

Mortality among Benzene-exposed Workers in China

Richard B. Hayes,¹ Song Nian Yin,² Mustafa Dosemeci,¹ Gui Lan Li,² Sholom Wacholder,¹ Wong Ho Chow,¹ Nathaniel Rothman,¹ Yao Zu Wang,³ Tan Rong Dai,⁴ Xin-Jie Chao,⁵ Zhong Lian Jiang,⁶ Pei-Zheng Ye,⁷ Hong Bin Zhao,⁸ Qing Rui Kou,⁹ Wan You Zhang,¹⁰ Juan Fei Meng,¹¹ Jie Sheng Zho,¹² Xia Fang Lin,¹³ Cheng Yu Ding,¹⁴ Chin Yang Li,¹⁵ Zhi-Nan Zhang,¹⁶ De Gao Li,¹⁶ Lois B. Travis,¹ William J. Blot,¹ and Martha S. Linet¹

¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; ²Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, Beijing, China; Stations of Public Health and Prevention of Infection, ³Shanghai, ⁴Chengdu, and ⁵Chongqing, China; Institutes of Labor, Health and Occupational Disease, ⁶Tianjin, ⁷Heilongjiang, ⁸Luoyang, ⁹Shenyang, ¹⁰Sichuan, ¹¹Jiangxi, ¹²Nanchang, ¹³Guangzhou, ¹⁴Jinzhou, China; ¹⁵Section of Hematopathology, Mayo Clinic, Rochester, Minnesota; ¹⁶Division of Hematology, Peking Union Medical Hospital, Chinese Academy of Medical Sciences, Beijing, China

A large cohort of 74,828 benzene-exposed and 35,805 nonexposed workers employed between 1972 and 1987 in 12 cities in China was followed to determine mortality from all causes. Benzene-exposed study subjects were employed in a variety of occupations including coating applications, and rubber, chemical, and shoe production. Mortality was slightly increased among workers with greater cumulative exposure to benzene ($p_{trend} < 0.05$), but this excess was largely due to cancer deaths ($p_{trend} < 0.01$). Deaths due to lymphatic and hematopoietic malignancies ($p_{trend} = 0.01$) and lung cancer ($p_{trend} = 0.01$) increased with increasing cumulative exposure to benzene. Investigations continue to relate benzene exposure to specific lymphatic and hematopoietic malignancies and other causes of death. — Environ Health Perspect 104(Suppl 6):1349–1352 (1996)

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Introduction

Benzene is a solvent widely used in industry and found in cigarette smoke, gasoline, automobile emissions, and other products (1). Benzene exposure has been related in numerous occupational studies to increased risk of acute nonlymphocytic leukemia (ANLL) (2) and, in some reports, to other lymphohematopoietic malignancies (3–5).

In 1981, the Chinese Academy of Preventive Medicine (CAPM) carried out a

national occupational survey in which more than 500,000 workers exposed to benzene in China were identified (6). Subsequently, 28,460 of these exposed workers and 28,257 nonexposed workers were followed for cancer mortality between 1972 and 1981 (7,8). Significantly elevated standardized mortality ratios were noted among exposed compared to nonexposed workers for leukemia (standard mortality ratio

[SMR] = 5.74) and lung cancer (SMR = 2.31), whereas elevated but nonsignificant excesses were noted for cancers of the liver, stomach, esophagus, intestine, nasopharynx, and lymphosarcoma (8). Since 1987, the U.S. National Cancer Institute (NCI) has collaborated with the CAPM to expand this study in cohort size, duration, recency of follow-up, and exposure assessment.

Previously (9), we described the overall risk for benzene-associated diseases in this cohort, including excess risk for leukemia and lymphoma among benzene-exposed workers. In the current study we utilize information on levels of benzene exposure and report on the exposure–response relationship with respect to benzene and mortality risk.

Methods

The methods for this expanded study are described in detail elsewhere (10,11). The benzene-exposed group was comprised of workers employed between 1972 and 1987 in 1427 selected benzene-exposed work units (departments) in 672 factories in 12 cities in China. Workers in a variety of industries and occupations that use benzene were studied; the occupational areas included painting, printing, and manufacture of footwear, paint, and other chemicals. A nonexposed comparison group was assembled from workers employed between 1972 and 1987 in work units in which benzene was not used in 69 of these factories or in 40 additional factories. Subjects were identified from initial employment, salary, and other factory records. We abstracted demographic data, including birth date, sex, and occupational data, including the dates of employment by work unit and job title for all jobs held by subjects in the study factories. Benzene-exposure jobs were determined from factory-level and job title-specific information on benzene use.

For the cohort study, average occupational exposure to benzene (in ranges of < 1 ppm, 1–<5 ppm, 5–<10 ppm, 10–<25 ppm, 25–<50 ppm, and 50 + ppm) was estimated by local industrial hygienists and other industrial health personnel for seven calendar periods (1949–1959, 1960–1964, 1965–1969, 1970–1974, 1975–1979, 1980–1984, 1985 and later) and for study-specific job titles (11). A total of 18,435 job and calendar period-specific exposure estimates were made, 38% based upon monitoring data collected primarily after

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Address correspondence to Dr. R.B. Hayes, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6130 Executive Blvd. MSC 7368, Bethesda, MD 20892-7368. Telephone: (301) 496-9093. Fax: (301) 402-1819. E-mail: hayesr@epndce.nci.nih.gov

Abbreviations used: ANLL, acute nonlymphocytic leukemia; HLM, hematopoietic and lymphoproliferative malignancies; ICD, International Classification of Diseases; RR, relative risk; SMR, standardized mortality ratio.

1975. When no monitoring data were available or when the measurement results were not consistent with other exposure information (including amount of benzene-containing materials, percent of benzene in the materials, average frequency of exposure, and changes in industrial hygiene controls), monitoring data from other calendar periods were used, with adjustment for historical changes and exposure frequency. If no monitoring data for the specific job were available in any calendar period, monitoring results for similar jobs were used after task descriptions and historical changes were considered. If none of the above sources were available, the field center staff used all available exposure information and their professional judgment to estimate the exposure.

Subjects were followed for selected lymphohematopoietic malignancies and other hematologic disorders and for vital status to 31 December 1987. We used factory personnel records at study factories and subsequent places of employment or, when necessary, contacted next-of-kin, work colleagues, treating physicians, or others. For deceased subjects, cause of death was obtained from medical records, other written factory records, or death certificates. Only after extensive search had failed to locate written records listing cause of death were treating physicians or next-of-kin contacted. For any worker suspected of having any hematopoietic or lymphoproliferative malignancy or nonmalignant related disorder, extensive efforts were made to obtain detailed medical records, hematological laboratory reports, histopathology reports,

and pathology specimens. Details of the specific information abstracted and the review of clinicopathologic material by expert U.S. and Chinese hematopathologists are described elsewhere (12,13).

For the statistical analysis, subjects employed less than 6 months and those hired before 1949 were excluded. Person-years were accumulated for the benzene-exposed workers, with a 1.5-year lag, from 1 January 1972 or, if hired later, from the first date of employment in a benzene-exposed job until death, loss to follow-up, or 31 December 1987. For the nonexposed comparison group, person-years were accumulated from 1 January 1972 or, if hired later, from the first date of employment. Analyses of mortality were made by internal comparison of disease rates in the benzene-exposed group to the rates in the unexposed group, with adjustment by Poisson regression for age and sex as appropriate, yielding relative risk (RR) for exposed versus nonexposed workers (14,15). Tests for trend of increasing risk with increasing level of benzene exposure were carried out.

Results

The study group consisted of 74,828 benzene-exposed and 35,805 nonexposed workers. On average, benzene-exposed subjects were followed for 10.5 years, while nonexposed subjects were followed for 11.7 years. Women contributed 47% of the person-years in the benzene-exposed study group and 40% in the nonexposed group. Overall, the study groups were young, with about 60% of the total person-years at risk contributed by subjects less

than 30 years old at study entry. In this young study population, about 2% died during the follow-up period (1,369 benzene-exposed and 598 nonexposed). Only 147 exposed (0.20%) and 90 unexposed (0.25%) workers were lost to follow-up.

As shown in Table 1, all-cause mortality is slightly increased among workers with greater cumulative exposure to benzene ($p_{trend} < 0.05$), but this excess is largely due to cancer deaths ($p_{trend} < 0.01$). In general, other nonmalignant causes of death were not related to cumulative benzene exposure except for occupational injuries.

Deaths due to all hematopoietic and lymphoproliferative malignancies (HLM) ($p_{trend} = 0.01$) and lung cancer ($p_{trend} = 0.01$) were increased among workers with greater cumulative exposure to benzene (Table 2). Other cancer sites showing suggestive but not statistically significant excesses include nasopharynx and esophagus.

Discussion

We found increased mortality due to lymphatic and hematopoietic malignancies, lung cancer, and occupational injuries in association with increased exposure to benzene. Suggestive associations were noted for other causes of death, including nasopharyngeal and esophageal cancer. Because of the known relationship of benzene as a risk factor for ANNL and preliminary evidence from this and other studies implicating benzene in the etiology of other HLMs (2-5), we are continuing statistical evaluations of this association.

In experimental studies (16,17) benzene has been found to cause cancer at

Table 1. Mortality^a among Chinese workers, by cumulative benzene exposure.

Cause of death (ICD, 9th Revision) ^b		None ^c	Cumulative exposure, ppm-years					p-Value for trend
			< 10	10-39	40-99	100-400	400+	
All causes	RR	1.0	1.1	1.0	1.1	1.1	1.2	0.01
	No. cases	598	158	193	210	394	376	
Infectious and parasitic (001-139)	RR	1.0	1.2	1.2	0.4	0.8	1.4	0.86
	No. cases	23	7	9	3	11	15	
Malignant neoplasms (140-208)	RR	1.0	1.1	0.9	1.0	1.3	1.4	0.002
	No. cases	218	59	63	70	163	155	
Circulatory system (390-459)	RR	1.0	0.6	1.0	1.1	1.1	1.0	0.29
	No. cases	210	28	73	84	147	134	
Respiratory system (450-519)	RR	1.0	4.2	2.2	0.8	0.9	1.9	0.80
	No. cases	14	12	11	4	9	18	
Digestive system (520-579)	RR	1.0	0.8	0.3	0.7	0.9	0.7	0.22
	No. cases	51	9	5	11	25	18	
Cirrhosis (571)	RR	1.0	0.8	0.4	0.8	1.1	0.9	0.89
	No. cases	35	6	4	8	22	15	
Urinary tract (580-629)	RR	1.0	1.2	0.7	0.8	0.7	0.9	0.65
	No. cases	16	6	4	4	6	6	
Occupational injury, poisoning	RR	1.0	1.5	0.8	4.7	0.7	5.4	0.04
	No. cases	4	2	1	5	1	5	

^aConsidered as relative risk (RR), adjusted for age and sex. ^bFrom the World Health Organization (25). ^cReferent category: RR = 1.0 for nonexposed workers.

Table 2. Cancer mortality^a among Chinese workers, by cumulative benzene exposure.

Cause of death ICD, 9th Revision ^b		None ^c	Cumulative exposure, ppm-years					p-Value for trend
			< 10	10-39	40-99	100-400	400+	
Malignant neoplasms (140-208)	RR	1.0	1.1	0.9	1.0	1.3	1.4	0.002
	No. cases	218	59	63	70	163	155	
Nasopharynx (147)	RR	1.0	2.7	4.4	-	2.5	2.9	0.23
	No. cases	3	2	4	0	4	4	
Esophagus (150)	RR	1.0	3.5	0.5	1.3	1.1	3.2	0.09
	No. cases	7	5	1	3	5	13	
Stomach (151)	RR	1.0	0.6	1.0	0.9	1.0	1.2	0.63
	No. cases	43	6	13	12	25	27	
Colon and rectum (153, 154)	RR	1.0	1.5	0.7	0.5	0.8	1.4	0.91
	No. cases	17	7	4	3	8	12	
Liver and gall bladder (155, 156)	RR	1.0	1.1	0.8	0.6	1.6	1.2	0.16
	No. cases	49	12	12	9	44	28	
Trachea, bronchus, and lung (162)	RR	1.0	1.2	1.0	1.4	1.4	1.7	0.01
	No. cases	41	10	13	19	38	41	
Brain and other central nervous system (191, 225)	RR	1.0	0.8	1.9	1.3	0.4	2.3	0.48
	No. cases	5	1	3	2	1	5	
Hematopoietic malignancies (200-208)	RR	1.0	2.5	2.1	2.9	3.1	2.0	0.01
	No. cases	12	9	8	10	18	9	

^aConsidered as relative risk (RR), adjusted for age and sex; ^bFrom the World Health Organization (25). ^cReferent category: RR = 1.0 for nonexposed workers.

multiple sites, suggesting that excesses of hematological and nonhematological tumors in humans could be causally related to exposure. Lung cancer mortality showed an exposure-response pattern in our study. Benzene exposure has not previously been related to lung cancer (2) except for an earlier report from a subset of the present cohort (8). In that report an overall excess was shown in a comparison of ever- and never-exposed workers (SMR = 2.3), but no evaluation of level of benzene exposure was made. In the current study, however, we show that the excess risk parallels increases in cumulative benzene exposure. Some benzene-exposed workers in this cohort were employed in occupations that have previously been associated with increased lung cancer risk; these workers include painters (18) and leather workers (19). We plan further studies to determine if the association of benzene with lung cancer risk is due specifically to benzene or to other types of exposure, including tobacco use.

Suggestive increases in risk were seen for nasopharyngeal and esophageal cancer. Continued monitoring will provide opportunities to study these associations in more

detail as additional tumors are identified in the aging study cohort. Excess mortality was also found due to industrial accidents among workers highly exposed to benzene.

A limited number of epidemiologic investigations have provided the scientific base for determining the quantitative relationship between benzene exposure and cancer risk (20-22). Because we have characterized exposure in detail for a large number of benzene-exposed men and women, data from this cohort should provide a substantive addition to current knowledge.

The study had several additional strengths. Although the present analysis is limited to mortality outcomes, cases of lymphatic and hematopoietic diseases have been identified and classified by disease type following review of available pathologic material and medical records (12,13). This detailed information will be utilized in future reports. Quantitative exposure estimates have been developed for cohort study subjects (11) and these estimates correlate with the occurrence of benzene hematotoxicity (23), supporting the validity of our approach to exposure estimation. Complementary to these investigations,

biomarker studies among a series of workers with current benzene exposure and among workers with a history of benzene toxicity are being analyzed to provide insight into mechanisms of benzene-associated disease in humans (24).

Several limitations should also be noted. Detailed evaluation of more than 110,000 study subjects necessitated a large number of investigators at many sites, requiring extensive efforts at study coordination. Although not unique to this study, exposure assessment relied upon limited measurement data, particularly for the early years of study. Efforts are continuing to refine and validate these estimates. The cohort is young and follow-up continues to characterize further the long-term effects of benzene exposure as the cohort ages.

In summary, mortality due to lymphatic and hematopoietic malignancies, lung cancer, and occupational accidents increased in direct relation to cumulative benzene exposure among industrial workers in China. The results are preliminary; further investigations are planned to characterize the scope of benzene as a human carcinogen in this large cohort of industrial workers.

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