the unavailability of death rates, state and local comparisons were limited to the years for 1960–1986 for total mortality and nonmalignant causes of death.

Table III shows the results of the SMR analysis for all causes of death and ten specific cause of death categories. SMRs vary for some causes, reflecting the geographic variability in population rates. The somewhat lower SMR for bladder cancer based on county rates results from the higher bladder cancer death rates that prevailed

in the local area of the Drake site. Table III also shows that, based on local rates, statistically significantly elevated SMRs were observed for "all causes," "all cancers," "bladder and other urinary organ cancer," and "cirrhosis of the liver." In addition, while not statistically significant, SMRs based on each of the external populations are elevated for most of the remaining causes of death examined. Although based on only three observed deaths, the 20–30-fold excess noted for "bladder and other urinary organ cancer" is likely to be real and a reflection of the known bladder cancer risk associated with BNA exposure.

DISCUSSION

As a long-term occupational health surveillance program, the primary function of the DHRS is to provide bladder cancer screening and diagnostic services. Thus far, the program has notified 90% of the cohort and identified 27 individuals with screening results that indicate a moderate to high risk for malignancy, including two cases of dysplasia. The registry has also helped to locate and confirm the identity of three living persons with diagnosed bladder cancer, and has identified three bladder cancer related deaths.

It is notable that the two cases of dysplasia were diagnosed on the third screening visit. Several more individuals have presented with histories of persistently abnormal screening results over several years and require close monitoring. These observations underscore the need for ongoing medical surveillance of this relatively young cohort. Over 60% of the registrants have yet to reach the average latency period of 19 years experienced by the known bladder cancer cases. In order to assess the need for continued surveillance of these men and women, an estimate of the number of cases to be expected over the next 20 years was performed based on the incidence rates derived from the six identified cases, making no assumptions about differences in exposure. Age-specific person-years at risk were projected in 5 year increments through the year 2008 by using internal death rates and accounting for competing causes of death. Based on the resulting crude and age adjusted rates, between six and ten new bladder cancer cases, respectively, can be expected to occur among the Drake cohort over the next 20 year period.

The DHRS also affords opportunities for research related to the myriad of methodological and logistical issues that surround the establishment and maintenance of large-scale exposure registries. Specifically, the Drake registry provides an operational framework for implementing, testing, and evaluating the many requisite components of a successful program, including health promotion and education activities and notification, recruitment, and compliance strategies, as well as the actual bladder cancer screening and diagnostic modalities. For example, the DHRS provides an important basis for research related to the utility of early biological markers as screening tools in an asymptomatic but high risk population. Specifically, QFIA measurements over three to five testing periods in conjunction with conventional PAP tests and diagnostic confirmation will help provide a definitive evaluation of that test's sensitivity and specificity. Moreover, it will help calibrate the QFIA as a forecaster of early changes by quantifying the lapse between a positive QFIA and clinical disease.

Data from the DHRS will also enable an independent epidemiologic assessment of bladder cancer and other risks associated with BNA exposure. The mortality

analyses conducted thus far clearly demonstrate the existence of an overall 20- to 30-fold risk of bladder cancer among these workers. As additional cases are diagnosed, these risks and associated latency periods can be further quantified.

The chief limitations of the program from an epidemiologic standpoint relate to the poor characterization of exposure, as well as the relatively short tenures experienced by most of the cohort. A rigorous exposure assessment is necessarily limited by lack of documentation and by the nature of the manufacturing operation itself. In both plants, scores of chemicals were processed in a small physical space where job duties were widely shared. Further, there has not been a clear enough association between clinical screening outcomes and risk factors such as age, date of hire, duration of employment, or job title to confidently assign workers to surrogate risk categories a priori. Ultimately, the DHRS raises the question of the life span of such registries and how they will be funded. In determining the feasibility of providing lifetime registry enrollment and screening of cohorts, attention must be paid to both the suitable payment mechanisms for such activity and the criteria for assigning responsibility to the private and public sectors. While the DHRS provides some specific answers to the logistics of developing an exposure registry, it raises other long-term societal questions that still need consideration.

ACKNOWLEDGMENTS

This study was conducted under a cooperative agreement between the Pennsylvania Department of Health, Division of Environmental Health, and the Centers for Disease Control/National Institute for Occupational Safety and Health. Funds were provided by the Agency for Toxic Substances and Disease Registry, Atlanta, Georgia. The authors gratefully acknowledge the tremendous contributions of their colleagues and consultants: Stephanie Larison, Dr. Walter English, Dr. S.N. Kapoor, Diana K. Compston, Michele LaValley, Dr. John Franz, Dr. William McClellan, and Sandra Tillet. They would also like to acknowledge the cooperation and assistance of Mr. Timothy Johnson, Mr. Howard LeBow, Mrs. Diana McDivitt, and Mrs. Linda Kobus.

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