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Cohort Study Among Workers Exposed to Benzene in China: I. General Methods and Resources

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Benzene is recognized internationally as a leukemogen, but the available data to clarify dose-response relationships and examine risks of malignancies other than leukemia are sparse. A collaborative study was therefore carried out to expand on a previous retrospective cohort mortality study of Chinese benzene-exposed workers. Methods and resources used in the 16-year follow-up of 74,828 benzene-exposed and 35,805 unexposed workers employed for any length of time during 1972–1987 in 712 factories in 12 cities in China are described. Details are provided of the study organization, assessment of benzene exposures since 1949, characterization of factories and workers by exposure status, city, and sex, identification and confirmation of cancers and other deaths, and quality control procedures. The distinguishing features of the study are discussed in relation to earlier cohort studies, and study limitations as well as strengths are presented.

Key words: benzene, occupational exposure, leukemia, hematopoietic neoplasms, cancer

INTRODUCTION

The evidence linking benzene exposure with leukemia was considered sufficient proof of human carcinogenicity by 1981 [IARC, 1982] based on identification of 13 myeloid leukemia cases in two small U.S. cohorts [Rinsky et al., 1981; Ott et al.,

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1978], 19 leukemia cases among 179 Italian and Turkish workers with benzene hemopathy [Vigiliani, 1976; Aksoy and Erdem, 1978], 34 leukemia cases (an estimated two-fold excess) among approximately 28,500 Turkish shoeworkers [Aksoy et al., 1974], and case-control studies with 50–257 leukemia cases in France, Sweden, and the United States [Goguel et al., 1967; Girard and Revol, 1970; Brandt et al., 1978; Linos et al., 1980]. Benzene exposure information was reported in only a few of these studies [Rinsky et al., 1981; Ott et al., 1978; Vigiliani, 1976; Aksoy and Erdem, 1978; Aksoy et al., 1974]. Among occupational groups exposed to benzene along with other possible carcinogens, excesses of leukemia and other hematopoietic malignancies were reported in some U.S. rubber manufacturing [McMichael et al., 1975; Monson and Nakano, 1976; Tyroler et al., 1976] and Government Printing Office workers [Greene et al., 1979], Japanese atomic bomb survivors [Ishimaru et al., 1971], but not others (workers in the British rubber industry [Parkes et al., 1982], European affiliates of a U.S. oil company [Thorpe, 1974], and petroleum refineries in Britain [Rushton and Alderson, 1980]).

Subsequent cohort [Decouflé et al., 1983; Tsai et al., 1983; McCraw et al., 1985; Bond et al., 1986; Wong et al., 1986; Yin et al., 1987a; Wong, 1987; Paci et al., 1989], case-control [Rinsky et al., 1987], and other [Aksoy, 1985] investigations among benzene-exposed chemical manufacturing, refinery, and other workers in the United States, United Kingdom, China, Italy, and Turkey have confirmed the benzene-leukemia association. Risk assessments suggest that 5–250 excess leukemias (45–50 cases on average) per 1,000 deaths would be expected subsequent to a time-weighted average exposure of 10 parts per million (ppm) benzene during a typical 30-year working life [Austin et al., 1988; Swaen and Meijers, 1989]. Although leukemia risk appears to be greater among workers with higher, continuous, and/or longer duration benzene exposures [McCraw et al., 1985; Austin et al., 1988; Swaen and Meijers, 1989], the available data are too sparse to precisely specify dose-response relationships.

Hematopoietic and lymphoproliferative disorders other than leukemia have been described in benzene-exposed workers in case reports [Browning, 1965; Aksoy, 1980; Aksoy et al., 1987] and a few cohort [McMichael et al., 1975; Monson and Nakano, 1976; Tyroler et al., 1976; Greene et al., 1979; Wong, 1987; Ott et al., 1989] and case-control [Rinsky et al., 1987] studies. A small apparent excess of lung cancer was noted among Turkish workers with long-term benzene exposure [Aksoy, 1980], and more recently in the Chinese benzene workers cohort [Yin et al., 1989], but there have been few systematic investigations of malignancies other than leukemia among benzene-exposed occupational groups.

Since the 1950s, benzene poisoning and leukemia have been recognized as possible consequences of benzene exposure in China. Yin et al. [1987b] carried out a nationwide benzene monitoring survey during 1979–1981 in China which revealed that approximately 529,000 workers were exposed to benzene or benzene mixtures. In a retrospective cohort mortality study of 28,460 benzene-exposed workers employed and followed up through 1972–1981, Yin et al. [1987a, 1989] identified 30 leukemia cases compared with 4 such cases among 28,257 unexposed workers. Workers with a history of chronic benzene poisoning, defined as persisting depression of the total white blood count at levels below 4,000/mm^3 for at least 6 months [Yin et al., 1987b] were found to have a notably increased risk of leukemia in the cohort investigation [Yin et al., 1987a,b]. The present study is an expansion (including additional exposed and unexposed workers, 6 more years of follow-up, and detailed evaluation of available exposure information from 1949 through 1987) of the initial retrospective cohort mortality investigation. A unique feature of the present expanded study is a detailed quantitative exposure assessment utilizing a new methodology. The present study has been collaboratively conducted by the Institute of Occupational Medicine of the Chinese Academy of Preventive Medicine (IOM, CAPM), the provincial or municipal Health and Disease Prevention Stations and Institutes of Occupational Medicine in 12 cities in China, and the U.S. National Cancer Institute (NCI).

The major objectives of the investigation are: to compare incidence rates for leukemia and its subtypes, other hematopoietic and lymphoproliferative neoplasms, and related nonmalignant hematologic disorders (all of these combined malignant and nonmalignant disorders herein abbreviated as HLP or hematolymphoproliferative disorders) among benzene-exposed and unexposed workers and among workers with benzene poisoning; to classify risk of leukemia, other HLP disorders, and other cancers by industry, occupation, job title, age and year of first exposure, and level and duration of exposure; to examine the role of other risk factors (including cigarette use, lifetime job-related and environmental exposures, medical and family history) in the benzene-leukemia relationship; and to determine rates of mortality from cancers other than leukemia and other HLP malignancies among benzene-exposed and unexposed workers by broad job and exposure characteristics.

In this paper we present an overview of the study, and describe the study and comparison populations, resources, and methods used in the two major (i.e., cohort and nested case-control) study components. The accompanying paper, entitled "A Cohort Study Among Workers Exposed to Benzene in China. II. Exposure Assessment," [Dosemeci et al., 1994] provides a detailed description of the methods used to retrospectively estimate benzene exposures of the exposed population during the study period and summary descriptive data.

METHODS

Study Organization

In China, the Ministry of Public Health and the Institute of Industrial Health oversee occupational health programs, while the IOM, CAPM (under the Ministry of Public Health) is responsible for occupational health research at the national level. Provincial and municipal institutes monitor regional occupational health activities, with district level bureaus of public health (and occupational medicine departments in large factories) comprising the responsible authorities at the local level. Agencies within this organizational structure supported and participated in data collection for the present study that was carried out in factories in 12 cities (Shanghai, Tianjin, Chengdu, Chongqing, Harbin, Shenyang, Jinzhou, Zhengzhou, Luoyang, Guangzhou, Nanchang, and Kaifeng) during 1987–1991 (see map in Fig. 1).

The field directors supervising data collection were occupational medicine physicians, industrial hygienists, and public health specialists, most of whom collaborated in the previous retrospective cohort mortality study [Yin et al., 1987a, 1989], and were employed at the provincial or municipal organizations. The senior abstractors managing day-to-day data collection were also employed at these agencies, and the 376 record abstractors were local medical college or technical school graduates.

Fig. 1. Location in China of field centers collaborating in cohort study of Chinese benzene workers, 1972–1987.

Study and Comparison Populations

Cohort component. The exposed population was substantially expanded from the earlier study to provide both a larger study group and a broader spectrum of benzene exposure levels. The number of unexposed workers was also increased from the earlier retrospective mortality study. The study population comprised workers in 672 factories in which benzene was used, and the comparison population was drawn from 40 control factories. Within the factories, workers were identified from work units, which are the key administrative entities. The majority of workers in China remain in their original work units for their entire working life. Work units typically consist of one or more rooms in which workers are employed in closely related production tasks. For example, an exposed painting work unit might consist of spray painters, brush painters, paint mixers, and helpers, although supervisory and janitorial workers who only experience intermittent or trace exposure to benzene may also be included. In the 1,427 exposed work units selected and in the unexposed factories, every worker employed for any length of time during 1972–1987 was eligible for the present study and included if identified from any of the written records indicated below.

The identification of eligible workers did not rely on the lists of workers included in the previous investigation [Yin et al., 1987a, 1989], but involved a de novo systematic review of factory records. The primary source of information used to identify study and comparison population members was salary records, which routinely include information on name, job title, and year and month of salary payment and other compensation. From the salary records, abstractors recorded each worker's entire job history from initial employment to December 31, 1987 or termination, if sooner. If the salary records were not available, other written data sources were utilized according to a predetermined and consistent strategy, starting with job registers (completed by factory workers at the start of employment), then physical examination forms, followed by hazardous work compensation registries. The records of each worker identified from an unexposed work unit were carefully reviewed and excluded from the comparison population if he/she had ever worked in an exposed study work unit.

Nested case-control component. To further assess dose-response relationships of benzene and other suspected risk factors with leukemia and other HLP disorders, a nested case-control study was carried out. For each exposed and unexposed leukemia or other HLP case, four controls were randomly selected from the pool of exposed and unexposed workers of the same sex, and from the same city and time period of first employment (pre-1962, 1962–1971, 1972–1981, 1982–1987). Also, for a given case, each eligible control must have entered the cohort at an age that was younger than the case's age at diagnosis, and must have remained in the cohort without developing a blood malignancy or related disorder up to an age that was older than the case's age at diagnosis. Controls were randomly selected without replacement from the risk set generated by the case at a ratio of 4:1 with one alternate control also being identified. The alternate control was only to be used in the event that an original control could not be traced.

Exposure Assessment

The major objective for the cohort component of the exposure assessment was to develop time period-specific quantitative estimates of benzene exposure by *job title* within work units, whereas for the case-control component, the derived estimates were intended to reflect the exposure of the *individual workers being studied.* The exposure assessment methods are described in detail in the accompanying paper [Dosemeci et al., 1994].

Disease and Mortality Follow-Up

Individual workers being studied were followed up to determine vital status and, for the deceased, the cause of death. Efforts were also made to identify all study persons, living or deceased, who developed benzene poisoning, leukemia, or other HLP disorder. For employed or retired factory workers in China, the place of employment is responsible for health care; thus, the study and comparison factories were the primary initial data sources for vital status and disease history. Movement of workers from one factory to another requires permission from both factories, and therefore occurs much less frequently in China than in other countries. Factory personnel records could generally be used to find information about moves to other factories, with vital and disease status then ascertained by tracing workers to their new place of employment, or by contacting next-of-kin, work colleagues, treating physicians, or others. All tracing was done in a predetermined and systematic manner, with all tracing activities documented on written forms.

For deceased study persons, cause of death was obtained from medical records, other written factory records, or death certificates at local police stations. Only if written documentation of cause of death could not be obtained from these sources were next-of-kin contacted. For all individuals whose cause of death was suspected to be cancer or serious hematopoietic disorder, hospital and other medical records were sought to verify the diagnosis. The specific histopathology, date of diagnosis, date of death, source of diagnostic-related information, hospital/place of death, and any other important diagnosis-related information were abstracted on a diagnostic validation form. At each of the 12 field centers, the cause of death and disease information and abstracts for cancer deaths were reviewed for all deaths by the field supervisor and coded according to an adaptation of the International Causes of Disease (ICD) Code 9th Revision.

Medical records and any available pathology slides and peripheral blood smears were sought to validate all leukemia and other HLP diagnoses, as described in detail elsewhere [Travis et al., in press]. Briefly, detailed information was collected by the field staff and sent to the NCI where it was translated and a detailed summary made by the investigators using a standardized medical record abstract form. The information abstracted included: history of initial symptoms; physical examination findings; relevant X-ray reports; pretreatment peripheral blood examinations; bone marrow aspirates and biopsies; and relevant lymph node or other tissue histopathology. All available blood smears, histopathologic slides, and the summarized medical record were reviewed for all leukemia and other HLP cases, and a detailed description of the histopathologic material was abstracted on to a standardized form by hematopathologists from the Peking Union Medical College Hospital, NCI, and the Mayo Clinic in Rochester, Minnesota [Travis et al., in press]. A diagnosis and a corresponding level of certainty were then assigned to each case.

To determine whether benzene-related leukemia and other HLP disorders were preceded by hematologic abnormalities, records of all available prediagnostic blood counts and peripheral blood smears of exposed cases and the corresponding exposed controls were sought and abstracted.

Quality Control Activities

Special attention was given to standardizing the multicenter data collection. Forms and training materials were developed in English, translated into Chinese, then back-translated to English. Training sessions and opportunities for supervisory staff to review data collection materials preceded each phase of data collection, as did pilot studies to thoroughly field test all procedures.

In each data component, hard copies of all forms were manually reviewed by the field directors at each center and at the Beijing data coordinating center at the IOM, CAPM; problem forms were returned for additional data retrieval or correction. Data entry was undertaken only after manual review showed no errors. The diagnostic validation information for each cancer death, the medical record abstract information for each person diagnosed with leukemia or other HLP disorder, and each form completed in the case-control component were manually reviewed by the investigators at NCI, and forms with inconsistencies, possible errors, or missing data were returned for additional data retrieval or correction.

After computerization, the exposure data were evaluated in more detail by the investigators for internal consistency and standardization among the 12 cities. For example, information on dates of factory operations, first use of benzene in the factory, and introduction of control measures was compared with dates provided in the exposure forms completed for each job title. The field staff in China were then asked for clarification of discrepancies. Exposure monitoring results were compared with the time period-specific quantitative estimates of benzene exposure by job title made by the center directors. Work history data for individual workers were used to evaluate the completeness of temporal coverage of the exposure information. Additional information was sought from the field staff in China when job or calendar-year period information was found to be missing or incomplete.

For the case-control component, Chinese and NCI investigators listened to the entire audiotaped questionnaire administration for the first three to five respondents interviewed in each city, and to randomly selected portions of the interviews for a sample of the remaining respondents. A supervisory-level staff member in Beijing, who was unaware of case/control status, compared each of the audiotaped interviews with the hard-copy forms. The written interview forms were then corrected, and additional data obtained from respondents by the field staff for any incomplete or inconsistent information.

In the analysis (ongoing), we compared the detailed subject-specific exposure information (considered as a "gold standard") with that collected for the same individual in the cohort component (in which exposure estimates based on information obtained at the job title level for each time period were extrapolated to individual subjects) to assess the quality of the latter. The few problems identified in these quality control checks were quickly addressed with additional local training sessions and ad hoc site visits by Chinese and American investigators.

Statistical Analysis

The primary aim of the statistical analysis (ongoing) was to determine whether incidence rates of leukemia and other HLP disorders and mortality rates for cancer were associated with benzene exposure. Both external and internal comparisons were undertaken.

For external comparisons, standardized mortality ratios (SMRs) were calculated as the ratio of the observed numbers of cases and the expected numbers under the assumption that the age- and sex-specific rates in a standard population applied. However, national and city-specific mortality rates for China were only available for the years 1973–1975 [Editorial Committee for the Atlas of Cancer Mortality in the People's Republic of China, 1979] and accurate cancer incidence data as far back as the 1970s have been routinely collected in only one of the study cities, Shanghai [Waterhouse et al., 1982]. In addition, general population disease rates in China might not be an appropriate comparison for disease rates in the benzene-exposed and unexposed populations due to the healthy worker effect [Fox and Goldblatt, 1982; Breslow and Day, 1987]. Therefore, assessments utilizing external comparisons have been limited.

For the internal comparisons, Poisson regression models were used to estimate risks [Breslow and Day, 1987], with each cohort member contributing to cause-specific person-year tables that partition person-years and disease events across levels of various demographic and exposure variables, with appropriate consideration of time dependency. Risk of leukemia and other HLP disorders incidence and cancer mortality were assessed with respect to level of benzene exposure, with statistical adjustment for demographic and other exposure variables.

We have treated exposure as a time-dependent variable in all analyses. For subjects included in the exposed group due to exposure to benzene, person-years of follow-up only began to accrue after the subject was first exposed to benzene. Duration of exposure stopped accruing when the subject stopped working in an exposed job, and only resumed when he/she began working at an exposed job again.

For the analysis of the nested case-control component of the study (ongoing), standard statistical methods were used, including conditional logistic regression [Breslow and Day, 1980]. Time-dependent exposure variables such as cumulative exposure were evaluated for a case and matched control at the date when the age at diagnosis of the case was reached.

RESULTS

Study and Comparison Population Characteristics

The study population included 74,828 workers exposed to benzene (38,832 males and 35,996 females) and the comparison population 35,805 nonexposed workers (20,795 males and 15,010 females) identified from a total of 712 factories: 603 with exposed work units only, 40 with unexposed only, and 69 with both exposed and unexposed (Table I). There was a high proportion of young workers in both exposed and unexposed populations, with approximately two thirds of person-years for each contributed by those born in 1940 or later, and more than 40% by workers born in 1950 or later (Table II). The distribution by age at hire was consistent with this pattern in that 36% of exposed and 46% of unexposed were under age 20, and 81% of exposed and 89% of unexposed were hired prior to age 30 by study and comparison factories (Table III). Although the person-years derived from those hired before 1959 were not negligible, about 60% of person-years for exposed and unexposed populations were contributed by workers hired between 1959 and 1978, whereas less than 20% of each resulted from follow-up of those first employed after 1980. The young age of workers in exposed and unexposed populations was further established in that about 60% of person-years for both populations was contributed by workers less than 30 years old, and 85% by workers under age 40 when follow-up began (Table IV). Exposed workers were followed up for an average of 10.5 and unexposed for an average of 11.7 years, since approximately 70% of exposed and 75% of unexposed person-years were contributed by workers who entered into follow-up prior to 1975. Only a relatively small fraction of the total person-years (13.2% for exposed and 10.0% for unexposed) were provided by workers whose follow-up began in 1980 or later (Table IV).

Written records were used to identify all exposed and unexposed workers, the primary data source being the salary list (used to identify 84.0%) (Table V). A slightly higher proportion of unexposed than exposed workers was identified from salary lists, whereas slightly more exposed than unexposed workers were ascertained from job registry records.

Follow-Up and Method of Confirmation of Cancer Diagnoses

At the end of the study period (December 31, 1987), 108,429 (73,312 exposed and 35,117 unexposed) of the workers were alive, 1,967 (1,369 exposed and 598

TABLE I. Distribution of Factories and Subjects by Exposure Status, City, and Sex: Cohort Study of Chinese Benzene Workers, 1972–1987

	Exposed			Nonexposed			Total			Total
Cities	Factories	Males	Females	Factories	Males	Females	Factories	Males	Females	both sexes
Shanghai	80	6,855	4,352	25	4,659	2,985	98 (7)[a]	11,514	7,337	18,851
Tianjin	54	5,005	4,661	7	1,611	1,199	61 (0)	6,616	5,860	12,476
Chengdu	87	3,985	3,949	33	2,014	1,429	90 (30)	5,999	5,378	11,377
Chong Qing	129	5,802	4,791	3	2,471	1,186	130 (2)	8,273	5,977	14,250
Harbin	81	3,250	4,806	11	1,889	2,334	84 (8)	5,139	7,140	12,279
Shenyang	19	3,383	3,547	3	1,855	1,879	22 (0)	5,238	5,426	10,664
Jinzhou	50	1,417	1,593	1	1,860	1,140	50 (1)	3,277	2,733	6,010
Zhengzhou	24	1,683	2,012	3	1,016	1,174	26 (1)	2,699	3,186	5,885
Luoyang	22	1,033	794	3	641	346	22 (3)	1,674	1,140	2,814
Guangzhou	18	1,811	1,505	2	552	170	20 (0)	2,363	1,675	4,038
Nanchang	80	3,726	2,838	9	1,800	856	81 (8)	5,526	3,694	9,220
Kaifeng	28	882	1,148	9	427	312	28 (9)	1,309	1,460	2,769
Total by sex		38,832	35,996		20,795	15,010		59,627	51,006	
All	672	74,828		109	35,805		712 (69)			110,633

[a]Numbers shown in parentheses represent factories which include both exposed and unexposed work units. These combination factories are included in the factory counts for both exposed and unexposed status, but only counted once for computing the total number of factories within each city.

TABLE II. Distribution of the Exposed and Unexposed Populations by Year of Birth: Cohort Study of Chinese Benzene Workers, 1972–1987

	Exposed			Nonexposed		
Year of birth	No.	Person-years	%	No.	Person-years	%
1900–1909	105	1,442	0.2	45	579	0.1
1910–1919	1,495	21,632	2.8	547	7,953	1.9
1920–1929	5,242	78,418	10.0	2,222	34,229	8.2
1930–1939	11,217	164,324	21.0	6,137	95,103	22.7
1940–1949	14,111	186,427	23.8	7,234	108,924	26.0
1950–1959	25,174	244,293	31.2	11,949	133,963	31.9
1960–1969	17,062	85,441	10.9	7,473	38,544	9.2
1970 and later	422	391	0.1	198	179	0.0
All subjects	74,828	782,368	100.0	35,805	419,474	100.0

TABLE III. Distribution of the Exposed and Unexposed Populations by Age and Year at Hire: Cohort Study of Chinese Benzene Workers, 1972–1987

	Exposed			Nonexposed		
	No.	Person-years	%	No.	Person-years	%
Age at hire						
0–19	28,313	284,154	36.3	16,423	191,334	45.6
20–29	34,169	350,666	44.8	15,745	182,024	43.4
30–39	9,255	109,268	14.0	2,778	35,592	8.5
40–49	2,677	33,192	4.3	736	9,021	2.2
50–59	388	4,767	0.6	120	1,467	0.3
60 and older	26	321	0.0	3	35	0.0
Year at hire						
Pre-1959	10,313	154,078	19.7	7,216	113,097	27.0
1959–1968	13,274	199,040	25.4	6,320	100,203	23.9
1969–1978	21,975	270,452	34.6	10,256	137,264	32.7
1979–1987	29,266	158,799	20.3	12,013	68,909	16.4

unexposed) deceased (1.8%), and only 237 (147 exposed and 90 unexposed) had vital status unknown (0.2%). Among exposed workers, 712 (1.0%) were determined to have benzene poisoning, 680 (95.5%) of whom were still alive. Written records were used to verify cause for 79.4% of all deaths and 87.5% of cancer deaths, and to confirm occurrence of 96.9% of hematopoietic malignancies and related blood disorders (Table V). The percentages were generally similar for the exposed and unexposed groups (data not shown).

Overall, approximately 38.7% of cancer diagnoses were based primarily on histopathology, 11.1% on cytology, 1.8% on gross pathology, 37.8% on radiologic or ultrasound exam, 2.8% on clinical diagnosis only, and 7.7% on other methods (e.g., verbal report by family or work colleagues, or unknown) (Table VI). The proportion of diagnoses established by histopathology or cytology did not vary greatly by exposure status for most of the specific cancer types (data not shown).

Nested Case-Control Component

There were 95 cases and 379 controls in the case-control component. Included were 51 cases with leukemia, 7 with myelodysplasia, 23 with non-Hodgkin's lym-

TABLE IV. Distribution of the Exposed and Unexposed Populations by Age and Year at Entry: Cohort Study of Chinese Benzene Workers, 1972–1987

	Exposed			Nonexposed		
	No.	Person-years	%	No.	Person-years	%
Age at entry						
0–19	19,839	158,941	20.3	10,044	90,018	21.4
20–29	31,345	305,876	39.1	14,757	166,793	39.8
30–39	14,024	180,756	23.1	7,011	103,571	24.7
40–49	7,242	103,126	13.2	3,106	46,425	11.1
50–59	2,158	30,831	3.9	810	11,672	2.8
60 and older	220	2,932	0.4	77	944	0.2
All ages	74,828	782,462	100.0	35,805	419,473	100.0
Year at entry						
1972–1975	37,538	545,696	69.7	20,356	315,166	75.1
1976–1979	14,840	133,590	17.1	6,631	62,550	14.9
1980–1983	13,904	85,012	10.9	5,683	35,534	8.5
1984–1987	8,546	18,071	2.3	3,135	6,224	1.5

phoma or other malignant neoplasms of lymphoid and histiocytic tissue, 2 with multiple myeloma, 9 with aplastic anemia, 2 with agranulocytosis, and 1 with another HLP disorder. Among the cases, 83 (87%) were deceased, with interviews completed by next-of-kin or others, while 6.8% of the controls were deceased. Interviews, completed for all cases and controls, included level of education; residence in urban vs. rural areas; detailed *lifetime* job history; residential exposure to benzene, xylene, toluene, or paint; past medical history (of cancer, benzene poisoning, aplastic anemia, and others); use of specific medications; history of diagnostic x-rays and radiation therapy; cigarette smoking history; use of hair dyes; and family cancer history.

For each of the 82 exposed cases, one exposed control was selected (the exposed control whose birth date was closest to that of the case) and all routine, serial prediagnostic blood counts of exposed cases were compared (analysis ongoing) with those of the exposed controls to determine whether benzene-related leukemia and other HLP disorders were preceded by specific hematologic abnormalities.

Quality Control Checks

The investigators and field center directors evaluated the completeness of cohort identification by randomly selecting 20–30 workers from the original salary lists in each of three to five randomly chosen factories in each city, and determining whether these persons were included in the cohort. In the 28 exposed and 19 unexposed factories evaluated, only 1.6% of exposed and 1.1% of unexposed workers identified by the investigator or field director on salary lists had not been included in the final roster of 4,320 exposed and 11,358 nonexposed persons.

The accuracy of abstracting demographic, job history, vital status, and cancer mortality information was evaluated by re-abstracting records for random samples of 10 workers from five factories in each city (a total of 50 workers from each city). Among the 600 workers for whom the follow-up form was re-abstracted, discrepancies in demographic factors and vital status ranged from 0.5–0.8%, for job title or work unit from 0.7%–3%, for duration of employment differences of 2–10 years from

TABLE V. Distribution of Data Sources Used to Identify the Cohort and Verify Causes of Death, Cancer, and Hematolymphoproliferative Disorder Diagnoses: Cohort Study of Chinese Benzene Workers, 1972–1987

Type of data obtained or verified	Salary list No. (%)	Job registry No. (%)	Medical records No. (%)	Other written records No. (%)	Oral information No. (%)	Family information No. (%)	Total No. (%)
Cohort identification	93,038 (84.1)	14,310 (12.9)	2,403 (2.2)	882 (0.8)	—	—	110,633 (100.0)
Verification of all causes of death	48 (2.4)	29 (1.5)	1,144 (58.2)	341 (17.3)	202 (10.3)	203 (10.3)	1,967 (100.0)
Verification of primary cancer diagnoses (excludes malignant blood disorders)	—	—	458 (67.6)	135 (19.9)	85 (12.5)	—	678[a] (100.0)
Verification of hematolymphoproliferative disorder diagnoses	—	—	85 (89.5)	7 (7.4)	3 (3.1)	—	95 (100.0)

[a]There was one subject in the cohort with two primary cancers (excluding malignant blood disorders), and a total of 678 diagnoses among the 677 subjects.

TABLE VI. Distribution of Methods Used to Confirm Primary Cancer Diagnoses by Cancer Type: Cohort Study of Chinese Benzene Workers, 1972–1987

Type of cancer	Histo-pathology No. (%)	Cytology No. (%)	Gross pathology No. (%)	Radiology No. (%)	Ultrasound No. (%)	Clinical evidence only No. (%)	Other No. (%)	Unknown No. (%)	Total No. (%)
Nasopharynx	11 (61.1)	1 (5.6)	1 (5.6)	5 (27.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	18 (100.0)
Esophagus	12 (35.3)	5 (14.7)	0 (0.0)	14 (41.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (8.8)	34 (100.0)
Stomach	75 (58.6)	1 (0.8)	3 (2.3)	38 (29.7)	0 (0.0)	2 (1.6)	6 (4.7)	3 (2.3)	128 (100.0)
Colon and rectum	37 (72.6)	1 (2.0)	2 (3.9)	3 (5.9)	1 (2.0)	1 (2.0)	5 (9.8)	1 (2.0)	51 (100.0)
Liver, gall bladder, extrahepatic bile ducts	27 (17.1)	1 (0.6)	2 (1.3)	38 (24.1)	70 (44.3)	5 (3.2)	7 (4.4)	8 (5.1)	158 (100.0)
Lung	44 (26.5)	16 (9.6)	2 (1.2)	96 (57.8)	0 (0.0)	4 (2.4)	0 (0.0)	4 (2.4)	166 (100.0)
Non-Hodgkin's lymphoma	17 (73.9)	4 (17.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.7)	0 (0.0)	0 (0.0)	23 (100.0)
Leukemia	11 (21.6)	36 (70.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	0 (0.0)	2 (3.9)	51 (100.0)
Other hematopoietic malignancies	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
Nonmalignant hematopoietic disorders	5 (26.3)	14 (73.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (100.0)
Other cancers	60 (48.8)	4 (3.3)	4 (3.3)	21 (17.1)	7 (5.7)	6 (4.9)	8 (6.5)	13 (10.6)	123 (100.0)
Total	299 (38.7)	85 (11.0)	14 (1.8)	215 (27.8)	78 (10.1)	22 (2.8)	26 (3.4)	34 (4.4)	773 (100.0)[a]

[a]There were two subjects in the cohort with one or more cancers or nonmalignant blood disorders, and a total of 773 diagnoses of these neoplasms and related disorders as shown above among the 771 subjects.

0.8–1.5%, and for differences of less than 2 years from 3.9–5.5%, and there were no discrepancies in determination of cancer as a cause of death.

In review of the individual worker follow-up forms for all persons reported as deceased, the diagnostic validation forms for all cancer deaths and the assigned diagnostic codes for all causes of death revealed very little missing or inconsistent information. In the evaluation of diagnostic code assignment, the investigators and trained nosologists found only a very small percent of the ICD code assignments to be inaccurate and these were corrected. Review of the medical record data showed that the level of information was quite detailed and generally complete for cases diagnosed in the 1980s and varying in completeness for cases diagnosed in the 1970s, as expected. Following extensive efforts to obtain the medical record and histopathology material sought, the field staff located detailed medical record information for 62% of the 95 cases, less detailed or sketchy records for 27% of cases, and learned that medical records had apparently been destroyed for 11% of cases. Pathology slides and/or peripheral blood smears were obtained for 23 (24%) cases.

There were a total of 3,179 job titles and 18,435 job title/calendar year periods for which detailed exposure information was obtained; only 0.8% of the latter had partially missing or internally inconsistent information, which was corrected. Few discrepancies (0.1–0.4%) were found between the work history information of individual workers and the job title/calendar year period exposure information obtained from factory records. Additional information was obtained to resolve all discrepancies. The center directors' confidence in the exposure estimates which they assigned to specific job titles during the seven calendar periods improved dramatically from 1949 through 1987. During 1949–1959, the directors felt unable to assign a level of confidence to 28% of the estimated exposure levels and assigned a rating of ''confident'' or ''very confident'' to 76.9% of the job title/calendar year period exposure estimates, whereas during 1985–1989, only 0.5% of the job titles were not assigned a confidence level corresponding to the exposure estimate; and a rating of ''confident'' or ''very confident'' was assigned to 93.9% of the exposure levels estimated for each of the job titles.

DISCUSSION

This collaborative NCI-CAPM investigation is one of the largest cohort studies of cancer risk among benzene workers carried out to date. Compared with prior cohort and case-control studies in China and elsewhere, this study had five unique strengths: 1) detailed characterization of exposure (on the job title level within a given work unit and time period for the cohort component and on the individual worker level for the case-control component); 2) a large number of benzene-exposed and unexposed workers, including the largest cohort of female benzene-exposed (35,996) workers ever evaluated; 3) a comprehensive assessment of lifetime exposure to benzene and other factors that may confound the benzene-leukemia relationship for persons in the nested case-control study; 4) a substantially larger number of leukemia and other HLP cases; and 5) detailed clinicopathologic characterization of these cases.

Three prior cohort studies also quantified benzene exposure, although the size of these cohorts and the number of leukemia cases were substantially smaller than the present study. Rinsky et al. [1981, 1987] carried out a detailed quantitative assessment of the relationship between cumulative benzene exposure and leukemia among 1,165 men employed in the manufacture of rubber hydrochloride (trade name Pliofilm), who had been exposed to benzene for at least 1 day during 1940–1965 and followed up through 1981. The overall SMR for leukemia (cause of death determined from death certificates) was 337, but with stratification according to estimated cumulative exposure, the SMRs for leukemia increased from 109 for cumulative benzene exposure totaling less than 40 ppm-years, to SMR = 322 for 40–199 ppm-years, SMR = 1,186 for 200–399 ppm-years, and SMR = 6,637 for exposures of 400+ ppm-years. These estimates were based on a total of nine observed leukemia cases (vs. 2.7 expected), however. In a retrospective follow-up of 594 Dow Chemical Company employees occupationally exposed to benzene in the production of alkyl benzene during 1938–1970 and followed up through 1982, Ott et al. [1978] and Bond et al. [1986] identified five leukemia deaths (all myelocytic type, based on death certificate and medical record data) compared with 2.1 expected. Estimated cumulative exposure to benzene ranged from 18 to 4,211 ppm-months. Among 4,602 benzene-exposed compared with 3,074 unexposed chemical workers from the same plants, Wong [1987] observed seven deaths from leukemia (four lymphatic, two chronic myeloid, and one acute, not further specified) among exposed workers vs. 5.96 expected, and found SMR = 284 for exposure of 5–14 years and SMR = 131 for exposure greater than 15 years duration. Risk rose with increasing cumulative exposure, to an SMR = 276 for leukemia among workers exposed for 720 ppm-months or longer. None of these studies assessed female workers, nor did any of these include a detailed clinicopathologic characterization of the hematopoietic malignancy cases.

Aksoy [1985] described a series of 51 leukemia cases identified in the hematology departments of the Istanbul and Cerrahpasa Medical Schools and the Istanbul Social Insurance Hospital during 1967–1983 among men (primarily), who were occupationally exposed to benzene in Turkey. A subset of these included 34 male leukemia cases diagnosed during 1967–1974 among approximately 28,500 shoe, slipper, and handbag workers in Istanbul, for an estimated crude incidence of leukemia of 13.6 per 100,000 person-years compared with 6 per 100,000 person-years among men in the general population. Ascertainment of cases, however, was limited to the hematology clinic and was probably incomplete for both the occupational cohort and the general population [Austin et al., 1988]. Two of the 51 cases occurred during a 6-year period in a modern tire cord manufacturing plant in Izmit where approximately 550 workers were employed yearly (estimated leukemia incidence of 60.6 per 100,000 person-years). The concentration of benzene in one place of the plant was recorded as 110 ppm and benzene content in one of the solvents used was 5%. Case-control studies of the relationship of benzene exposure with leukemia risk included both hospital-based [Goguel et al., 1967; Girard and Revol, 1970; Brandt et al., 1980] and population-based [Linos et al., 1980; Ishimaru et al., 1971] investigations, but exposure assessment was limited to questionnaire evaluation of exposures to specific chemicals or occupational history. Neither the cohort nor the case-control studies examined the role of potential confounders in the benzene-leukemia relationship.

The collaborative study in China greatly increases the numbers of benzene-exposed workers evaluated for leukemia and other cancer risk. The identification of 82 exposed cases with leukemia, other HLP and related disorders increases the total previously identified in cohort studies by over four-fold; the large study size will enable more precise assessment of relative risks and dose-response relationships than previously possible. Among the study strengths, the follow-up of a comparison population of nonexposed workers eliminates the total reliance on external standard populations for estimation of cancer mortality and leukemia and HLP disorder incidence rates, thus controlling for unknown characteristics of factory workers that may influence cancer and, particularly, leukemia risk. Because Chinese factory workers do not change jobs as commonly as workers in many other populations, and medical care, leave of absence, and retirement pensions are all overseen by the employing factory, it was possible to achieve an extraordinarily high follow-up rate and virtually complete ascertainment of all deaths as well as incident leukemia and other HLP disorders. In addition, there was a notably high level of participation in the case-control study by subjects and next-of-kin.

Although more than half of the exposure data collected relate to the often high-level benzene exposures of the 1950s through the early 1970s, a large proportion of exposed workers (close to 50%) were first employed after 1975 (contributing about 30% of the person-years of exposed workers), when benzene exposure began to drop substantially in many factories, thus allowing assessment of risk in relation to a spectrum of benzene exposures.

Limitations of this large, multicenter study included variation in understanding and experience of the more than 400 study staff; the inability to include such a large number of data collectors in the group training sessions; and differing resources among the centers. To overcome potential problems related to these limitations, field center directors were encouraged to train their staff immediately upon return from the initial training sessions, extensive attention was given to standardizing all procedures, and each center's application of study procedures was carefully evaluated in substantial pilot studies. The numerous quality control measures employed throughout the study ensured rapid identification of weaknesses so that corrective measures could be applied.

In summary, the information generated by this large collaborative cohort study of Chinese workers exposed to benzene should further extend our understanding of the relationship of benzene, by exposure level, to the occurrence of leukemia and other HLP disorders. Possible associations of benzene with nonhematopoietic cancers should also be clarified. The case-control component should yield information about the role of nonoccupational benzene exposures and other factors that may confound the benzene-leukemia relationship. This study should also provide some of the first risk estimates of leukemia, other HLP disorders, and other cancers among female benzene-exposed workers. Finally, the collaborators developed procedures and quality control measures, enabling successful completion of a large multicenter international study, that may be applicable to other, similar types of collaborative epidemiologic studies and possibly also to international multicenter clinical trials.

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REFERENCES

Aksoy M (1980): Different types of malignancies due to occupational exposure to benzene: A review of recent observations in Turkey. Environ Res 23:181–190.

Aksoy M (1985): Malignancies due to occupational exposure to benzene. Am J Ind Med 7:395–402.

Aksoy M, Erdem S (1978): Follow-up study on the mortality and the development of leukemia in 44 pancytopenic patients with chronic benzene exposure. Blood 44:285–292.

Aksoy M, Erdem S, Dincol G (1974): Leukemia in shoe-workers exposed chronically to benzene. Blood 44:837–841.

Aksoy M, Ozeris S, Sabuncu H, Inanici Y, Yanardag R (1987): Exposure to benzene in Turkey between 1983 and 1985: A haematological study on 231 workers. Br J Ind Med 44:785–787.

Austin H, Delzell E, Cole P (1988): Benzene and leukemia. A review of the literature and a risk assessment. Am J Epidemiol 127:419–439.

Bond GG, McLaren EA, Baldwin CL, Cook RR (1986): An update of mortality among chemical workers exposed to benzene. Br J Ind Med 43:685–691.

Brandt L, Nilsson PG, Mitelman F (1978): Occupational exposure to petroleum products in men with acute non-lymphocytic leukemia. Br Med J 1:553–554.

Breslow NE, Day NE (1980): "Statistical Methods in Cancer Research. Vol I. The Analysis of Case-Control Studies." Lyon: IARC Sci Publ 32:162–189.

Breslow NE, Day NE (1987): "Statistical Methods in Cancer Research. Vol II. The Design and Analysis of Cohort Studies." IARC Sci Publ No. 82. Lyon: International Agency for Research on Cancer.

Browning E (1965): "Toxicity and Metabolism of Industrial Solvents." Amsterdam, The Netherlands: Elsevier, pp 3–65.

Decouflé P, Blattner WA, Blair A (1983): Mortality among chemical workers exposed to benzene and other agents. Environ Res 30:16–25, 1983.

Dosemeci M, Li G-L, Hayes RB, Yin SN, Linet M, Chow WH, Wang YZ, Jiang ZL, Dai TR, Zhang WV, Chao XJ, Ye PZ, Kou QR, Fan YH, Zhang XC, Lin XF, Meng JF, Zho JS, Wacholder S, Kneller R, Blot WJ (1994): A cohort study among workers exposed to benzene in China. II. Exposure Assessment Methods. Am J Ind Med 26:401–411.

Editorial Committee for the Atlas of Cancer Mortality in the People's Republic of China (1979): "Atlas of Cancer Mortality in the People's Republic of China." Shanghai: China Map Press.

Fox AJ, Goldblatt PO (1982): "Longitudinal Study. Socio-demographic Mortality Differentials." London: Her Majesty's Stationery Office.

Girard PR, Revol L (1970): La frequence d'une exposition benzenique au cours des hemopathies graves. Nouv Rev Fr Hematol 10:477–484.

Goguel A, Cavigmezus A, Bernard J (1967): Le leucémies benzéniques de la région Parisienne 1950 et 1965 (Etude de 50 observations). Nouv Rev Fr Hematol 7:465–480.

Greene MH, Hoover RN, Eck RL, Fraumeni JF Jr (1979): Cancer mortality among printing plant workers. Environ Res 20:66–73.

IARC (1982): Some industrial chemical and dyestuffs. IARC Monogr Eval Carcinog Risks 29:93–148.

Ishimaru T, Okada H, Tomiyasu T, Tsuchimoto T, Hoshino T, Ichimaru M (1971): Occupational factors in the epidemiology of leukemia in Hiroshima and Nagasaki. Am J Epidemiol 93:157–165.

Linos A, Kyle RA, O'Fallon WM, Kurland LT (1980): A case-control study of occupational exposures and leukemia Int J Epidemiol 9:131–135.

McCraw DS, Joyner RE, Cole P (1985): Excess leukemia in a refinery population. J Occup Med 27:220–222.

McMichael AJ, Spirtas R, Kupper LL, Gamble JF (1975): Solvent exposure and leukemia among rubber workers: An epidemiologic study. J Occup Med 17:234–249.

Monson RR, Nakano KK (1976): Mortality among rubber workers. I. White male union employees in Akron, Ohio. Am J Epidemiol 103:284–296.

Ott MG, Teta MJ, Greenberg HL (1989): Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. Am J Ind Med 16:631–643.

Ott MG, Townsend JC, Fishbeck WA, Langner RA (1978): Mortality among individuals occupationally exposed to benzene. Arch Environ Health 33:3–10.

Paci E, Buiatti E, Seniori Costantini A, Miligi L, Pucci N, Scarpelli A, Petrioli G, Winkelmann R, Kaldor JM (1989): Aplastic anemia, leukemia and other cancer mortality in a cohort of shoe workers exposed to benzene. Scand J Work Environ Health 15:313–318.

Parkes HG, Veys CA, Waterhouse JAH, Peters A (1982): Cancer mortality in the British rubber industry. Br J Ind Med 39:209–220.

Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ (1987): Benzene and leukemia. N Engl J Med 316:1044–1050.

Rinsky RA, Young RJ, Smith AB (1981): Leukemia in benzene workers. Am J Ind Med 2:217–245.

Rushton L, Alderson M (1980): The influence of occupation on health. Some results from a study in the UK oil industry. Carcinogenesis 1:739–743.

Swaen GMH, Meijers JMM (1989): Risk assessment of leukaemia and occupational exposure to benzene. Br J Ind Med 46:826–830.

Thorpe JJ (1974): Epidemiological survey of leukemia in persons potentially exposed to benzene. J Occup Med 16:375–382.

Travis LB, Li CY, Zhang ZN, Li DG, Yin SN, Chow WH, Li GL, Dosemeci M, Blot W, Fraumeni JF, Jr, Hayes RB, Linet MS (in press): Hematopoietic malignancies and related disorders among benzene-exposed workers in China: Clinicopathologic findings in 31 patients. Leuk Lymph.

Tsai SP, Wen CP, Weiss NS, et al. (1983): Retrospective mortality and medical surveillance studies of workers in benzene areas of refineries. J Occup Med 25:685–692.

Tyroler HA, Andjelkovic D, Harris R, Lednar W, McMichael A, Symons M (1976): Chronic diseases in the rubber industry. Environ Health Perspect 17:13–20.

Vigiliani EC (1976): Leukemia associated with benzene exposure. Ann NY Acad Sci 271:143–151.

Waterhouse J, Muir C, Shanmugaratnam K, Powell J (1982): Cancer incidence in five continents. IARC Sci Publ 42:382–385.

Wong O (1987): An industry-wide mortality study of chemical workers occupationally exposed to benzene. II. Dose-response analyses. Br J Ind Med 44:382–395.

Wong O, Morgan RW, Bailey WJ, Swencicki RE, Claxton K, Kheifets L (1986): An epidemiological study of petroleum refinery employees. Br J Ind Med 43:6–17.

Yin SN, Li GL, Fu ZI, Jin C, Chen YJ, Luo SJ, Ye FZ, Zhang JZ, Wang GC, Zhang XC, Wu HN, Zhong QC (1987a): Leukemia in benzene workers: A retrospective cohort study. Br J Ind Med 44:124–128.

Yin SN, Li GL, Liu Y Tian F, Du C, Jin C (1987b): Occupational exposure to benzene in China. Br J Ind Med 44:192–195.

Yin SN, Li GL, Tain FD, Fu ZI, Jin C, Chen YJ, Luo SJ, Ye PZ, Zhang JZ, Wang GC, Zhang XC, Wu HN, Zhong QC (1989): A retrospective cohort study of leukemia and other cancers in benzene workers. Environ Health Perspect 22:207–221.