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LEUKEMIA AMONG WORKERS EXPOSED TO BENZENE *

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ABSTRACT

Because of the overwhelming excessive risk of leukemia among workers exposed to benzene in the study population, analyses for mortality from lymphatic and hematopoietic malignancies are reported at this time. Although follow-up for vital status is less than 75% completed, the results already demonstrate a statistically significant ($p<0.002$) excess of leukemia in benzene workers as compared to expectations based on either the U.S. white male population or on an industrial population employed over the same period of 'time in the same State as the study population.

A 5-fold excessive risk of total leukemia and a 10-fold excess of myelomonocytic leukemias aredemonstrated even under conditions leading to an underestimate of the true leukemia risk. Those conditions are the treatment in the analyses of individuals whose vital status was unknown as being alive until the last day of the study period.

The environment of the workers in this study population was not contaminated with solvents other than benzene, and existing records indicate that the benzene levels themselves were generally below the recommended guidelines at the time of their measurement.

INTRODUCTION

One of the earliest reports of benzene-related hematologic disorders, which is consistent with what is now known to result fran benzene poisoning was published in Paris in 1897.[1] By 1928, a clearly established case of leukemia was associated with benzene exposure in Italy.[2] Since that time, numerous cases of leukemia among individuals having prior exposure to benzene have been reported in France,[3] in Italy,[4] in Switzerland,[5] in Japan,[6] in Turkey,[7] in the United States (U.S.),[8] and in the Soviet Union.[9] A significant excess of chromosomal aberrations also has been observed in benzene-exposed workers as compared to controls.[10]

Ishimaru, et al.,[6] have demonstrated a significant association between leukemia and occupations with probable exposure to benzene. Aksoy *et* al.,[7] have reported a significantly greater incidence of leukemia among shoe workers exposed to benzene as contrasted with the incidence of leukemia in the general population. In 1976, Vigliani[4] reported that 150 cases of leukemia attributed to benzene had been identified in Italy alone. McMichael et al.,[11] have demnstrated an excess of leukemia among rubber mrkers having had prior exposure to solvents including benzene. However, this study is subject to criticism because of exposure to a variety of solvents in the rubber products manufacturing industry.

Parallel with these observations of benzene-related hematologic disorders, production of benzene rapidly expanded. Approximately 10.2 billion pounds were produced in the U.S. in 1973, 3.5 billion pounds in Japan in 1972 and 1.2 billion pounds in the U.K. in 1972.[12] Prior to World War I, the major industrial use of benzene was as a solvent in the rubber industry. During World War I, the demand for toluene in the manufacture of explosives greatly stimulated benzene production. Today benzene is used principally as a chemical raw material in the synthesis of compounds such as styrene, phenol, and cyclohexane, which accounts for 87% of its use. During the 50-year period following the first reported benzene-associated leukemia, benzene has not been widely acknowledged nor uniformly controlled as a carcinogen in the U.S.[13] The failure to control benzene as a carcinogen has resulted primarily from the reluctance of Industry and Government to accept the accumulated case reports and epidemiologic observations as scientific evidence of the leukemogenic properties of benzene. Today, in the U.S. alone, an estimated two million workers have potential exposure to benzene.[14] For these reasons, a study was undertaken to determine mortality patterns among workers occupationally-exposed to benzene. Workers employed in the production of a natural rubber cast film (rubber hydrochloride, marketed under the trade name Pliofilm) at either of two localities in Ohio were selected for study.

INDUSTRIAL *HYGIENE* ASSESSMENT

Process Description

In the production of Pliofilm, natural rubber was masticated in an internal mixer (Banbury), passed through a mill, and conveyed to mixing tanks where benzene was added and the mixture was agitated. The resulting solution was pumped to a blending tank. As the process continued, the solution was transferred into a reactor vessel, where it was treated with HCl to form rubber hydrochloride. At this stage, additional benzene was added to adjust the percent of solids in the solution. From the reactor vessel, the rubber hydrochloride was transferred to a neutralizing tank, where Pliofilm scraps, soda ash, steam, plasticizers and additional benzene were added. After filtration, the rubber hydrochloride solution was pumped to a casting unit where it was spread on a continuous conveyor, the benzene was evaporated, and the finished film was taken up on a roll. The gas containing benzene was exhausted from the casting unit, passed through a wet scrubber, and channeled into an activated charcoal absorber unit, where benzene was recovered and recycled. The rolls of Pliofilm were transferred to another room where they were inspected for quality, trimmed, cut to customer specification and packed for subsequent usage, primarily for food wrapping. In the production of Pliofilm, the only material known to be associated with hematologic disorders was benzene, Other materials used in the process included hydrochloric acid (HCl), soda ash and small amounts of antioxidants and plasticizers. The manufacturing process

was essentially identical at both Ohio localities.

Environmental Monitoring

In 1942, Wilson, as a former member of corporate management recommended a policy for the rubber industry, which would include Pliofilm operations, of periodic air monitoring and a complete blood count for all new employees.[15] Furthermore, Wilson stated "a closed system of ventilation where the workman comes in contact with no fumes is ideal. Any other type of ventilation is not entirely *safe.*" Shortly thereafter, extensive exhaust ventilation equipment was known to have been installed in the Pliofilm department in one locality. The Industrial Commission of Ohio (ICO) surveyed this department in 1946 and stated: "Tests were made with benzol detectors and the results indicate that concentrations have been reduced to a safe level and in most instances range from zero to 10 or 15 parts per million" (ICO report, Nov. 1946). A further investigation of benzene exposure at this facility in 1956 concluded that exhaust ventilation controls were of excellent design (ICO report, Jan. 1956). In the early 1960's, benzene point-source concentrations were measured by company personnel using detector tubes. A total of 112 surveys were conducted at this facility over the 11 year period, 1963-1974. These and earlier surveys have indicated that employees' benzene exposure was generally below the recommended concentration in effect at the time of each *survey.*[13,14,16-18]

See Table 1.

Historical environmental data for the second locality in Ohio is less well defined. However, based on walk-through observations, discussions with company personnel, and the meager environmental data that was retained, it is assumed that employees' benzene exposure at this location was consistently well-within the recommended limits.

RETROSPECTIVE COHORT STUDY

Methods

All white males having had direct exposure to benzene at any time during the period of January 1, 1940 through December 31, 1949 were selected for study. In each plant, the departments and jobs involving direct exposure to benzene were determined following a walk-through survey by NIOSH personnel which included a review of the Pliofilm process, of engineering controls and of available air sampling data. Company personnel also assisted in these determinations. Job classifications involving benzene exposure were determined without knowledge of the mrkers vital status.

Follow-up of all study cohort members was attempted from the time of termination of employment to June 30, 1975. To date, vital status determination has been made for approximately 75%of the 748 Cohort members. Persons for whom vital status could not be-determined were assumed to be alive so as not to overestimate the true risk of lymphatic and hematopoietic malignancies associated with benzene exposure.

Causes of death were determined from death certificate reporting and were coded by a qualified nosologist using the International Classification of Diseases (ICD codes) in effect at the time of death; these codes were then converted to 7th Revision numbers. A modified life-table technic was used to generate person-years at risk of dying according to five-year age group and five-year calendar time periods.

Person-years of observation and causes of death were determined for the time period January 1, 1950 through June 30, 1975, the period of observation for risk of dying. Person-years of observation and deaths occurring prior to January 1, 1950 were excluded from the data analyses since vital statistics on lymphatic and hematopoietic malignancies were not published prior to that date.

Two populations were chosen as control groups for generating the numbers of expected deaths in the study population. The first group consisted of the U.S. white male general population specific for age and *calendar* time period. The second group consisted of 1447 white males who were initially employed in the State of Ohio at a fibrous glass construction products facility between January 1, 1940 and December 31, 1949 and who had achieved five or more years of employment by June 1, 1972, which was the cut-off date for vital status ascertainment in the fibrous glass control population.[19]

Results

As shown in Table 2, 140 deaths frm all causes were observed among benzene exposed mrkers as contrasted with 187.6 expected deaths. This deficit is partially a reflection of incomplete follow-up of the study population at the time of this report. Table 2 also shows a significant excess of deaths from malignancy of the lymphatic and hematopoietic system (200-205) when compared to that expected on the basis of U.S. white male rates. This is a reflection of excessive deaths fran leukemia (204). To date, seven leukemia deaths have been observed versus 1.38 expected ($p<0.002$) based on U.S. white &e rates and 1.48 expected ($p<0.002$) based on rates for fibrous glass mrkers. Even more striking is the observation that all seven leukemia deaths were fran either the myelogenous or monocytic type. Data for cell type, age at death and interval since initial exposure to benzene are shown in Table 3. The period between initial exposure and death ranged from 2 to 21 years. These observations indicating a specific type of leukemia are highly consistent with the data of Vigliani[4] which show a predominance of the acute myelogenous leukemia among workers exposed to benzene in the rotogravure and shoe-manufacturing industries in Italy. Since data for specific types of leukemia mortality in the U.S. are not readily available for the study period, incidence rates for myeloid, monocytic leukemia and total leukemia frm the Connecticut Tumor Registry[20] for the period 1960-1962 were applied to the age distribution of the benzene exposed cohort to generate the specific proportion of total leukemia cases which would be

of the myelomonocytic types. Of the total expected number of incidence cases of leukemia, 50.37% were calculated to be of the myelomonocytic types. This proprtion was applied to the total number of expected leukemia deaths in the study cohort which had been previously generated on the basis of U.S. white male population rates. The results indicated an expectation of 0.6967 (0.5037 x 1.3831 = 0.6967) deaths from myelogenous and monocytic leukemia as compared to seven observed; the SMR being 1004. Thus, Pliofilm workers exposed to benzene can be estimated to be at a 10-fold increased risk of dying fran myelomonocytic leukemia.

As a result of past failure to control benzene as a carcinogen, millions of workers, without knowledge of the hematopoietic dangers, are continually being exposed to benzene in the occupational setting. In dation, unknown numbers of consumers, including *children,* are exposed to benzene through use of products around the haw such as del airplane glue, and paint strippers (sane containing up to 50% benzene).

It is now hoped that the current findings which demonstrate overwhelmingly an increased risk of leukemia in mrkers exposed to benzene will stimulate efforts to control occupational and consumer exposure to benzene, an agent known for almost a century to be a powerful bone marrow poison.[4]

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TABLE 1

CHRONOLOGY OF RECOMMENDED BENZENE CONCENTRATIONS IN THE WORKPLACE IN THE UNITED STATES

Year	Standard, ppm		Reference
1941	100	MAC	16,17
1947	50	8-hr. TWA	14
1948	35	8-hr. TWA	14
1957	25	8-hr. TWA	14
1963	25	Ceiling	14
1969	10	8-hr. TWA	18
1971	10	8-hr. TWA	13

MAC = Maximum Allowable Concentration

TWA = Time Weighted Average

TABLE 2

Status on April 13, 1977, of Observed Deaths from Specific Causes Among White Males Between 1/1/50 and 6/30/75 Who Were Exposed to Benzene and Employed Sometime Between 1/1/40 and 12/31/49, as Contrasted With Expected Deaths Based on Both the U.S. White Male Population (USWM) and on an Industrial Population Exposed to Fibrous Glass (FG).

	Benzene Exposed Workers			
Causes † of death (ICD codes)	Deaths Observed	Deaths Expected	Comparison Group	SMR
All causes	140	187.5809	(USWM)'	075
(200-205)	9	3.4497	(USWM)	260+
(204)	7	1.3831	(USWM)	506++
(200-205)	9	5.1020	(FG)	176
(204)	7	1.4758	(FG)	474++

† ICD 7th Revision Codes

(200-205) = Total Lymphatic and Hematopoietic Cancer; (204) = Leukemia only

+ $p<0.05$

++ $p<0.002$

SMR = OBS./EXP. x 100

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TABLE 3

CASES OF LEUKEMIA AMONG WORKERS EXPOSED TO BENZENE
DURING TIE MANUFACTURE OF PLIOFILM

Case Number	Type of Leukemia	Age at Death (years)	Period Between Initial Exposure and Death (years)
1	Acute myelogenous	60	13
2	Acute myelogenous	65	10
3	Acute myelogenous	62	21
4	*Acute* myelogenous	57	19
5	Monocytic	57	15
6	Chronic myelogenous	29	2
7	Monocytic	36	17
8*	Myelogenous	28	3

* Indicates leukemia case which did not fit into cohort definition. The subject began employment in 1950.

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