



Mortality among Chemical Workers Exposed to Benzene and other Agents

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A historical cohort mortality study was conducted of 259 male employees of a chemical plant where benzene has been used in large quantities. The study group included all persons who were employed by the Company any time between January 1, 1947 and December 31, 1960. The cohort was followed through December 31, 1977 at which time 58 known deaths were identified. The only unusual finding was four deaths from lymphoreticular cancers when 1.1 would have been expected on the basis of national mortality rates. Three of the deaths were due to leukemia and one was caused by multiple myeloma. In addition, one of the leukemia deaths had multiple myeloma listed on the death certificate. The findings are consistent with previous reports of leukemia following occupational exposure to benzene and raise the possibility that multiple myeloma could be linked to benzene. also.

INTRODUCTION

Benzene is now recognized as a cause of leukemia in humans, even though its carcinogenic properties have not been adequately demonstrated in laboratory animals (IARC, 1979). The epidemiologic evidence includes studies of leukemia among shoeworkers using benzene-containing adhesives (Aksoy *et al.*, 1972; 1974) and among workers using benzene in the manufacture of a plastic-like packaging material (Infante *et al.*, 1977). Case reports implicate a variety of other trades with potential benzene exposure (Goguel *et al.*, 1967; Girard *et al.*, 1971; Vigliani, 1976). In some instances acute myeloid leukemia is the predominant cell type (Vigliani, 1976; Aksoy *et al.*, 1976; Infante *et al.*, 1977), while in others different types are involved (Goguel *et al.*, 1967; Girard *et al.*, 1971).

We were presented with an opportunity to evaluate the cancer experience of workers employed at a single chemical plant where benzene has been used in the production process. This particular industrial environment had not previously been studied. At the outset, we were aware that toxic chemicals other than benzene were present and accounted for a portion of the total exposure experienced by the workforce.

MATERIALS AND METHODS

Description of the Plant and Manufacturing Processes

The plant under study started as a small petroleum refinery in 1915 and was converted to a chemical manufacturing plant during the period from 1937 to 1949. As an oil refinery, the plant produced a full line of refinery products that included

gasolines, light oils, bunker oils, lubricating oils, and wax. No petrochemical operations, such as aromatic extraction and ethylene production, were carried out. Thus, exposures would have been those encountered in any refinery producing similar products and include acid gases (hydrogen sulfide, sulfur dioxide), aromatics (benzene, toluene, xylene), gasoline additives, and polynuclear aromatics associated with asphalt production. Benzene and other aromatics were present only as stream constituents.

Since 1949, the principal products made at the plant have been two forms of alkyl benzene compounds (branched and linear alkylates). These compounds are sulfonated elsewhere and used by other companies as an ingredient in the production of household detergents. The process for making these "detergent alkylates" is a continuous one utilizing benzene, paraffins, and chlorine. Briefly, it consists of taking paraffins and fractionating them into specific cuts. Chlorine is then vaporized with steam and reacted with the paraffin cuts. The resulting chloroparaffin is sent to an alkylation reactor where it is reacted with benzene. Muriatic acid and aqueous aluminum chloride are produced as by-products. It should be noted that a number of smaller processes have been carried out at the plant since 1949 in which other chemicals were either used as raw materials or produced as end points or intermediate reaction products. For example, paraformaldehyde and chloromethyl ether compounds were involved in one operation while trimethylamine was used in another one. To our knowledge, no chemical used at the plant, other than benzene, is carcinogenic for the lymphatic or hematopoietic systems either in man or laboratory animals.

Retrospective characterization of benzene exposures prevalent in the 1950s and 1960s is difficult in the absence of adequate records describing historical air levels or even qualitative impressions of previous day-to-day working conditions. All we can safely say is that benzene exposures resulted largely from multiple fugitive emissions peculiar to past process technology as well as the particular quality control and maintenance procedures practiced in the past. Furthermore, it is known that the amount of benzene used at the plant averaged about 5.8 million gallons per year during the period 1950-1961.

In addition to exposures that resulted from day-to-day contact with the process itself, another source of benzene exposure originated from habits developed by individual workers. For example, according to union officials, it had been common practice for some workers to clean their hands, clothing, and tools with benzene. Furthermore, it was mentioned that some workers would siphon off benzene for home use. Although we recognize that these reports are anecdotal in nature, they do suggest that at least some workers received benzene exposures that were in excess of levels given off by the "ordinary run" of the manufacturing processes.

Description of the Study Group

The study group consists of the 259 men who were employed at the plant in white- or blue-collar jobs anytime between January 1, 1947 and December 31, 1960. Only three women worked there during that time period and are not in-

cluded here. Individuals whose last employment was prior to 1947 and those who were hired for the first time after 1960 are excluded from the study. Subjects were identified from year-end rosters and turnover reports maintained at a central location of the Company. Some persons who worked at the plant as "casual labor" on whom no record was retained and employees of outside contractors (e.g., plumbers, construction workers, electricians) who worked on the premises but were never on the Company payroll could not be included.

Dates of employment and basic demographic information were determined for every subject but personal employment records showing detailed work histories and job changes were not available for everyone. Incomplete job histories led us to include all male employees for the sake of completeness. Workers who may have had little or no exposure to the production process tend to dilute the study group. Thus, risk estimates based on our data may understate the actual risks associated with benzene.

Table 1 shows the distribution of study subjects according to year of first employment at the plant. Seventy-four persons started work prior to 1947, the year production of detergent alkylates began. Race was not consistently recorded by the Company, but of 157 workers whose race was noted, either on the employment record or death certificate, only 10 (6%) are non-white.

Follow-up

The 259 study subjects were followed for mortality through December 31, 1977 the closing date of the study. As of this date, 48 subjects were still employed with the Company, 67 had retired and 144 had terminated for other reasons. Persons in the latter group who had not died while still on the employment rolls had to be traced using sources outside the company such as the Social Security Administration and the state motor vehicle bureau. Table 2 shows the results of the follow-up process. Sixty-three subjects (24% of the cohort) had died. Of the 28 persons completely lost to follow-up, 11 are known to be alive as recently as 1976 or 1977. A better follow-up rate was achieved for subjects employed one year or more (95%) than for all subjects (89%).

Death certificates were obtained from state and city vital statistics offices when the company lacked a copy of the original version. Underlying cause of death was selected by a qualified nosologist following the World Health Organization (WHO)

TABLE 1
DISTRIBUTION OF SUBJECTS BY YEAR OF FIRST EMPLOYMENT AT PLANT

Year of first employment	Number of subjects
Total	259
1915-1924	32
1925-1939	22
1940-1946	20
1947-1952	63
1953-1955	49
1956-1960	13

TABLE 2
DISTRIBUTION OF SUBJECTS BY VITAL STATUS AT CLOSE OF STUDY

Vital status on January 1, 1978	All subjects	Subjects with at least one year employment
Total	259	194
Known alive	168	125
Known dead	58	55
Presumed dead ^a	5	5
Unknown (lost to follow-up)	28	9

^a Date of death known but death certificate not recovered.

rules in effect in the year of death. All causes of death were coded using the numbering system in the U.S. edition of the Eighth Revision of the International Classification of Diseases (ICDA-8) for ease of computer processing (USDHEW, 1967).

Analytic Methods

The cause-specific mortality experience of the study group was analyzed by a modified life table technique implemented by an updated version of a widely used computer program (Monson, 1974). The age- and calendar year-specific death rates of the U.S. white male population over the period 1947-1975 were used for comparison. Since race is unknown for 102 workers, we thought it inadvisable to selectively exclude only the 10 known nonwhites. Five in the latter group died and inclusion of nonwhites tends to overstate mortality risks slightly for all causes combined.

In analyses of mortality rates for all 259 subjects, a person entered the study on January 1, 1947 if he began employment on or before that date. Otherwise, he entered the study on the day employment started. Table 3 presents the study

TABLE 3
DISTRIBUTION OF SUBJECTS BY AGE AT ENTRY TO STUDY AND YEAR OF ENTRY TO STUDY

Age at entry	Total	Year of entry		
		1947-1949	1950-1954	1955-1960
All subjects				
Total	259	89	76	94
<25	58	9	19	30
25-34	104	18	40	46
35-44	49	20	13	16
45-64	48	42	4	2
Subjects with at least 1 year employment				
Total	194	64	40	70
<25	28	6	6	16
25-34	80	16	24	40
35-44	39	21	6	12
45-64	47	41	4	2

TABLE 4
DISTRIBUTION OF PERSON-YEARS AT RISK OF DYING BY ATTAINED AGE

Attained age	All subjects	Subjects with at least 1 year employment
Total	5942.5	4355.1
<35	1321.2	756.2
35-44	1775.8	1226.7
45-54	1525.7	1170.5
55-64	866.3	760.1
65+	453.6	441.6

group according to age at entry to study and year of entry to study. It can be seen that workers who entered the study in the earlier years are, on the average, older than more recent entrants since the former group includes the existing workforce as of January 1, 1947 while the latter group is composed of newly hired workers. The mean age at entry for all subjects was 33.8 years. When analyses are confined to those who completed at least one year of employment, a person entered the study on January 1, 1947 if he satisfied the one year employment criterion on or before that date. If one year of employment was achieved after January 1, 1947, the person's "entry date" coincided with the date on which one year of employment was reached. The mean age at entry for subjects with a least one year employment was 36.1 years. Person-years were counted from the entry date to date of death or December 31, 1977, whichever came first. Individuals in the "presumed dead" category were tabulated with total deaths but were not assigned to a specific cause category. Persons lost to follow-up were treated as alive on the closing date of the study which tends to understate mortality risks somewhat.

Table 4 shows the distribution of person-years generated by the study group according to attained age. Twenty-six percent of all person-years occurred between ages 45 and 54, 15% between 55 and 64, and 8% at ages 65 and over. Admittedly, the total number of person-years limits our ability to detect a real elevation in relative risk of an infrequent disease like leukemia. For example, with exactly 5000 person-years, a rough estimate of the probability of concluding that the plant's leukemia death rate exceeds the general population rate (say 10 per 100,000) when, in fact, a twofold risk exists, is only 0.08 (based on the Poisson distribution with $\alpha = 0.05$ and a one-sided test). If the actual relative risk is three, this probability increases to 0.19, and reaches 0.46 if the true relative risk is 5. Thus, it was clear at the outset that we had a good chance of not detecting an increased risk for leukemia even though one might indeed exist.

RESULTS

Table 5 shows the mortality experience of the entire study group in relation to the U.S. white male population for major cause of death categories. Deaths from all causes were not too different from expectation (SMR = 0.97). Furthermore, results for each of four major cause of death categories suggest no unusual mortality in the plant population.

TABLE 5
OBSERVED AND EXPECTED NUMBERS OF DEATHS AND STANDARDIZED MORTALITY
RATIOS (SMRs) BY MAJOR CAUSE CATEGORY—ALL SUBJECTS

Cause of death (ICDA Nos., 8th-rev.)	Observed	Expected ^a	SMR ^b (95% confidence limits)
All causes	63	64.8	0.97 (0.75–1.24)
All malignant neoplasms (140–209)	10	12.3	0.81 (0.39–1.50)
Circulatory disease (390–458)	36	33.7	1.07 (0.75–1.48)
Respiratory disease (460–519)	4	3.6	1.11 (0.30–2.84)
Accidents, poisonings, violence (800–999)	5	6.6	0.75 (0.24–1.76)
All other known causes	3 ^c	8.6	0.35 (0.07–1.02)
Unknown cause (no death certificate)	5	—	—

^a Based on the age and calendar year—specific death rates of the U.S. white male population.

^b SMR = Standardized mortality ratio = observed deaths divided by expected deaths. 95% confidence limits obtained using method described in Haenszel *et al.* (1962).

^c Includes one death each from obesity (277), spinal cord compression (349.6), chronic pyelonephritis (590.0).

Table 6 depicts site-specific cancer mortality confined to the 194 subjects who were employed at least 1 year at the plant. The 1-year employment criterion was chosen, *a priori*, as a convenient way of focusing on a subgroup with longer exposure and more complete follow-up data. Only one cancer death was observed among those who worked less than 1 year (cancer of the throat, not further specified). In the former group, single cases of primary cancers of the large intestine, rectum, pancreas, and lung were observed. A striking result concerns the four cancers of lymphatic and hematopoietic tissues, when only 1.06 were expected. This difference is statistically significant at the 0.05 level based on the Poisson distribution (Pearson and Hartley, 1958). Three of these deaths were

TABLE 6
OBSERVED AND EXPECTED NUMBERS OF DEATHS BY SPECIFIC CANCER SITE—SUBJECTS
WITH AT LEAST 1 YEAR EMPLOYMENT

Site (ICDA Nos., 8th rev.)	Observed	95% Confidence limits	Expected ^b	SMR
All sites (140–209)	9	4.12–17.08	10.77	84
Large intestine (153)	1	0.03–5.57	0.99	100
Rectum (154)	1	0.03–5.57	0.39	256
Pancreas (157)	1	0.03–5.57	0.61	164
Lung, bronchus, trachea (162)	1	0.03–5.57	3.21	31
Lymphatic and hematopoietic tissue (200–209)	4	1.09–10.24	1.06	377*
Other and unspecified sites	1	0.03–5.57	4.51	

^a Based on the age and calendar year—specific death rates of the U.S. white male population. 95% confidence limits obtained from Table 40 in Pearson and Hanley, 1958.

^b Metastatic carcinoma of the left lung (1970).

Leukemia (204)

3**

0.44

681**

multiple myeloma
(203)

a

0.23

870*

* Workers had at least 1 yr of employment.

Source: Deconfeli, *et al.*, *Env. Res.* 30:15–25, 1983

charged to leukemia as the underlying cause (0.44 expected, $P < 0.01$) while the fourth was due to multiple myeloma.

To investigate these cases further, next of kin were contacted with the cooperation of the company and union, and copies of medical records were obtained with informed consent. Details of their employment and clinical histories are summarized in Table 7. Of the three leukemias, one was chronic lymphocytic of 14 years duration and two were acute leukemia, one monocytic and the other myelomonocytic. The latter case (Case B) is particularly interesting since it developed 2 years after institution of radio- and chemotherapy for multiple myeloma. The sideroblastic anemia is a well-recognized preleukemic state and in this instance preceded overt leukemia by 2 months. This case is the only decedent for whom a nonneoplastic blood disease was mentioned on the death certificate. It is noteworthy that onset of multiple myeloma in cases A and B was at a relatively young age compared to the age-specific incidence in the general population. In addition, both cases showed identical paraprotein types, IgG, Kappa. In terms of employment, one of these persons (Case C) had substantial work experience at the plant before it was converted to a chemical plant while Case B started employment only after the facility had been operating as a chemical plant for several years. Employment was generally continuous between the first and last employment dates except for Case A who did not work at the plant for about 5 years between 1947 and 1960 and was absent for medical reasons for long durations during the last 2 years of his employment. Detailed work histories showed that Cases A, B, and D had worked exclusively in blue-collar jobs but the work history for Case C could not be located. It was not possible to determine from the limited employment information whether all four individuals had been exposed to any particular nonbenzene chemical.

DISCUSSION

Although the study group is small, it is noteworthy that the only significant excess mortality occurred in the category of cancers of the hematopoietic system. Furthermore, the appearance of two cases of multiple myeloma is surprising since this malignancy is only one-third as frequent as leukemia among U. S. white males (Cutler and Young, 1975).

Geographic and racial factors are not likely to account for the leukemia excess since white males in the city where the plant is located have about the same leukemia death rate as the total U.S. white male population. Furthermore, inclusion of nonwhites in the study group would tend to understate leukemia risks since this group has experienced lower mortality than whites (Mason and McKay, 1974). In principle, the study design would have produced a slightly higher than expected relative risk for multiple myeloma since the local rate is greater than that of all U. S. white males and because nonwhite males have somewhat higher rates than whites (Mason and McKay, 1974). However, the geographic factor is only about 30% and both cases of multiple myeloma are white males.

Cases of multiple myeloma have been reported following occupational exposure to benzene in several occupational settings (Torres *et al.*, 1970; Aksoy, 1980; R. A. Rinsky, personal communication, 1981) but the data are too scanty for a firm

TABLE 7
 EMPLOYMENT AND MEDICAL DATA FOR SUBJECTS DYING OF CANCERS OF THE LYMPHATIC AND HEMATOPOIETIC TISSUES

Case	Sex/ race	Year of first employment	Year of last employment	Year/age diagnosis	Diagnosis	Year/age death	Comments
A	M/W	1943	1976	1970/45	Multiple myeloma (IgG, Kappa)	1977/52	Treated for 5 years with daily Alkeran and intermittent radia- tion therapy. Then treated for 1 year with Cytoxan, Vincristine, and Prednisone when disease became aggressive.
B	M/W	1944	1955	1971/52 1973/55	Multiple myeloma (IgG, Kappa) Sideroblastic anemia	1975/55	Treated with radiation therapy to lumbar vertebra in 1971. Treated with Mephalan and Prednisone on daily basis until 1973. Treated with Cytoxan, Vincristine and Prednisone for leukemia in 1973.
C	M/W	1919	1957	1965/73	Acute monocytic leukemia*	1965/73	Died from leukemia before treatment instituted.
D	M/W	1945	1967	1960/58	Chronic lymphatic leukemia	1974/72	Treated with Cytoxan and Prednisone for 6 years.

* Underlying cause of death listed as acute undifferentiated leukemia on death certificate.

estimate of risk. In addition, excess mortality from this tumor was found among workers in the U. S. petroleum refining and petrochemical industry but there was no information on specific exposures experienced by the cases (Thomas *et al.*, 1980).

Review of hospital records for Case B was particularly informative since the type of leukemia reported on the death certificate was "acute undifferentiated" while the medical chart showed this to be "acute myelomonocytic," a type previously linked both to benzene and chemotherapy (Kyle *et al.*, 1975). The two-year latent period from initiation of chemotherapy to development of leukemia in this case is typical of that seen in other instances- of therapy-induced leukemia in myeloma patients (Bergsagel *et al.*, 1979). Alternatively, occupational exposures could have accounted for both malignancies.

Recent advances in immunopathologic classification have shed new light on the interrelationships among various lymphoreticular neoplasms. Of particular relevance to this study is the fact that both multiple myeloma and chronic lymphocytic leukemia are disorders of B-cell lineage (Blattner, 1980). Surveys of rubber workers exposed to various organic solvents (one of which might have been benzene) have found increased risks for chronic lymphatic leukemia (McMichael *et al.*, 1975; Monson and Fine, 1978). It may be that long-term, low-level exposures to various organic solvents, alone or in combination with other agents, induce B-cell neoplasms through a chronic immunosuppressive mechanism (Matanoski *et al.*, 1975). Evidence for such a model has been found where alterations in B-cell populations and immunoglobulin levels were documented in animals exposed to benzene (Irons *et al.*, 1979). Future studies of industrial populations exposed to benzene could take into account these newer immunopathologic classifications and help clarify previously unsuspected relationships.

The possible deficit for cancer of sites other than lymphatic and hematopoietic tissues in Table 6 is interesting (5 observed deaths versus 9.71 expected), although not statistically significant at the $\alpha = 0.05$ level. In fact, the lower than expected rate of lung cancer is enhanced if an adjustment is made to account for the 60% greater mortality among white males living in the local area relative to the total U.S. (Mason and McKay, 1974). This is surprising, especially when viewed against the added risk to maintenance workers at the plant of handling asbestos insulation products. On the other hand, the observed number of cancer deaths could be understated due to incomplete follow-up. In any case, a real deficit for these sites would not be readily explicable.

In summary, the present findings are consistent with previous reports of leukemia following occupational exposure to benzene. In addition, the study augments prior observations of a possible link between benzene and multiple myeloma. Finally, the limited medical data suggest an etiologic role for benzene in the pathogenesis of tumors of B-cell lineage and highlight the need for broader examination of lymphoreticular neoplasms in similar studies.

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