Validation of Benzene Exposure Assessment

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INTRODUCTION

Benzene exposure has been related in numerous occupational studies to increased risk of acute myeloid leukemia (AML) and, in some reports, to other lymphohematopoietic malignancies.[1] Since 1987, the U.S. National Cancer Institute (NCI) has collaborated with the Chinese Academy of Preventive Medicine (CAPM) to study the health effects of benzene exposure in a large cohort of industrial workers in 12 cities in China. The study design and the extensive efforts to estimate historical exposures have been reported elsewhere.[2,3]

A relationship between benzene exposure and hematotoxicity has been recognized since 1862.[4] Benzene poisoning is a compensable condition in China,[5] and it provided the opportunity to examine the relationship between historical benzene exposure and the reported occurrence of benzene poisoning. We used these data and the strong association between benzene exposure and poisoning as an indirect means to validate the historical exposure-assessment procedure.

The validity of an exposure-assessment method used in an epidemiologic study is always a concern of investigators in the field.[6] Few studies have been carried out to validate assessment methods for specific exposures.[7-9] Usually, validation of an assessment method is carried out by comparing the estimated results with the results of actual monitoring data. Unfortunately, in retrospective exposure-assessment studies, we are not always able to validate historical estimates directly because of the lack of historical monitoring data. One way of solving this problem is to estimate current levels of exposure, using available information for selected settings,[6] and monitoring the current level of exposure for the same settings. An alternative approach is to use a well-established association between an exposure and an effect to validate

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the exposure-assessment method used in the study.[9,10] If a strong dose-response relationship is observed between the exposure and the disease, confidence in the exposure-assessment method increases.

This report presents the results of a validation study for a retrospective assessment procedure to evaluate historical benzene exposures that we used in a follow-up study of workers exposed to benzene in China.[8,9] The association between a clinical diagnosis of chronic benzene poisoning[5] and estimated historical benzene exposures[9] was used to evaluate the accuracy of the estimates developed from the assessment method.

METHODS

Exposure-Assessment Method Used in the Cohort Study

The general characteristics of the cohort are described elsewhere.[2] Historical estimates of benzene exposure since 1949 were developed for 74,828 workers employed in 672 benzene-exposed factories.[3] Exposure estimates were made for 18,435 factory/work unit (department)/job title/calendar-year time period combinations. Under the direction of the principal investigators at the CAPM and NCI, the field center directors and other senior collaborating occupational health personnel from each of the 12 field centers (Shanghai, Tianjin, Chengdu, Chongqing, Harbin, Shenyang, Jinzhou, Zhengzhou, Luoyang, Guangzhou, Nanchang, and Kaifeng) supervised all data-collection activities. Exposure data from factories and work history information on study subjects were collected from factory records by 370 abstractors in the 12 cities. Abstractors worked closely with work-unit supervisors, industrial hygienists, safety officers, and other long-term factory employees to identify the relevant historical exposure information.

The exposure assessment procedures included several steps: a study-specific standardized job-title dictionary focusing on the benzene-specific industries and occupations was developed for use in the collection of the work histories and historical exposure information. The large number of job titles of workers in Chinese benzene-producing or -using factories was classified into 60 benzene exposure-specific job-title categories in 11 major activity groups. The individual work history information abstracted from written factory records included the names of study factories, work units (department), and job titles held by subject, with starting and ending dates of each job. A job-title code was assigned to each job based upon the job-title dictionary. Historical exposure information was collected at each factory, using the following three forms: (1) *nonexposed factory form:* to collect information on exposure to other potential occupational risk factors for hematopoietic disorders in control factories with no benzene exposure; (2) *exposed factory form:* to collect factory-level exposure information in facilities where benzene was used or produced, including 8477 benzene measurements available since the 1950s; and (3) *exposed job-title form:* to collect exposure information at the job-title level for a total of 18,435 factory/work-unit/job-title/calendar-year combinations in seven time periods (1949-1959; 1960-1964; 1965-1969; 1970-1974; 1975-1979; 1980-1984; and 1985-1987). A factory exposure-assessment team consisting of industrial hygienists, safety officers, supervisors, and long-term employees used these data to develop a summary estimate of benzene exposure for each factory/work-unit/job-title/calendar-year combination. The estimate of benzene exposure level was developed in six concentration ranges (<1 ppm; 1-5 ppm; 6-10 ppm; 11-25 ppm; 26-50 ppm; and >50 ppm). A concentration range was assigned to each factory/work-unit/job-title/calendar-period combination.

We used the following strategies in estimating exposure to benzene: if benzene-monitoring data were consistent with the other descriptive exposure information, then the estimate was derived from the mean of the measurements after adjustment for the frequency of exposure to benzene. If there were no monitoring information for the specific work unit/job title/calendar period or if the measurement results were not consistent with the other exposure information, then monitoring results for similar job combinations were used after task-description comparisons and historical changes were considered. If there were no monitoring data for the similar job combination in the same calendar period, monitoring data for the same work-unit/job combination in other calendar periods were used, after adjustments for historical changes and exposure frequency. If none of the preceding sources were available for the given combination, the field center team used all available exposure information and their professional judgment to estimate the exposure level.

Following data collection and exposure assignment, all forms were sent to the data-editing and -processing center in Beijing. Machine editing, including logic and range checks, was carried out. Data were reviewed to resolve discrepancies between benzene exposure estimates and abstracted exposure information. Discrepancies between the completed work history forms and exposure data-collection forms were resolved by further data retrieval from the field centers. Various exposure indices were developed for each study subject by merging the work histories and the exposure information files, including the duration of exposure, intensity of exposure, and cumulative exposure.

Validation Study

The association between benzene exposure and clinical diagnosis of benzene poisoning has been used as an indirect validation of the exposure-assessment method. Duration of exposure, intensity of exposure, and cumulative exposure to benzene were the exposure variables and the diagnosis of benzene poisoning (BP) was the outcome variable. We abstracted historical information on benzene toxicity among benzene-exposed cohort members. Workers were screened for evidence of benzene-associated poisoning in factory clinics. Cases of BP were identified from factory records. Diagnosis required (1) white blood cell (WBC) count <4000 per mm^3 blood or WBC count between 4000 and 4500 per mm^3 blood and platelet count <80,000 per mm^3 blood, demonstrated in repeated blood tests performed over several months; (2) having worked in a factory with documented benzene exposure for at least six months; and (3) other causes of abnormal blood counts excluded.[11]

In the statistical analysis, subjects employed less than six months or those hired before 1949 were excluded. In addition, subjects from one city were excluded from the analyses, because we were unable to distinguish subjects with suspected benzene poisoning from subjects with chronic benzene poisoning. Person-years were accumulated after a 1.5-year lag from January 1, 1972 or from the first date of a benzene-

TABLE 1. Characteristics of the Validation Study Subjects by Gender

Characteristics	Men	Women	Total
Number of benzene poisoning subjects	171	241	412
Number of exposed subjects	32,055	30,179	62,234
Number of person-years	324,388	290,121	614,509

exposed job, whichever was later. Relative risks (RR) estimates, adjusted for age and sex, were obtained by Poisson regression analyses,[12] using EPICURE statistical analysis software.[13]

RESULTS

In total, there were 18,435 benzene exposure estimates, 38% based on monitoring data, primarily collected after 1975. The overall exposure levels for the seven time periods was 16.7 ppm, ranging from 20.4 ppm in the first period to 11.5 ppm in the last period, while the percentage of benzene in raw materials or products declined over the periods 1949-1959 to 1985-1987 from 40% to 28%.

Benzene exposure level varied by industry and occupation. The highest level of exposure to benzene was in the rubber-plastic industry (mean = 31 ppm), whereas the glass-products industry had the lowest exposure to benzene (mean = 6 ppm). The leather, chemical, and machinery industries showed similar exposure patterns (mean = 16 ppm, 14 ppm, and 15 ppm, respectively).

Like the findings for major industries, the highest benzene exposure was observed among rubber workers, especially among rubber glue applicators and vulcanizers with an average estimated exposure level of 53 and 41 ppm, respectively. Painters (spray, electrostatic, drip painters, and paint mixers), the largest occupational group in the cohort, had consistent exposure levels of about 20 ppm in the early years and 15 ppm in recent years. Chemical manufacturing workers (organic, insecticide, and benzene-production workers) showed variable exposure levels over the seven calendar-year periods, ranging between 38 ppm and 17 ppm.

Characteristics of the validation study are presented in TABLE 1. There were 412 benzene-poisoning cases among 62,234 exposed subjects (614,509 person-years) in 11 cities in China. TABLE 2 presents the results of the relative-risk analyses by various exposure indices. Relative risks of benzene poisoning increased with increasing duration of benzene exposure. Relative risks of benzene poisoning by duration of exposure are 1.3 (95%CI = 1.0-1.8), 1.6 (95%CI = 1.2-2.1), and 2.7 (95%CI = 1.9-3.9) for periods of 5-9 years, 10-19 years, and 20 and more years, respectively, compared to subjects who have less than five years of exposure to benzene. When we examined relative risks of BP by intensity of exposure at one and a half years prior to the diagnosis of benzene poisoning, compared to subjects who had less than 5 ppm exposure at that time, we obtained relative risks of 2.2 (95%CI = 1.7-2.9), 4.7 (95%CI = 3.4-6.5), and 7.2 (95%CI = 5.3-9.8) for intensity of 5-19 ppm, 20-

TABLE 2. Relative Risks of Benzene Poisoning by Duration of Exposure, Intensity of Exposure, and Cumulative Exposure

Duration of Exposure	<5 years	5-9 years	10-19 years	20 + years
Relative risk [n] (95% CI)	1.0 [92] —	1.3 [91] (1.0-1.8)	1.6 [148] (1.2-2.1)	2.7 [80] (1.9-3.9)
Intensity of Exposure[a]	**<5 ppm**	**5-19 ppm**	**20-39 ppm**	**40 + ppm**
Relative risk [n] (95% CI)	1.0 [109] —	2.2 [140] (1.7-2.9)	4.7 [58] (3.4-6.5)	7.2 [64] (5.3-9.8)
Cumulative Exposure	**<40 ppm-years**	**40-99 ppm-years**	**100-399 ppm-years**	**400 + ppm-years**
Relative risk [n] (95% CI)	1.0 [109]	1.7 [74] (1.3-2.3)	2.0 [128] (1.5-2.6)	2.4 [100] (1.8-3.2)

[a] Recent intensity of exposure (ppm) at 1.5 years prior to the diagnosis.

39 ppm, and 40 and more ppm categories. Relative risks of benzene poisoning by cumulative exposure to benzene are 1.7 (95% CI = 1.3-2.3), 2.0 (95% CI = 1.5-2.6), and 2.4 (95% CI = 1.8-3.2) for cumulative exposure of 40-99 ppm-years, 100-399 ppm-years, and 400 and more ppm-years, respectively, compared to subjects with cumulative exposure of less than 40 ppm-year.

DISCUSSION

We present a validation study for the retrospective exposure-assessment method that we used in a follow-up study of workers exposed to benzene in China. We were able to detect a very strong relationship between benzene and benzene poisoning using the assessment method that we used in the cohort mortality study. This suggests that our estimated exposure values are valid enough to detect the association between benzene exposure and hematotoxicity, and are reasonable measures to use in the evaluation of the relationship between benzene exposure and cancer risk. We observed higher relative risk with recent intensity than any other measure of exposure, suggesting that the level of recent exposure to benzene has more effect on risk of benzene poisoning than duration of exposure and cumulative exposure.

There are various advantages in conducting an occupational epidemiologic investigation in China, including the large number of study subjects, fewer jobs held per subject, fewer exposures per subject, easier access to factory records, standardized methods of recordkeeping utilized nationally, and administrative systems for tracing and follow-up. The average number of jobs held by a subject in the present study was 1.4, in contrast with 5-10 in most occupational studies in the United States.[14] Because Chinese workers hold fewer jobs than workers in western industrialized countries, the potential for confounding by other hazardous substances is reduced.

One of the limitations of the exposure assessment method used in this study was the lack of walk-through surveys by a single industrial hygiene coordinator. Clearly, this approach was impractical given the large number (N = 672) of study factories. Nevertheless, a standardized approach was developed and intensive training undertaken to use the experience of the individual factory industrial hygienists and safety officers. Another limitation was the lack of personal sampling for air monitoring. Nearly all of the benzene measurements were based on short-term area sampling. Although multicenter decision making may lead to differences in interpretation of the historical exposure information, every effort was made to standardize the assignment of exposure, including central training of the field center directors and centralized review procedures carried out at the CAPM and at NCI. Because of these limitations and the historical nature of the retrospective exposure assessment, exposure ranges were used rather than quantitative point estimates.

Several studies have compared the results of exposure estimates used by various investigators.[9,10,15-23] These comparisons were carried out to measure the agreement between raters,[15-17] between assessment methods,[18,19] between information sources,[20,21] or between exposure measures.[22,23] Most of these comparisons were carried out on estimates of exposures rather than their effects on risk estimates. Few investigators[9,10,22,23] have used relative risks of an outcome in the comparison process as we did in the present presentation.

In conclusion, the strong association observed between benzene exposure and benzene poisoning provides confidence in the validity of the method that we developed for the assessment of retrospective exposure to benzene in the cohort study of workers exposed to benzene in China.

SUMMARY

We conducted a methodologic study to validate a quantitative retrospective exposure assessment method used in a follow-up study of workers exposed to benzene. Assessment of exposure to benzene was carried out in 672 factories in 12 cities in China. Historical exposure data were collected for 3179 unique job titles. The basic unit for exposure assessment was a factory/work-unit/job-title combination over seven periods between 1949 and 1987. A total of 18,435 exposure estimates was developed, using all available historical information, including 8477 monitoring data. Overall, 38% of the estimates were based on benzene monitoring data. The highest time-weighted average exposures occurred in the rubber industry (30.7 ppm), particularly for rubber glue applicators (52.6 ppm). Because of its recognized link with benzene exposure, the association between a clinical diagnosis of benzene poisoning (hematotoxicity) and benzene exposure was evaluated (412 cases and 614,509 person-years) to validate the exposure-assessment method. Relative risks of benzene hematotoxicity increased very sharply with increasing estimated intensity of benzene exposure. Odds ratios were 2.2 (95% CI: 1.7-2.9), 4.7 (95% CI: 3.4-6.5), and 7.2 (95% CI: 5.3-9.8) for the intensity levels of less than 5 ppm, 5-19 ppm, 20-39 ppm, and 40 and more ppm, respectively. This sharp trend between benzene hematotoxicity and estimated exposure to benzene indicated that the exposure-estimation method used in this cancer epidemiology study is reliable.

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