istry in carcinoma in situ of the breast. Cancer 1992;69:1174-81.
(*16*) Chaudhuri B, Crist KA, Mucci S, Malafa M, Chaudhuri PK. Distribution of estrogen receptor in ductal carcinoma in situ of the breast. Surgery 1993;113:134-37.
(*17*) Hellman J, Harris JR, Canellos GP. Cancer of the breast. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer principles and practice of oncology. Philadelphia: Lippincott, 1982:914-70.

## Notes

Supported by a grant from the Association for International Cancer Research. C. S. Potten and A. Howell are funded by the Cancer Research Campaign.

We thank Mrs. Marjorie Gaskell for typing the manuscript, Miss Lesley Shaw for technical assistance, and Dr. E. B. Faragher for statistical assistance.

Manuscript received October 10, 1996; revised April 24, 1997; accepted May 5, 1997.

# Benzene and the Dose-Related Incidence of Hematologic Neoplasms in China

*Richard B. Hayes, Song-Nian Yin, Mustafa Dosemeci, Gui-Lan Li, Sholom Wacholder, Lois B. Travis, Chin-Yang Li, Nathaniel Rothman, Robert N. Hoover, Martha S. Linet**

*For the Chinese Academy of Preventive Medicine–National Cancer Institute Benzene Study Group*

***Background:*** **Benzene is a widely distributed environmental contaminant known to cause leukemia, particularly acute nonlymphocytic leukemia, and perhaps other hematologic neoplasms and disorders. Few epidemiologic studies, however, have been able to address relationships between the extent of benzene exposure and the level of risk.** ***Purpose:*** **A large cohort study was carried out in China to evaluate the risks of developing specific hematologic neoplasms and selected related disorders in relationship to quantitative estimates of occupational benzene exposure.** ***Methods:*** **A cohort of 74 828 benzene-exposed and 35 805 unexposed workers employed from 1972 through 1987 in 12 cities in China was identified and followed to determine the incidence of hematologic neoplasms and related disorders. Estimates of benzene exposure were derived from work histories and available historic benzene measurements. Existing pathologic material and supporting medical records were reviewed to establish diagnoses of disease. Relative risks (RRs) (i.e., ratios of incidence rates for specific hematologic neoplasms and related disorders in the benzene-exposed group to incidence rates in the unexposed group) were determined by use of Poisson regression analysis, with stratification by age and sex.** ***Results:*** **For workers historically exposed to benzene at average levels of less than 10 parts per million (ppm), the RR for all hematologic neoplasms combined was 2.2 (95% confidence interval [CI] = 1.1-4.2), and, for the combination of acute nonlymphocytic leukemia and related myelodysplastic syndromes, the RR was 3.2 (95% CI = 1.0-10.1). For individuals who were occupationally exposed to benzene at constant levels of 25 ppm or more, the RR for the combination of acute nonlymphocytic leukemia and related myelodysplastic syndromes was 7.1 (95% CI = 2.1-23.7). Workers with 10 or more years of benzene exposure had an RR of developing non-Hodgkin's lymphoma of 4.2 (95% CI = 1.1-15.9), and the development of this neoplasm was linked most strongly to exposure that had occurred at least 10 years before diagnosis (i.e., distant exposure) (*P* for trend = .005, two-sided). In contrast, the risk for the combination of acute nonlymphocytic leukemia and related myelodysplastic syndromes was significantly increased among those with more recent benzene exposure (*P* for trend = .003, two-sided), but it was not linked to distant exposure (*P* for trend = .51, two-sided).** ***Conclusions:*** **The results of this study suggest that benzene exposure is associated with a spectrum of hematologic neoplasms and related disorders in humans. Risks for these conditions are elevated at average benzene-exposure levels of less than 10 ppm and show a tendency, although not a strong one, to rise with increasing levels of exposure. The temporal pattern of benzene exposure appears to be important in determining the risk of developing specific diseases. [J Natl Cancer Inst 1997;89:1065-71]**

**Affiliations of authors:* R. B. Hayes, M. Dosemeci, S. Wacholder, L. B. Travis, N. Rothman, R. N. Hoover, M. S. Linet, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; S.-N. Yin, G.-L. Li, Chinese Academy of Preventive Medicine, Institute of Occupational Medicine, Beijing, China; C.-Y. Li, Section of Hematopathology, Mayo Clinic, Rochester, MN.

*Correspondence to:* Richard B. Hayes, Ph.D., National Institutes of Health, Executive Plaza North, Rm. 418, Bethesda, MD 20892.

*See* ''Notes'' following ''References.''

Benzene is a widespread contaminant in the air and groundwater, originating from industrial sources, cigarette smoke, gasoline, and automobile emissions (*1*). There is scientific agreement that benzene causes leukemia, particularly acute nonlymphocytic leukemia (ANLL), but controversy still exists with regard to the level of risk at low exposures (*2-4*) as well as the potential association with other hematologic neoplasms (*5*). The epidemiologic evidence for a dose–response relationship between benzene and leukemia derives primarily from three small cohort studies (*6-8*) and their recent updates (*9-11*). These investigations have generally reported on workers exposed to benzene at relatively high levels, or they have identified such small numbers of leukemia cases as to preclude stable exposure–response estimates.

In 1981, the Chinese Academy of Preventive Medicine (CAPM) carried out a national occupational survey and identified more than 500 000 benzene-exposed workers, characterized by a broad range of benzene exposure levels (*12*). A subsequent follow-up survey of 28 460 benzene-exposed and 28 257 unexposed workers from 1972 through 1981 found an increased risk of mortality due to leukemia (standardized mortality ratio [SMR] = 5.7), but the exposure–response relationship was not quantified (*13*).

Since 1987, the U.S. National Cancer Institute has collaborated with the CAPM and its team in 12 Chinese cities to identify all incident cases of hematologic neoplasms and related disorders in an expanded study population with 6 additional years of follow-up. A major focus of the collaborative effort was to evaluate quantitative data with regard to benzene exposure. Here, we assess the exposure–response relationship between the extent of benzene exposure and the risk for hematologic neoplasms and selected related disorders.

## Materials and Methods

### Study Population and Exposure Assessment

The benzene-exposed group consisted of 74 828 workers employed from 1972 through 1987 in 672 factories in 12 cities in China. A variety of industries and occupations using benzene was studied, including painting, printing, and the manufacture of footwear, paint, and other chemicals. An unexposed comparison group was assembled from workers employed during the same period in work units where benzene was not used in 69 of these factories and in 40 additional factories located in the 12 study cities. The unexposed group consisted of 35 805 workers. This investigation was approved by the CAPM Institutional Review Board in accordance with an assurance filed with the U.S. Department of Health and Human Services. Subjects were identified through factory administrative records, from which demographic and job history data (job title and dates of employment) were abstracted (*14,15*). Average occupational exposure (time-weighted average) to benzene (in ranges of <1 part per million [ppm], 1 to <5, 5 to <10, 10 to <25, 25 to <50, and ⩾50 ppm) was estimated by local industrial hygienists and other occupational health personnel, using available ambient benzene exposure measurements and detailed production and related process information, for seven calendar periods (1949 through 1959, 1960 through 1964, 1965 through 1969, 1970 through 1974, 1975 through 1979, 1980 through 1984, and 1985+) for study-specific job titles in each factory. Work histories were then linked to the benzene-exposure data to provide individual time-specific benzene-exposure estimates.

### Subject Follow-up

With the use of occupational personnel and health records and, as needed, contacts with physicians, colleagues, next of kin, or others, subjects were followed through December 31, 1987, for the occurrence of hematologic neoplasms and other selected hematologic disorders as well as for vital status and cause of death. For cases of hematologic neoplasms and other selected hematologic disorders, available pathologic material and medical records were reviewed by expert U.S. and Chinese hematopathologists (*16*). Because myelodysplastic syndromes (MDS) (*17*) may be precursors to ANLL (*18*) and were not systematically distinguished from ANLL in past epidemiologic studies, ANLL and MDS were combined for several analyses.

On average, benzene-exposed and unexposed subjects were followed for 10.5 years and 11.7 years, respectively. Most person-years of follow-up occurred during active employment (88% among benzene-exposed and 91% among unexposed workers); only a small percentage of person-years were attributable to workers who had moved from the study cities (2.5% among benzene-exposed and 2.4% among unexposed workers). Approximately 2% of the study subjects died during follow-up (1369 benzene exposed and 598 unexposed). Only 147 (0.2%) exposed and 90 (0.3%) unexposed workers were lost to follow-up.

### Statistical Analysis

Subjects employed less than 6 months and those hired before the exposure assessment period (1949 through 1987) (1.4% of exposed and 0.8% of unexposed) were excluded from the analysis. Person-years at risk were accumulated from 6 months after study entry (January 1, 1972, or, if hired later, the date of hire) to the earliest of the following events: date of diagnosis of cancer or a related disease, date of death, date of first employment in a job of unknown exposure (<1% of person-years), date of loss to follow-up (<1% of subjects), or end of follow-up (December 31, 1987). Subjects were categorized by occupations in coatings applications (mostly painters), chemicals production, shoe production, and other or mixed occupations (i.e., more than one of the above categories).

To provide stable risk estimates, fairly broad groups were defined for duration of exposure (<5, 5-9, and ⩾10 years), average (<10, 10-24, and ⩾25 ppm), and cumulative exposure (<40, 40-100, and ⩾100 ppm-years) to benzene. Each measure of benzene exposure for each individual was allowed to change with time; person-years and disease events were assigned to benzene-exposure levels with a 1.5 year lag (i.e., according to the level 1.5 years previously). A lag period of 1.5 years was used in making these calculations because more recent exposures are unlikely to be biologically linked to the development of diagnosed cancers (*19,20*). To evaluate the temporal component of disease development further, we partitioned the cumulative exposure at a given time into recent (1.5 to 10 years earlier) and distant (10 or more years earlier) exposure. Because a substantial number of individuals were historically exposed to a relatively stable average amount of benzene while working, we also developed a measure of constant exposure, where follow-up was censored 1.5 years after the individual's exposure level changed (<10, 10-24, and ⩾25 ppm) for the first time. Ratios of incidence rates for hematologic neoplasms and related disorders in the benzene-exposed group compared with rates in the unexposed group (RRs = relative risks) were determined using Poisson regression analysis (*21*), with stratification by age and sex. Tests for linear trend (two-sided) of increasing risk with increasing extent of benzene exposure were carried out, on the basis of the mean of years in duration–exposure categories, the log of the mean of parts per million in average-exposure categories, and the log of the mean of parts per million-years in cumulative exposure categories.

## Results

The RR for all hematologic neoplasms combined among workers who were occupationally exposed to benzene was 2.6 (95% confidence interval [CI] = 1.4-4.7) (Table 1). Statistically significant excesses were found for ANLL (RR = 3.0; 95% CI = 1.0-8.9) and for the combined group of ANLL/MDS (RR = 4.1; 95% CI = 1.4-11.6) (Table 1). Excesses were also noted for other leukemias (RR = 2.0; 95% CI = 0.7-5.4) and non-Hodgkin's lymphoma (NHL) (RR = 3.0; 95% CI = 0.9-10.5), but the results were not statistically significant.

Increased risk was found for hematologic neoplasms among workers hired before 1972 (the beginning of the cancer risk assessment period) (RR = 2.9; 95% CI = 1.5-5.4) and thereafter (RR = 2.5; 95% CI = 1.1-5.4). Fifteen of the 16 benzene-exposed NHL cases occurred among workers hired before 1972 (RR = 4.1; 95% CI = 1.2-14.4). For ANLL, significantly increased risk was found for workers hired after 1972 (RR = 5.1; 95% CI = 1.5-17.2), while the risk for ANLL/

**Table 1.** Relative risk for hematologic neoplasms and related conditions, on the basis of selected occupational characteristics, for workers exposed to benzene

| Study group | Person-years, $\times 10^3$ | Mean exposure, ppm*,† | Mean exposure, y* | Relative risk (No. of cases) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | All hematologic neoplasms‡ | NHL | Leukemia | ANLL | ANLL/MDS | Other leukemias |
| All exposed subjects | 698 | 22.5 | 9.3 | 2.6 (58) 95% CI§ = 1.4-4.7 | 3.0 (16) 95% CI = 0.9-10.5 | 2.5 (38) 95% CI = 1.2-5.1 | 3.0 (21) 95% CI = 1.0-8.9 | 4.1 (28) 95% CI = 1.4-11.6 | 2.0 (17) 95% CI = 0.7-5.4 |
| Exposed subjects: y of hire | | | | | | | | | |
| <1972 | 404 | 24.9 | 13.2 | 2.9 (44) | 4.1 (15) | 2.4 (25) | 2.6 (12) | 4.0 (19) | 2.2 (13) |
| ⩾1972 | 294 | 19.2 | 4.0 | 2.5 (14) | 0.5 (1) | 3.4 (13) | 5.1 (9) | 5.1 (9) | 2.0 (4) |
| Exposed subjects: occupation | | | | | | | | | |
| Coatings‖ | 350 | 21.5 | 9.4 | 2.1 (23) | 1.6 (4) | 2.2 (17) | 2.9 (10) | 4.2 (14) | 1.7 (7) |
| Rubber | 34 | 53.5 | 11.1 | 1.8 (2) | 4.0 (1) | 1.3 (1) | 3.0 (1) | 6.1 (2) | — (0) |
| Chemical | 88 | 24.8 | 8.5 | 5.0 (14) | 7.8 (5) | 3.6 (7) | 4.5 (4) | 4.5 (4) | 2.8 (3) |
| Shoe | 68 | 21.8 | 7.9 | 1.9 (5) | 1.6 (1) | 2.5 (4) | 1.5 (1) | 1.3 (1) | 3.2 (3) |
| Other/mixed | 158 | 17.4 | 9.8 | 2.7 (14) | 4.1 (5) | 2.5 (9) | 3.1 (5) | 4.4 (7) | 2.0 (4) |
| All unexposed subjects (referent)¶ | 405 | 0 | 0 | 1.0 (13) | 1.0 (3) | 1.0 (9) | 1.0 (4) | 1.0 (4) | 1.0 (5) |

*Time-weighted average, lag 1.5 y.

†ppm = part(s) per million.

‡Hematologic neoplasms (International Classification of Diseases [ICD]9: 200-208); NHL = non-Hodgkin's lymphoma (ICD9: 200, 202); leukemia (ICD9: 204-208); ANLL = acute nonlymphocytic leukemia (ICD9:205.0, 206.0, 207.0); MDS = myelodysplastic syndromes (ICD-02: 9980-9989); other leukemias: includes leukemias other than ANLL and leukemias not otherwise specified (ICD9: 204, 205.1-205.9, 206.1-206.9, 207.1-207.9, 208). *See* (*34*) for ICD9 and (*35*) for ICD-02.

§CI = confidence interval.

‖Coatings: painters and other coating application workers.

¶Referent: relative risk = 1.0 for unexposed workers, with all risks adjusted for age and sex.

MDS was significantly increased among both earlier (RR = 4.0; 95% CI = 1.3-11.9) and later (RR = 5.1; 95% CI = 1.5-17.2) hires. Although occupation-specific results were limited by small numbers, risks for ANLL/MDS were elevated among coatings workers (RR = 4.2; 95% CI = 1.4-12.6), rubber workers (RR = 6.1; 95% CI = 1.1-33.3), chemical workers (RR = 4.5; 95% CI = 1.1-18.1), and among those with other or mixed occupations (RR = 4.4; 95% CI = 1.3-15.2). Risk for NHL was also elevated among several occupational groups, but only chemical workers showed a statistically significant excess (RR = 7.8; 95% CI = 1.9-32.5).

Benzene-exposed subjects experienced significantly increased risks for hematologic neoplasms at average benzene exposures of less than 10 ppm (RR = 2.2; 95% CI = 1.1-4.2) and cumulative exposures of less than 40 ppm-years (RR = 2.2; 95% CI = 1.1-4.5) (Table 2). Trends of increasing risk for hematologic neoplasms were seen with respect to increasing average exposure (including the subcohort of subjects with a constant level of occupational exposure) and cumulative exposure to benzene. Risk for NHL increased with increasing duration of exposure, from 0.7 (95% CI = 0.1-7.2) among those exposed for fewer than 5 years to 4.2 (95% CI = 1.1-15.9) associated with exposures of 10 or more years, but the exposure–response patterns were less clear for the other measures of exposure.

ANLL and ANLL/MDS both showed patterns of increasing risk with increasing average exposure to benzene, with more consistent exposure–response patterns for ANLL/MDS than for ANLL alone. The link of ANLL/MDS with average exposure was strongest when restricted to subjects with constant levels of occupational exposure: RRs rose from 3.2 (95% CI = 1.0-10.3) for those with constant low-level exposures (<10 ppm) to 7.1 (95% CI = 2.1-23.7) for those with constant high-level exposures (⩾25 ppm). Risk for ANLL/MDS did not increase with duration of exposure to benzene (Table 2). The RRs associated with fewer than 5 years, 5-9 years, and 10 or more years of exposure were 11.7 (95% CI = 2.9-47.3; based on four cases), 5.2 (95% CI = 1.4-19.3; based on five cases), and 2.8 (95% CI = 0.8-8.9; based on 10 cases), respectively, among benzene-exposed workers hired before 1972 and 5.7 (95% CI = 1.5-21.5; based on six cases), 3.5 (95% CI = 0.6-19.8; based on two cases), and 7.2 (95% CI = 0.8-65.6; based on one case) among workers hired in 1972 or later. In neither time period was longer duration of benzene exposure clearly linked to increasing risk of ANLL/MDS. Risk for ANLL/MDS increased with increasing cumulative exposure to benzene, but the highest risks were not seen at the highest exposure level (cumulative ppm-years: 40-99, RR = 6.0 [95% CI = 1.8-20.6]; cumulative ppm-years: ⩾100, RR = 4.4 [95% CI = 1.4-13.5]). Although there was some evidence of increased risk for leukemias other than ANLL among benzene-exposed workers (Table 1), clear patterns of increasing risk with increasing exposure were not observed (Table 2).

We partitioned cumulative benzene exposure into recent (<10 years prior to diagnosis) and distant (⩾10 years prior to diagnosis) exposure. NHL was strongly linked with distant exposure to benzene ($P$ for trend = .005; based on 13 exposed cases), but the association with exposure in the most recent 10 years was weak ($P$ for trend = .15; based on 16 exposed cases). NHL showed no clear link with work that involved only recent exposure (RR = 1.5 [95% CI = 0.3-7.6]; based on three exposed cases) (Table 3). In contrast, risk of ANLL/MDS was signifi-

**Table 2.** Relative risk (RR)* for hematologic neoplasms and related conditions according to extent of exposure to benzene

| Hematologic condition† | Benzene-exposed group | | | | | | | | | | | | | | | | Unexposed referent group |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Average, ppm‡ | | | | Constant, ppm§ | | | | Duration, yrs | | | | Cumulative, ppm-yrs | | | | |
| | <10 | 10-24 | ⩾25 | *P* for trend‖ | <10 | 10-24 | ⩾25 | *P* for trend | <5 | 5-9 | ⩾10 | *P* for trend | <40 | 40-99 | ⩾100 | *P* for trend¶ | |
| All hematologic neoplasms | | | | | | | | | | | | | | | | | |
| Cases | 24 | 16 | 18 | | 21 | 8 | 11 | | 16 | 17 | 25 | | 18 | 11 | 29 | | 13 |
| RR | 2.2 | 3.1 | 2.8 | .003 | 2.1 | 3.2 | 2.9 | .002 | 3.1 | 3.3 | 2.0 | .24 | 2.2 | 2.9 | 2.7 | .004 | |
| 95% CI# | 1.1-4.2 | 1.5-6.5 | 1.4-5.7 | | 1.0-4.1 | 1.3-7.6 | 1.3-6.6 | | 1.5-6.6 | 1.6-6.8 | 1.0-3.9 | | 1.1-4.5 | 1.3-6.5 | 1.4-5.2 | | |
| NHL | | | | | | | | | | | | | | | | | |
| Cases | 7 | 2 | 7 | | 7 | 0 | 3 | | 1 | 4 | 11 | | 6 | 1 | 9 | | 3 |
| RR | 2.7 | 1.7 | 4.7 | .04 | 3.0 | — | 3.5 | .15 | 0.7 | 3.3 | 4.2 | .01 | 3.3 | 1.1 | 3.5 | .02 | |
| 95% CI | 0.7-10.6 | 0.3-10.2 | 1.2-18.1 | | 0.8-11.6 | — | 0.7-17.3 | | 0.1-7.2 | 0.7-14.7 | 1.1-15.9 | | 0.8-13.1 | 0.1-11.1 | 0.9-13.2 | | |
| Leukemia | | | | | | | | | | | | | | | | | |
| Cases | 15 | 13 | 10 | | 12 | 7 | 7 | | 14 | 11 | 13 | | 11 | 8 | 19 | | 9 |
| RR | 2.0 | 3.7 | 2.3 | .02 | 1.7 | 4.0 | 2.8 | .009 | 4.0 | 3.1 | 1.5 | .98 | 1.9 | 3.1 | 2.7 | .04 | |
| 95% CI | 0.9-4.5 | 1.6-8.7 | 0.9-5.7 | | 0.7-4.1 | 1.5-10.7 | 1.0-7.4 | | 1.7-9.6 | 1.3-7.5 | 0.6-3.6 | | 0.8-4.7 | 1.2-8.0 | 1.2-6.0 | | |
| ANLL | | | | | | | | | | | | | | | | | |
| Cases | 7 | 9 | 5 | | 6 | 4 | 5 | | 9 | 6 | 6 | | 5 | 5 | 11 | | 4 |
| RR | 2.0 | 5.8 | 2.6 | .04 | 1.9 | 4.9 | 4.4 | .008 | 5.6 | 3.6 | 1.6 | .81 | 1.9 | 4.3 | 3.6 | .06 | |
| 95% CI | 0.6-7.0 | 1.8-18.9 | 0.7-9.9 | | 0.5-6.8 | 1.2-19.8 | 1.2-16.4 | | 1.7-18.7 | 1.0-12.9 | 0.4-5.7 | | 0.5-7.0 | 1.1-16.0 | 1.1-11.6 | | |
| ANLL/MDS | | | | | | | | | | | | | | | | | |
| Cases | 11 | 9 | 8 | | 10 | 4 | 8 | | 10 | 7 | 11 | | 7 | 7 | 14 | | 4 |
| RR | 3.2 | 5.8 | 4.1 | .01 | 3.2 | 5.1 | 7.1 | .0003 | 6.6 | 4.3 | 2.8 | .48 | 2.7 | 6.0 | 4.4 | .01 | |
| 95% CI | 1.0-10.1 | 1.8-18.8 | 1.2-13.2 | | 1.0-10.3 | 1.3-20.6 | 2.1-23.7 | | 2.0-21.6 | 1.3-14.8 | 0.9-9.1 | | 0.8-9.5 | 1.8-20.6 | 1.4-13.5 | | |
| Other leukemias | | | | | | | | | | | | | | | | | |
| Cases | 8 | 4 | 5 | | 6 | 3 | 2 | | 5 | 5 | 7 | | 6 | 3 | 8 | | 5 |
| RR | 1.9 | 2.1 | 2.1 | .27 | 1.6 | 3.2 | 1.4 | .31 | 2.7 | 2.7 | 1.4 | .83 | 2.0 | 2.1 | 1.9 | .36 | |
| 95% CI | 0.6-5.9 | 0.6-7.8 | 0.6-7.1 | | 0.5-5.2 | 0.8-13.4 | 0.3-7.4 | | 0.7-9.7 | 0.8-9.3 | 0.5-4.6 | | 0.6-6.6 | 0.5-9.0 | 0.6-6.0 | | |
| Person-y, $\times 10^3$ | 352 | 157 | 188 | | 324 | 88 | 121 | | 249 | 170 | 278 | | 300 | 119 | 279 | | |

*Referent: RR = 1.0 for unexposed workers, with all risks adjusted for age and sex.

†NHL = non-Hodgkin's lymphoma; ANLL = acute nonlymphocytic leukemia; MDS = myelodysplastic syndromes; other leukemia; includes leukemias other than ANLL and leukemias not otherwise specified (*see* Table 1 for ICD codes).

‡ppm = part(s) per million.

§This category encompasses a group of person-years for workers who were always exposed at the indicated levels.

‖*P* values are two-sided.

¶Groups for trend test: unexposed and exposure of <10, 10-39, 40-99, 100-399, and ⩾400 ppm-years.

#CI = confidence interval.

cantly increased among those who had only recent benzene exposure (RR = 6.0 [95% CI = 1.9-18.4]; based on 14 exposed cases). Risk of ANLL/MDS was also strongly associated with increasing amounts of recent (*P* for trend = .003) but not distant (*P* for trend = .51) exposure.

NHL was linked to distant cumulative exposure to benzene among coatings workers (the largest occupational group, mostly painters) (*P* for trend = .10; based on three exposed cases) and among those with other benzene-exposed occupations (*P* for trend = .005; based on 10 exposed cases). ANLL/MDS was linked to recent cumulative exposure among coatings workers (*P* for trend = .001; based on 14 exposed cases) and among workers in other occupations (*P* for trend = .06; based on 14 exposed cases). When the year of initial employment in study factories (<1960, 1960-1971, and ⩾1972) was included in the statistical regression models, the findings were unchanged (data not shown).

## Discussion

In earlier reports (*22*,*23*), we showed that employment in benzene-exposed jobs in China, regardless of the exposure level, was linked to hematologic disease mortality and the incidence of leukemia, NHL, MDS, and aplastic anemia. This investigation provides evidence that benzene may cause hematologic neoplasms and related disorders at average exposures of less than 10 ppm and cumulative exposures of less than 40 ppm-years. Increasing risks for ANLL were linked with increasing levels of benzene exposure, particularly for exposures that had occurred within the 10 years prior to diagnosis, and showed a stronger link for the combined categories of ANLL/MDS than for ANLL alone. Risk for NHL increased with duration of exposure and was strongest among workers who had distant (⩾10 years) exposure. No excess was noted for NHL among workers hired since 1972, but follow-up for this group was relatively short.

In rodents, benzene causes a range of neoplasms, including lymphomas and tumors of epithelial origin, but, for reasons not understood, increased risk for granulocytic leukemias has not been reported (*24-26*). In earlier epidemiologic studies, benzene has been linked most strongly with ANLL, while results for other hematologic neoplasms have been inconsistent (*5*). However, the epidemiologic database for quantitative assessment of cancer risk associated with benzene exposure is sparse.

No increases in risk were found in a

**Table 3.** Relative risk (RR)* for selected hematologic conditions among benzene-exposed workers according to recency of exposure

| | NHL† | | | | ANLL/MDS† | | | |
|---|---|---|---|---|---|---|---|---|
| | Recent exposure, ppm-yrs‡ | | | | Recent exposure, ppm-yrs‡ | | | |
| Distant exposure, ppm-yrs§ | None | <40 | ⩾40 | Total | None | <40 | ⩾40 | Total |
| None | | | | | | | | |
| Cases | | 3 | 0 | 3 | | 5 | 9 | 14 |
| P-Y ($\times 10^3$)‖ | Referent | 218 | 136 | 354 | Referent | 218 | 136 | 354 |
| RR | | 2.5 | — | 1.5 | | 3.7 | 9.1 | 6.0 |
| 95% CI¶ | | 0.5-13.2 | — | 0.3-7.6 | | 1.0-13.9 | 2.8-29.7 | 1.9-18.4 |
| <40 | | | | | | | | |
| Cases | 0 | 3 | 1 | 4 | 0 | 3 | 4 | 7 |
| P-Y ($\times 10^3$) | 3 | 97 | 46 | 147 | 3 | 97 | 46 | 147 |
| RR | — | 3.4 | 2.6 | 3.1 | — | 2.4 | 7.4 | 3.8 |
| 95% CI | | 0.7-17.4 | 0.3-25.3 | 0.7-14.3 | | 0.5-10.7 | 1.8-29.7 | 1.1-13.0 |
| ⩾40 | | | | | | | | |
| Cases | 0 | 2 | 7 | 9 | 0 | 1 | 6 | 7 |
| P-Y ($\times 10^3$) | 6 | 32 | 159 | 197 | 6 | 32 | 159 | 197 |
| RR | — | 6.4 | 4.7 | 4.9 | — | 2.0 | 2.7 | 2.5 |
| 95% CI | | 1.0-41.1 | 1.2-18.9 | 1.3-18.9 | | 0.2-18.5 | 0.8-9.8 | 0.7-8.7 |
| Total | | | | | | | | |
| Cases | 0 | 8 | 8 | | 0 | 9 | 19 | |
| P-Y ($\times 10^3$) | 9 | 347 | 342 | | 9 | 347 | 342 | |
| RR | — | 3.4 | 2.9 | | — | 2.9 | 5.3 | |
| 95% CI | | 0.9-13.0 | 0.8-10.8 | | | 0.9-9.3 | 1.8-15.6 | |

Linear trend tests: (never exposed [referent], >0 to <10, 10-39, 40-99, 100-399, and ⩾400 ppm-yrs, in time period).

NHL
Recent exposure, $P = .15$.
Distant exposure, $P = .005$.

ANLL/MDS
Recent exposure, $P = .003$
Distant exposure, $P = .51$

*Referent: RR = 1.0 for unexposed workers, with all risks adjusted for age and sex.
†NHL = non-Hodgkin's lymphoma; ANLL = acute nonlymphocytic leukemia; MDS = myelodysplastic syndromes (*see* Table 1 for ICD codes).
‡Recent exposure: cumulative benzene exposure (parts per million [ppm]-years, lag 1.5 years) in period <10 years prior to diagnosis.
§Distant exposure: cumulative benzene exposure (ppm-years, lag 1.5 years) in ⩾10 years prior to diagnosis.
‖P-Y ($\times 10^3$) = person-years per 1000.
¶CI = confidence interval.

case–control study (*3*) of leukemia (based on 14 exposed cases), multiple myeloma (based on seven exposed cases), or NHL (based on nine exposed cases) among Canadian petroleum distribution workers exposed predominantly to less than 1 ppm benzene. Also, among Scandinavian service station workers exposed on average to less than 1 ppm benzene, no excesses were found of leukemia (based on 28 exposed cases) or acute myeloid leukemia (based on 13 exposed cases) (*4*). Among 4602 benzene-exposed and 3074 unexposed U.S. workers (*6*), risk rose in an exposure–response fashion for lymphatic and hematopoietic cancers (based on 18 cases) and for leukemia and aleukemia (based on six cases) with respect to benzene exposure categorized as none, less than 15 ppm-years, 15-59 ppm-years, and 60 ppm-years or more. In another study (*7*) among 956 benzene-exposed workers in Michigan, seven deaths caused by lymphatic or hematopoietic cancer were identified, including four caused by leukemia (all myelogenous leukemias). Average exposures to benzene were 1-5 ppm for three of the individuals who died of leukemia and about 18 ppm for the fourth. Compared with general population rates, total deaths caused by myelogenous leukemia were significantly elevated; the RRs were 1.7 among workers with less than 42 ppm-years' cumulative benzene exposure (based on two cases) and 2.5 among workers with 83 ppm-years or more of benzene exposure (based on one case).

In a third cohort study (*8*), 1165 rubber hydrochloride manufacturing workers in the United States were followed through 1981, and 15 deaths caused by lymphatic or hematopoietic cancer, including nine caused by leukemia (six by ANLL) and four caused by multiple myeloma, were identified. The leukemia deaths occurred among workers who were generally exposed to benzene at levels of more than 20 ppm, and the risk increased with increasing exposure, showing significant excesses with cumulative exposures of greater than 200 ppm-years, consistent with an exponential in risk with increasing cumulative dose (*8*). Updated reports (*11*,*27*) on this cohort, with follow-up through 1987, show similar dose–response results for acute myeloid leukemia (AML) (based on six cases) (*11*) but indicate that risk for the non-AML leukemias (based on eight cases) was also in excess (*27*). Other investigators (*10*,*28*) suggest that exposures in this cohort may have been higher, but this suggestion has also been disputed (*29*).

In contrast to the findings among rubber hydrochloride workers (*8*,*11*), our study shows excess risk at relatively low levels of exposure (<10 ppm average and <40 ppm-years cumulative), but it shows a relatively modest dose–response effect, with proportionally smaller increases in risk at increasing levels of exposure. While the precise shape of the benzene exposure–response curve can only be estimated with caution from either of these studies, our larger study is in agreement with human (*30*) and rodent (*31*) metabolic studies showing a shift at higher lev-

els of benzene exposure in the proportion of the likely toxic precursors, such as hydroquinone and muconaldehyde.

MDS is a known precursor of acute myeloid leukemia after treatment with alkylating agents (*18*). Earlier, we showed (*22*) that MDS was linked to employment in benzene-related jobs (RR = ∞; 95% CI = 1.7 to ∞; based on seven cases), and here we relate ANLL/MDS to the extent of benzene exposure. Earlier mortality studies of benzene-exposed populations may have failed to identify this association because MDS has only begun to be more widely recognized in the past 10-15 years and patients may die of complications relating to the cytopenias of MDS before its evolution to ANLL. In our study, ANLL/MDS was linked to recent benzene exposure, and additional distant exposure did not appear to further increase risk. This finding suggests that recent benzene exposure is predictive of subsequent risk for ANLL/MDS, analogous to the short latency and wavelike increase then decrease in risk seen for several forms of radiation-induced leukemia (*19*) and for chemotherapy-related AML (*18*). In contrast, recent exposure was only weakly linked to NHL, suggesting that benzene-related NHL may be associated with a longer induction period. Our study included workers who were hired before the period of risk analysis began (January 1972), and we do not have information on the number of hematologic neoplasms that occurred in this earlier time period. Continued follow-up of the cohort, particularly those hired since 1972, will provide improved insight into the temporal development of benzene-associated diseases.

While this investigation in China substantially increases the number of person-years of follow-up and, in particular, the number of hematologic neoplasm outcomes for determining quantitative relationships between benzene exposure and disease risk, certain design aspects should be recognized. As in previous epidemiologic investigations, benzene-exposure estimates were based on historic data (*15*), characterizing only average exposure levels over broad time periods. We have shown (*32*) that our benzene-exposure ranking and the occurrence of benzene poisoning are in good agreement, providing indirect support for the general validity of our approach, but the precise calibration of exposure levels was not possible, particularly for distinguishing small differences in low-level exposures. Hematologic disease diagnoses for this investigation were based on careful nosologic review of available pathologic material and related documentation by expert hematopathologists (*16*), an improvement over previous death certificate-based studies (*6,7,11*). This effort was of particular importance in China, because recent nationwide vital statistics and cancer incidence validation studies are unavailable. Because benzene-exposed workers are known to be at excess risk for leukemia, it is possible that additional early cases were identified in the exposed group compared with the unexposed group due to more thorough surveillance. Such a bias, however, could not have been substantial, because overall excesses were similar when restricted to exposed and unexposed deceased individuals (*22*).

We compared disease rates among the benzene-exposed population with rates among a nonexposed industrial population. This comparison was an advantage because population data on cancer incidence and mortality rates in China are limited and because an earlier study (*33*) found that comparisons of cancer rates in benzene-exposed workers with general population rates tended to underestimate leukemia risk among benzene-exposed workers. Our earlier investigation in this cohort (*22*) showed that benzene-exposed and unexposed workers were closely comparable for total mortality (RR = 1.1; 95% CI = 1.0-1.2) and cancer mortality (RR = 1.2; 95% CI = 1.0-1.4) but that death rates in both groups were substantially lower than those expected by comparison with available vital statistics data for China. This latter finding underscored the need for an internal comparison with an unexposed population of Chinese workers from the same geographic areas.

As in most industrial settings, the workers in this investigation were likely exposed to a number of chemicals other than benzene and the observed risks could be due to some other exposures. However, the subjects in this study were employed in a variety of occupations, and excesses of hematologic disease were not restricted to a particular subset of benzene-related occupations, with the possible exception of the notably higher risks for NHL among chemical workers. This observation suggests that the effects are more likely due to the common exposure to benzene than due to other exposures.

While this study is larger than previous investigations and includes workers with a wide range of exposures to benzene, the estimates of risk, as measured by statistical CIs, are still fairly broad, and would benefit from the larger numbers that could be provided by continued follow-up of this population. Nevertheless, the observation of doubled risk for ANLL/MDS at an average exposure of less than 10 ppm benzene, the proportionally smaller increases in risk with increasing exposure, the elevated risk for ANLL/MDS with recent exposure, and the possible links with NHL are all provocative new observations that should enhance our efforts to understand benzene carcinogenesis in human populations.

## References


(*1*) Wallace LA. Major sources of benzene exposure. Environ Health Perspect 1989;82:165-9.

(*2*) Hricko A. Rings of controversy around benzene [news]. Environ Health Perspect 1994; 102:276-81.

(*3*) Schnatter AB, Armstrong TW, Nicolich MJ, Thompson FS, Katz AM, Huebner WW, et al. Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers. Occup Environ Med 1996;53:773-81.

(*4*) Lynge E, Andersen A, Nilsson R, Barlow L, Pukkala E, Nordlinger R, et al. Risk of cancer and exposure to gasoline vapors. Am J Epidemiol 1997;145:449-58.

(*5*) McMichael AJ. Carcinogenicity of benzene, toluene and xylene: epidemiological and experimental evidence. IARC Sci Publ 1988;3-18.

(*6*) Wong O. An industry wide mortality study of chemical workers occupationally exposed to benzene. II. Dose response analyses [published erratum appears in Br J Ind Med 1987;44:776]. Br J Ind Med 1987;44:382-95.

(*7*) Bond GG, McLaren EA, Baldwin CL, Cook RR. An update of mortality among chemical workers exposed to benzene [published erratum appears in Br J Ind Med 1987;44:215]. Br J Ind Med 1986;43:685-91.

(*8*) Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, et al. Benzene and leukemia. An epidemiologic risk assessment. N Engl J Med 1987;316:1044-50.

(*9*) Paxton MB, Chinchilli VM, Brett SM, Rodricks JV. Leukemia risk associated with benzene exposure in the pliofilm cohort. II. Risk estimates. Risk Anal 1994;14:155-61.

(*10*) Crump KS. Risk of benzene-induced leukemia: a sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates. J Toxicol Environ Health 1994;42: 219-42.

(*11*) Wong O. Risk of acute myeloid leukaemia and

multiple myeloma in workers exposed to benzene. Occup Environ Med 1995;52:380-4.
(*12*) Yin SN, Li Q, Liu Y, Tian F, Du C, Jin C. Occupational exposure to benzene in China. Br J Ind Med 1987;44:192-5.
(*13*) Yin SN, Li G, Tain F, Fu ZI, Jin C, Chen YJ, et al. Leukaemia in benzene workers: a retrospective cohort study. Br J Ind Med 1987;44: 124-8.
(*14*) Yin SN, Linet MS, Hayes RB, Li GL, Dosemeci M, Wang YZ, et al. Cohort study among workers exposed to benzene in China: I. General methods and resources. Am J Ind Med 1994;26:383-400.
(*15*) Dosemeci M, Li GL, Hayes RB, Yin SN, Linet M, Chow WH, et al. A cohort study among workers exposed to benzene in China: II. Exposure assessment. Am J Ind Med 1994;26: 401-11.
(*16*) Travis LB, Li CY, Zhang ZN, Li DG, Yin SN, Chow WH, et al. Hematopoietic malignancies and related disorders among benzene-exposed workers in China. Leuk Lymphoma 1994;14: 91-102.
(*17*) Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the myelodysplastic syndromes. Brit J Haematol 1982;51:189-99.
(*18*) Park DJ, Koeffler HP. Therapy-related acute myelocytic leukemia. In: Wiernik PH, Canellow GP, Dutcher JP, Kyle RA, editors. Neoplastic diseases of the blood. New York: Churchill Livingstone, 1996:381-407.
(*19*) Committee on the Biological Effects of Ionizing Radiation. Health effects of exposure to low levels of ionizing radiation. BEIR V. Washington (DC): National Academy Press, 1990:1-421.
(*20*) Curtis RE, Boice JD Jr, Stovall M, Bernstein L, Greenberg RS, Flannery JT, et al. Risk of leukemia after chemotherapy and radiation treatment for breast cancer. N Engl J Med 1992; 326:1745-51.
(*21*) Breslow NE, Day NE. Statistical methods in cancer research. Volume II—The design and analysis of cohort studies. IARC Sci Publ 1987;82:1-406.
(*22*) Yin SN, Hayes RB, Linet MS, Li GL, Dosemeci M, Travis LB, et al. A cohort study of cancer among benzene-exposed workers in China: overall results. Am J Ind Med 1996;29: 227-35.
(*23*) Hayes RB, Yin SN, Dosemeci M, Li GL, Wacholder S, Chow WH, et al. Mortality among benzene-exposed workers in China. Environ Health Perspect 1996;104:1349-52.
(*24*) Maltoni C, Ciliberti A, Cotti G, Conti B, Belpoggi F. Benzene, an experimental multipotential carcinogen: results of the long-term bioassays performed at the Bologna Institute of Oncology. Environ Health Perspect 1989;82:109-24.
(*25*) Huff JE, Haseman JK, DeMarini DM, Eustis S, Maronpot RR, Peters AC, et al. Multiple-site carcinogenicity of benzene in Fischer 344 rats and B6C3F1 mice. Environ Health Perspect 1989;82:125-63.
(*26*) Farris GM, Everitt JI, Irons RD, Popp JA. Carcinogenicity of inhaled benzene in CBA mice. Fundam Appl Toxicol 1993;20:503-7.
(*27*) Savitz DA, Andrews KW. Risk of myelogenous leukemia and multiple myeloma in workers exposed to benzene [letter]. Occup Environ Med 1996;53:357-8.
(*28*) Paxton MB, Chinchilli VM, Brett SM, Rodricks JV. Leukemia risk associated with benzene exposure in the pliofilm cohort: I. Mortality update and exposure distribution. Risk Anal 1994;14:147-54.
(*29*) Utterback DF, Rinsky RA. Benzene exposure assessment in rubber hydrochloride workers: a critical evaluation of previous estimates. Am J Ind Med 1995;27:661-76.
(*30*) Rothman N, Li GL, Dosemeci M, Bechtold W, Marti GE, Wang YZ, et al. Hematotoxicity among workers heavily exposed to benzene. Am J Ind Med 1996;29:236-46.
(*31*) Henderson RF, Sabourin PJ, Bechtold WE, Griffith WC, Medinsky MA, Birnbaum LS, et al. The effect of dose, dose rate, route of administration, and species on tissue and blood levels of benzene metabolites. Environ Health Perspect 1989;82:9-17.
(*32*) Dosemeci M, Yin SN, Linet M, Wacholder S, Rothman N, Li GL, et al. Indirect validation of benzene exposure assessment by association with benzene poisoning. Environ Health Perspect 1996;104:1343-7.
(*33*) Wong O. An industry wide mortality study of chemical workers occupationally exposed to benzene. I. General results. Br J Ind Med 1987; 44:365-81.
(*34*) World Health Organization. International Classification of Diseases. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Geneva: World Health Organization, 1977:1-773.
(*35*) World Health Organization. International Classification of Diseases for Oncology. Geneva: World Health Organization, 1990:1-144.

## Notes

Members of the Chinese Academy of Preventive Medicine-National Cancer Institute Benzene Study Group are as follows: Y.-Z. Wang (Stations of Public Health and Prevention of Infection, Shanghai, China), Z.-L. Jiang (Institutes of Labor Health and Occupational Disease, Tianjin, China), T.-R. Dai (Stations of Public Health and Prevention of Infection, Chengdu, China), W.-U. Zhang (Institutes of Labor Health and Occupational Disease, Sichuan, China), X.-J. Chao (Stations of Public Health and Prevention of Infection, Chonqing, China), P.-Z. Ye (Institutes of Labor Health and Occupational Disease, Heilongjiang, China), Q.-R. Kou (Institutes of Labor Health and Occupational Disease, Shenyan, China), X.-C. Zhang (Institutes of Labor Health and Occupational Disease, Henan, China), X.-F. Lin (Institutes of Labor Health and Occupational Disease, Guangzhou, China), J.-F. Meng (Institutes of Labor Health and Occupational Disease, Jiangxi, China), C.-Y. Ding (Institutes of Labor Health and Occupational Disease, Jinzhou, China), J.-S. Zho (Institutes of Labor Health and Occupational Disease, Nanchang, China), and D.-G. Li, Z.-N. Zhang (Peking Union Medical Hospital, Chinese Academy of Medical Sciences, Beijing, China).

We thank Dr. William J. Blot, former chief of the Analytic Studies Branch, National Cancer Institute, for his important contributions to the earlier phases of this investigation. We also wish to acknowledge the support provided by Nancy Odaka of Westat, Inc., Rockville, MD, and Tom Helde, Information Management Services, Inc., Rockville, MD, in data management for this study.

Manuscript received November 18, 1996; revised April 4, 1997; accepted May 9, 1997.