Review Article

An overview of published benzene exposure data by industry in China, 1960-2003

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Abstract

This article presents an overview of occupational benzene exposures in China based on data published in Chinese medical journals. The data were derived from 384 reports of benzene poisoning or industrial hygiene surveys published in Chinese medical journals between 1960 and 2003. The following information was extracted whenever available: industry, occupation, task, date, benzene levels, sampling location, workplace descriptions and, for case reports, medical diagnosis. Each paper provided one or more sets of benzene data, each set representing a sampling location or job title with one to several measurements. Two criteria based on data quality were applied to select suitable data for analyses. The selected exposure data were analyzed by industry and time period. 905 sets of benzene measurements from 72 industries were reported in the 384 papers selected for this review, and 621 sets (68.6%) presented average benzene concentrations, which covered 55 industries. The distribution of the reported average benzene exposures was skewed with a median of 51.5 mg/m^3. The average benzene concentrations were below 100 mg/m^3 for 406 (65%) of the 621 reported average concentrations. The medians of the reported averages in mg/m^3 for the six industries with the highest exposures were: 124.8 for leather products, 98.7 for electronic devices, 75.4 for machinery, 50.4 for shoes, 50.3 for office supplies and sports equipment manufacturing, and 39.8 mg/m^3 for spray painting.

These data describe the concentrations and changing patterns of occupational benzene exposure by industry and time period in China.

Key Words: Benzene, Occupational exposures, benzene poisoning, literature database, China

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Introduction

Benzene is one of the most widely used industrial chemicals in China. A wide variety of industries and occupations in China use benzene or benzene-containing solvents and adhesives, particularly the shoe and suitcase industries (1). The Chinese occupational medical literature is replete with reports of benzene overexposure and benzene poisoning (2, 3). In 1979-1981 the Chinese Academy of Preventive Medicine (CAPM) carried out a national occupational health survey of more than 500,000 workers in China, who were identified as having been exposed to benzene (4). The reported median was 18.1 mg/m^3 and the 95% range of benzene concentrations at workplaces was 0.06-844.74mg/m^3 or 0.02-266 ppm (1 ppm=3.18 mg/m^3); with some workers exposed to levels in excess of 1000 mg/m^3. The data showed a skewed distribution with a second mode at approximately 200 mg/m^3 and approximately 20% of the data are at or above this value (4). The nature of the distribution makes the median of these data a difficult to interpret. Measurements of occupational benzene exposure from the 1950s to the late 1980's taken at factories in Shanghai were reported in a recent report (5). This database of benzene measurements is maintained by the Shanghai Municipal Institute of Public Health Supervision (IPHS). The arithmetic average of benzene measurements for workplaces reported in the database was 132.7 mg/m^3 and the median was 2.8 mg/m^3.

In addition to *ad hoc* industrial hygiene surveys reported in the literature, there are incidents of acute poisoning and investigations of exposures associated with such events. For example, an investigation of 17 cases of serious benzene poisoning and 9 deaths in 2002 associated with small-scale suitcase manufacturing reported exposures as high as 2040 mg/m^3 (6). Industries in China have been regulated with occupational exposure limits (OEL) for benzene since the 1950's. These limits have gone through revisions over the years as shown in Table 1. The development of OELs in China has been discussed in a number of recent articles (1,7).

[Insert Table 1.]

The current article presents an overview of occupational benzene exposures reported in Chinese medical journals between 1960 and 2003. The review includes 384 papers of benzene poisoning case investigations or industrial hygiene surveys, covering 72 industries in China (8). Included in the overview is an analysis of benzene exposure data by industry and time period.

Material and Methods

Information sources

The published literature was identified primarily through Internet searching of the China National Knowledge Infrastructure, (CNKI), which covers 1994 to 2003 and the Chinese Biomedical Literature Database, (CBMD), which covers 1978 to 1994. Manual searching was also carried out to supplement the online search, particularly for conference proceedings and articles published before 1978. Through this process, a total of 384 benzene poisoning case reports or industrial hygiene surveys published in Chinese journals were identified.

From each paper, the following information was extracted whenever available: industry, occupation, task, year, benzene levels (minimum, average and/or maximum), workplace descriptions, and, for case reports, medical diagnosis (9). Each paper provided one or more sets of benzene measurements, with each set representing a sampling location or job title and one or more measurements. Two selection criteria (described below) were used to determine the eligibility of data being included for analysis. Exposure data were analyzed by industry and time period. Table 2 provides an example of the data extracted for the database.

[Insert Table 2.]

Selection Criteria

Two criteria were applied to select published data for analysis. The first criterion was used to select information for overall trend analysis and the second for analyses by industry.

For the selection of reports for the comparison of exposure level by industry, the most important factors were the number of measurements in each set of measurements and the number of sets of measurement for the industry. A set of measurements consisted of: the sampling location or job title, the benzene measurements taken, and the year.
Table 2 presents data from 5 published articles on benzene measurements. Article B in Table 2 provided three sets of measurements, covering three different jobs, while article E in Table 2 provided two sets of data, covering two different locations.

For the analyses in this report, we chose a weighted selection score (WSS) (described further below) of 18. This criterion considers the number of samples in a set and the number of measurement sets in a given industry. A score of 18 was the minimum for an industry to be included in the trend analyses. For example, using the leather industry data in Table 2:

WSS= 60+60+60+7+26+1+12=226.

Alternatively, if only report C had been available for the leather industry, the WSS = 7, which is below our required score of 18 and would thus not be included in the trend analyses.

A key component of the Weighted Selection Score (WSS) criterion for data sets in our review was the quantitative strength of the data. Our “rule of thumb” for this hinged on a commonly accepted sample size of 6 measurements as a basis for a reliable estimate of an average concentration in typical industrial hygiene surveys (10).
The second criterion, used to select information for the analysis of exposure trends by industry by time period, required (a) the published papers for the industry to include both average exposure concentration data and the year, and (b) at least 6 reports for each year.

Results

General feature of occupational exposure to benzene

The articles included in the database were published between 1960 and 2003. Figure 1 shows that only a few articles were published in the early 1960s and none for the time period between the mid 1960's and the late 1970's (the 10-years of the "Cultural Revolution" and its negative impact lasted for a few concessive years). Staring in the 1980s, with the improvement of the national economy and health services, the frequency of inspections and air monitoring at workplaces greatly increased, resulting in a surge in the number of published papers.

[Insert Figure 1.]

Figure 2 shows the distribution of average benzene exposure levels included in the present analysis.

[Insert Figure 2.]

9 sets (1.4%) reported having not-detected levels of benzene, which were shown as "0" in our database; 406 sets(65.4%)presented concentrations below 100 mg/m^3, and 147 sets (23.7%) presented levels between 100 and 500 mg/m^3. In addition, there were measurements of exposure that far exceeded 500 mg/m^3. For example, there were 15 sets (2.4%) that reported benzene exposure concentrations above 3000 mg/mg^3 (Table 3). The highest levels were found for the following occupations: paint coating/spraying and glue brushing (e.g., in shoes and suitcase industries). Some measurements were as high as several thousand mg/m^3. Levels of more than 10,000 mg/m^3 were reported for work in confined spaces without adequate ventilation; which was usually associated with acute benzene poisoning. As further examples, acute benzene poisoning cases were reported among workers who painted the inner walls of oil storage tanks, worked in poorly ventilated basements, or in deep wells.

[Insert Table 3.]

Comparison of benzene exposure by industry

39 industries provided data for both average benzene concentrations and sample size. According to the selection criteria defined above, 27 (69.2%) industries (1972-2002) of the 39 met the required WSS of 18 and were included in the analysis by industry. The results, given in Table 4, show that the average benzene exposures in the 9 industries with the highest reported concentrations exceeded the previous OEL standard of 40 mg/m^3, and more than 85% (23 of 27) of the industries had average exposure levels above the new standards of either 10 mg/m^3 (PC-STEL) or 6 mg/m^3 (PC-TWA).

[Insert Table 4.]

Table 4 compares benzene measurements by industry, sorted by the median of the reported average exposures. The top 15 industries, ranked by median benzene concentration, are: toy manufacturing, leather products, electronic devices, coal products, machinery, crude oil processing, petroleum & geological prospecting, shoes manufacturing (leather), office supplies and sports equipment, paint spraying, furniture, miscellaneous parts of electric appliances, automobile, other textile industries/printing and dyeing, and synthetic chemical industry. Table 4 shows the six industries with the highest exposures were leather products, electronic devices, machinery, shoes, office suppliers and sports equipment manufacturing, and spray painting.

Historical trends of the benzene exposure data

According to selection criterion II, the medians of the exposure levels for the 22 years between 1979 and 2001 were adequate for temporal trend analysis. The median of the averages for each five year period are shown in Table 5.

[Insert Table 5.]

Figure 3 shows the trend by year for the median exposure levels. Figure 4 shows the trend by 5 year averages of the median exposures.

(Insert Figures 3 and 4.)

These trends were most likely influenced by several historical events. First, the national economy started growing in the late 1970's, which resulted in increased numbers of small-scale industries (SSIs) in rural areas. Second, the improvement of occupational health services after the mid 1990's brought about more stringent health inspections and workplace monitoring and resulted in more published data. Third, the new Occupational Disease Prevention and Control Act was adopted by the Standing Committee of the National People's Congress in 2001, which required the reporting of benzene over-exposures in industries, including in the SSIs in rural areas(11).

As shown by Figures 5 to 8, average benzene exposure levels in several major industries showed a similar but variable decline over the years. More significant declines were evident for the earlier periods. Most of these industries show slightly increased exposure concentrations at the beginning of the 21st century.

[Insert Figures 5 to 8.]

Discussion and conclusions

The following six industries had the highest benzene exposure levels. The median values of the reported average concentrations and the ranges of the averages are also shown.

Leather products, 124.8 (3.7 to 267.8) mg/m^3

Electronic devices, 98.7 (4.5 to 254.9) mg/m^3

Machinery, 75.4 (4.2 to 152.7) mg/m^3

Shoes, 50.4 (1.3 to 1488.6) mg/m^3

Office supplies and sports equipment manufacturing, 50.3 (10.7 to 256.0) mg/m^3

Spray painting. 39.8 (Not-detected to 226.8) mg/m^3

The percentage of industries with reported data exceeding the prior OEL of 40 mg/m^3 was 33% (9 of 27). More than 85% (23 of 27) of industries showed average exposure levels above the new standards of either 10 mg/m^3 (PC-STEL) or 6 mg/m^3 (PC-TWA).

With the improvement of occupational health services, the overall average benzene exposure levels appeared to decline over the years. In particular, industries traditionally with high exposures such as leather products manufacturing, shoe, paint spraying and furniture industries showed declines as well. Relatively high levels (270.38 mg/m^3) were observed during the period between 1981 and 1985; but dropped to 73.85 mg/m^3 in the second half of 1980s. The exposure levels declined further to 48.42 mg/m^3 during the period between 1996 and 2000. However, the exposure levels fluctuated due to the influence of the national economic development and newly implemented legislations. For example, the average of the reported exposures rose to 121.25 mg/m^3 at the beginning of the 21 century, which might partially be due to the wider disclosure of over-exposures in small workshops commonly found in rural areas. Additionally, the current public awareness and the frequency of health inspection might bias the results to a certain extent.

There are a number of limitations associated with the published information and the analyses currently presented. These include:

1) Different sampling and analytical methods were employed over the decades covered. Although this may introduce some bias, we believe that the differences are minor and will not to remarkably significantly alter the findings of this review.

2) Our analysis did not distinguish between benzene poisoning case reports and industrial hygiene surveys. Benzene poisoning case reports refer to investigation of the Chinese regulation-defined occupational benzene poisoning either acute or chronic benzene poisoning cases may thus represent high-end exposures. On the other hand, industrial hygiene surveys were commissioned for a variety of reasons, and are not necessarily targeted at facilities with benzene poisoning cases or high benzene exposures. The industrial hygiene survey reports thus may or may not better represent typical conditions.

3) Our selection criteria may have excluded some informative but smaller data sets.We believe the criteria gave us the more reliable data to use in our analysis, resulting in more robust summaries.

4) The original investigators who reported the data may have had a range of investigative needs and approaches that introduced indeterminate biases into their reported data. For example, what motivated or initiated the authors to write up benzene poisoning reports or industrial hygiene surveys and submit them for publication?

5) The data in the original reports are area samples that represent concentrations in the air at the location and time measured. However, these concentrations might not directly reflect worker exposures, particularly for full-shift exposures, because they did not account for various potential exposure zones.

6) The data for trend analyses in this report are averages given in the reports. These averages should give a good estimate of the typical concentrations. However, the averages do not give insights into the range and variability of the concentrations in the industries covered.

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TABLES

Table 1. Past and current benzene OELs in China

Years	Standard and Reference for the Standard
1950's	**50mg/m^3**, Provisional Hygienic Standards for the Design of Industrial Premises (Standard-101-56), co-promulgated by the State Committee of Economy Construction and Ministry of Health, P.R. China, 1956
1960's to 2000	**40mg/m^3**, Hygienic Standards for the Design of Industrial Premises (GBJ) 1-62, co-promulgated by the State Committee of Economy Planning and Ministry of Health, P.R. China, 1962
2001(2002?)- to present	**6mg/m^3,** permissible concentration- time weighted average (PC-TWA) **10mg/m^3,** permissible concentration- short term exposure limit **(**PC-STEL) Occupational Exposure Limits for Hazardous Agents in the Workplace (GBZ 2-2002, Ministry of Health, P.R. China, 2002.

Table 2. Examples for leather manufacturing from the benzene exposure database

Article	No. cases and diagnosis	Industry	No. Sets	Year	Task/area description	Min Conc. (mg/m^3)	Aver Conc. (mg/m^3)	Max Conc. (mg/m^3)	No. sample
A	5(atypical anemia)	Leather manufacturing (shoes)	1	1983		0	370	1530	NA
B	77(chronic poisoning)	Leather manufacturing (shoes)	3	1985	Soles adhesive brushing	NA	1128.39	NA	60
					Underlay adhesive brushing	NA	440.39	NA	60
					Assembly finishing	NA	48.43	NA	60
C		Leather manufacturing (watch bands)	1	1989		45	122.5	300	7
D	17 (chronic poisoning)	Leather manufacturing (shoes)	1	NA		4.3	NA	308	26
E		Leather manufacturing (suitcases)	2	2001	Garment I	NA	191.71	NA	1
					Garment II	NA	126.44	NA	12

Table 3. Frequency and percentage of average concentrations

Concentration(mg/m3)	Frequency of Data Sets	Percentage(%)	Cumulative Percentage
0~	125	20.1	20.1
10~	64	10.3	30.4
20~	75	12.1	42.5
40~	142	22.9	65.4
100~	147	23.7	89.1
500~	26	4.2	93.3
1000~	19	3.1	96.4
2000~	8	1.3	97.7
3000~	15	2.4	100.0
Total	621	100.0	

Table 4. Comparison of the average benzene concentrations (mg/m^3) by industry

Code	Type of Industry	No. Sets	No. samples	Minimum	Maximum	Median	Average
296	Toy manufacturing	2	2531	1.5	264.3	132.9	132.9
252	Leather products*	18	1487	3.7	267.8	124.8	124.1
449	Electronic devices manufacturing*	6	1930	4.5	254.9	98.7	120.2
363	Coal products manufacturing	3	23	12.8	130.5	96.0	79.8
42?43	Machinery manufacturing*	6	6815	4.2	152.7	75.4	75.6
361	Crude oil processing	3	992	7.4	93.2	62.6	54.4
512	Petroleum & geological prospecting	3	22	5.8	62.6	57.2	41.9
243	Shoes manufacturing, leather*	70	12197	1.3	1488.6	50.4	149.9
291	Office supplies and sports equipment*	6	106	10.7	256.0	50.3	79.4
321	Spray painting*	29	1186	0	226.8	39.8	53.4
270	Furniture manufacturing	8	618	2.0	72.0	39.3	36.6
444	Msc. Electronic parts manufacturing	7	197	3.0	105.6	33.6	50.5
472	Automobile manufacturing	6	3478	0	196.1	32.8	56.8
238	Other textile industries/printing &	1	178	26.2	26.2	26.2	26.2

	dyeing						
314	Organic chemical industry	19	650	12.8	130.5	23.8	39.3
341	Rubber products manufacturing	15	182	0.1	633.6	22.9	114.6
520	Civil engineering & construction	3	137	1.2	345.2	20.3	122.2
374	Pottery & porcelain products manufacturing	3	26	7.1	40.0	20.2	22.4
450	Electronic circuit manufacturing	3	26	7.1	40.0	20.2	22.4
998	Other industries	10	6799	2.2	85.5	18.5	23.8
342	Plastic products manufacturing	2	1216	2.3	28.2	15.2	15.2
499	Other precision instruments manufacturing	2	44	8.7	19.9	14.3	14.3
320	Paint manufacturing	37	525	1.0	127.5	13.2	23.9
31	Chemical industry	18	859	0	123.9	7.6	19.3
294	Printing industry	8	6416	0	23.6	6.5	7.2
407	Household metal hardware Manufacturing	1	1139	2.3	2.3	2.3	2.3
401	Metal-based products processing	10	77	0	38.0	1.4	7.5

Table 5. Average exposure levels (mg/m3) as the mean of the medians by 5-year period

Year	1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2002
	151.73	270.38	73.85	64.34	48.42	121.25

Figures

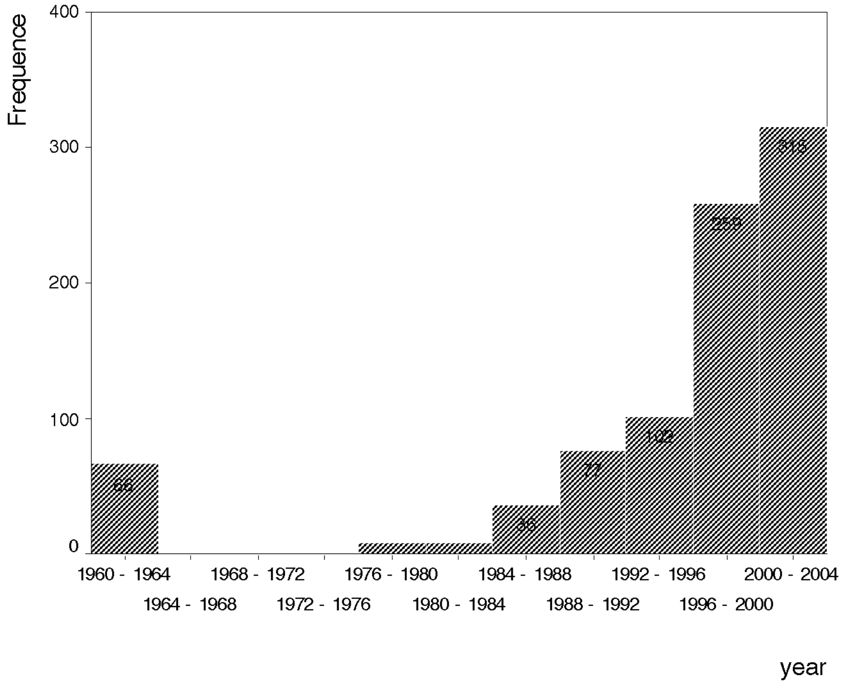

Figure 1. Time period covered in the database

Numbers in each bar represent the number of reports included in the analyses for that time period.

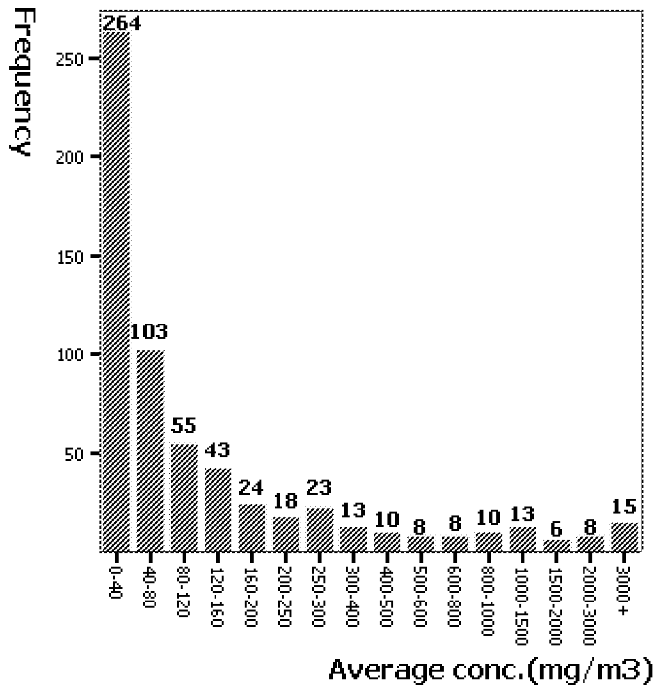

Figure 2. Distribution of the average benzene exposure levels.

Numbers in the bars denote the number of reports in the analyses in the given concentration range.

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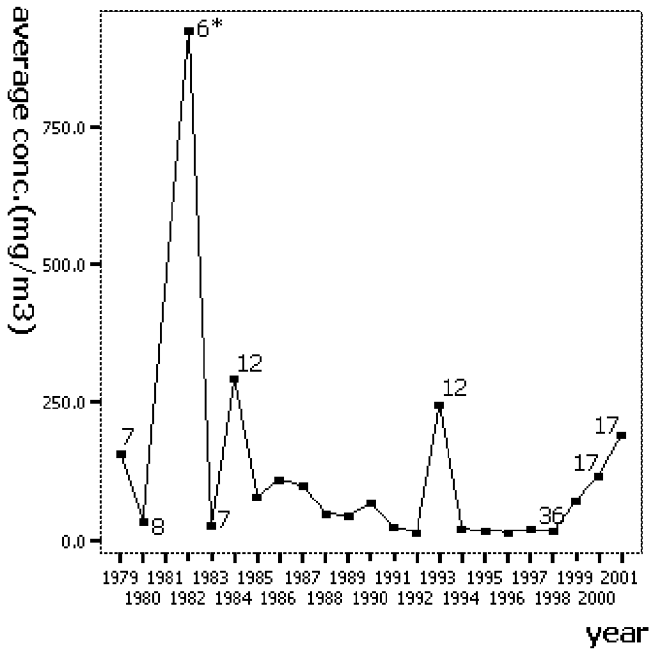

Figure 3. Overall tendencies of the exposure level in median by years

* Indicates the number of measurement sets in the database

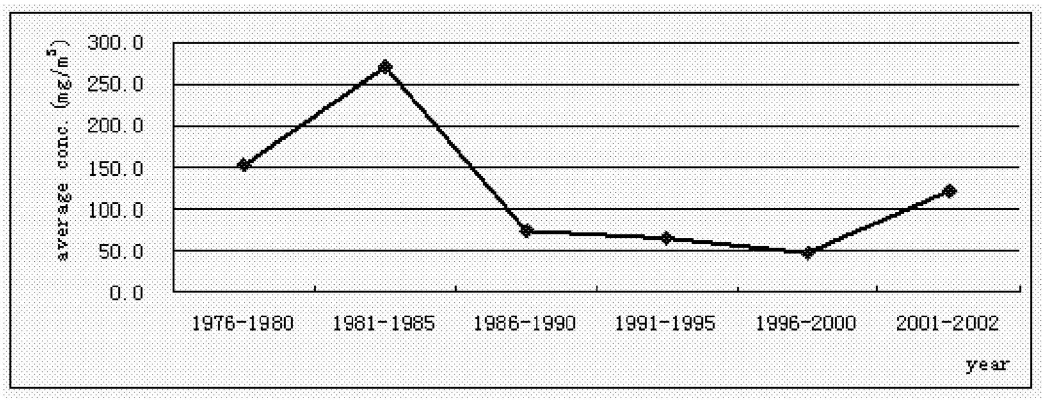

Figure 4. Trend of the exposure levels as average of the reported medians for each of the 5 year periods

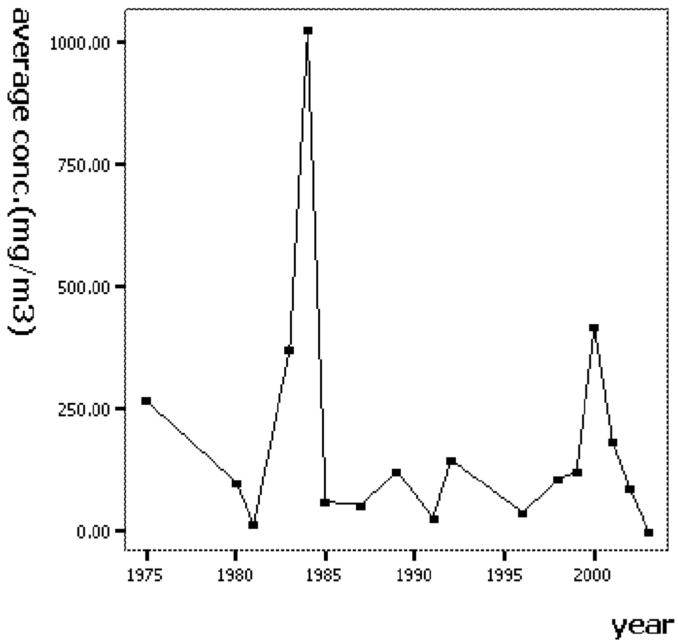

Figure 5. Tendency of the average exposure levels in leather manufacturing

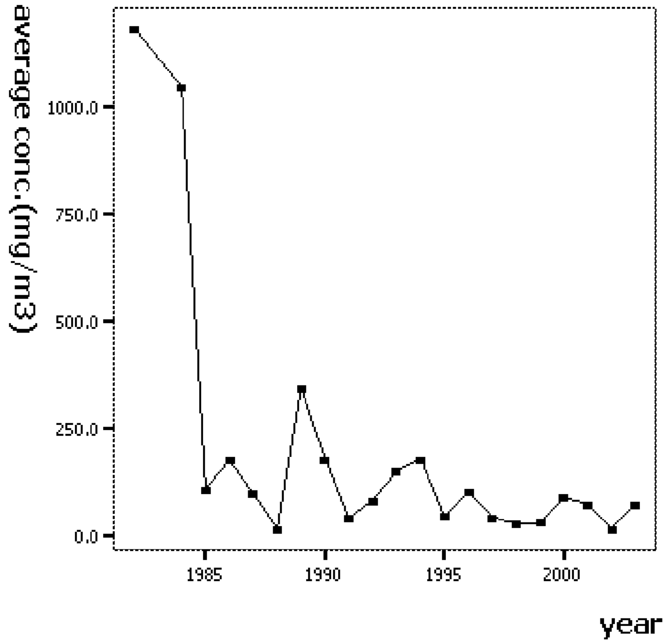

Figure 6. Tendency of the average exposure levels in leather shoes manufacturing

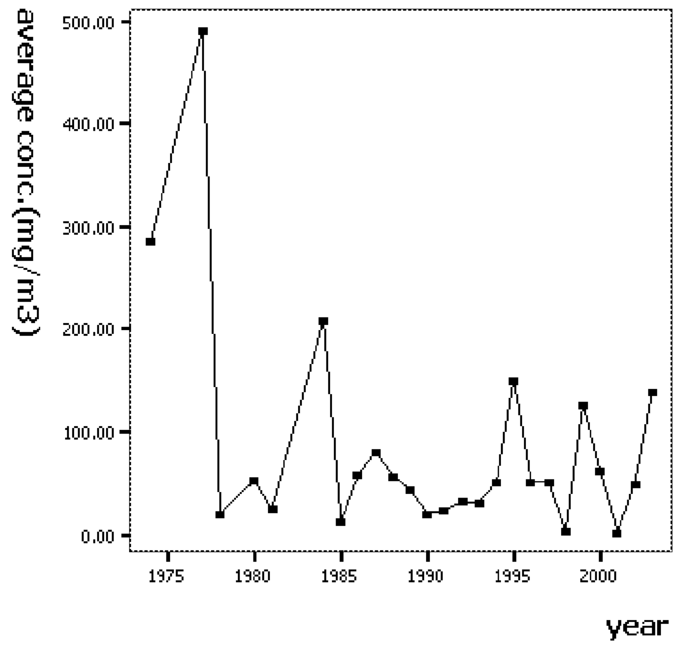

Figure 7. Tendency of the average exposure levels in spray painting

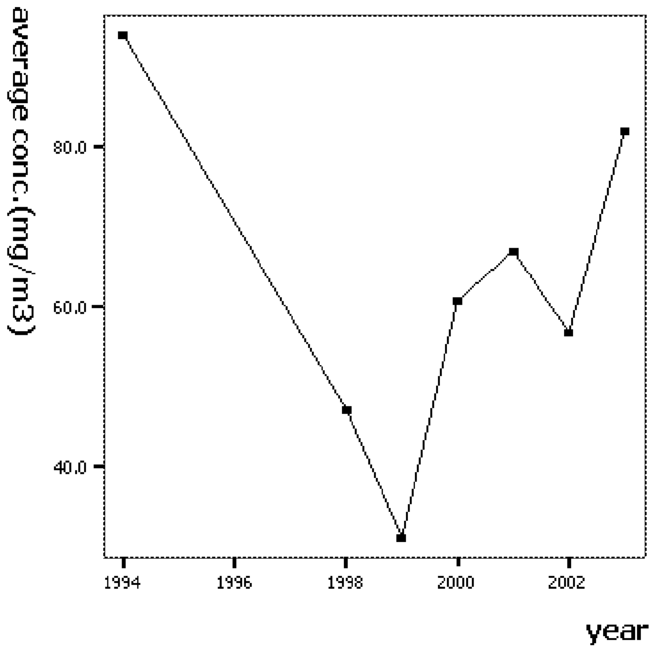

Figure 8. Tendency of the average exposure levels in furniture manufacturing

Exposure to Benzene and Non-Hodgkin's Lymphoma,
An Epidemiologic Overview and An Ongoing Case-control Study in Shanghai

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ABSTRACT

The interest in the relationship between benzene exposure and non-Hodgkin's lymphoma (NHL) appears to have been generated from a 1979 publication, which reported an increased risk of NHL among persons potentially exposed to benzene and/or coal tar fractions. More recently (1997), an increased risk of NHL was reported among workers exposed to benzene and other chemicals in a variety of industries in China. On the contrary, no increased risk of NHL was reported in a cohort of workers at two rubber hydrochloride plants in Ohio, who were exposed to extremely high levels of benzene and were found to have an increased risk of acute myeloid leukemia. In another large cohort of some 7000 US workers exposed to benzene, no increased risk of NHL was reported. Similarly, no increased risk of NHL was reported in a combined cohort of 308,000 petroleum workers in the US, UK, Canada, Australia, Italy and Finland, who were exposed to benzene-containing petroleum products. The lack of an association between benzene exposure and NHL in cohort studies is supported by case-control studies from countries all over the world.

To further investigate the relationship between benzene exposure and NHL, we are conducting a hospital-based case-control study in Shanghai. Cases are newly diagnosed NHL patients at 29 hospitals in Shanghai. For each case, two matched controls are selected among patients without any lymphatic or hematopoietic diseases at the same hospital. Demographic, employment, medical and lifestyle information is obtained through questionnaires (primary and secondary). Sources for benzene exposure information include a database of 50,000+ benzene measurements maintained by the Shanghai Municipal Institute of Public Health Supervision (IPHS), Shanghai District IPHS, Chinese medical journals, factory visits and ad hoc measurements. Patient enrollment started in 2003 and it is estimated that we will have 400-450 NHL cases by December 2006. Some of the occupations or industries reported among enrolled study subjects (cases and controls) with potential exposure to benzene include shoe workers, painters, mechanics or machinists, and printers. Some of the unique features of the study are discussed.

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Introduction

Lymphoma refers to a group of malignancies in which the cells of lymphoid tissue multiply uncontrollably. Lymphomas with the characteristic Reed-Sternberg cells are called Hodgkin's lymphomas, and all others by default are known as non-Hodgkin's lymphomas (NHL). As such, NHL represents a heterogeneous group of malignancies whose common link is a characteristic monoclonal expansion of malignant B or T cells, and is the single largest group of neoplasms of the immune system. According to the National Cancer Institute's (NCI) Cancer Surveillance, Epidemiology and End Results (SEER) Program, approximately 45,000 new cases of NHL were diagnosed in 1994 in the US.[1] The average annual age-adjusted incidence rates during 1987-1991 were 17.9/100,000 for men and 11.5/100,000 for women. NHL risk increases rapidly with age. For ages 65 and older, the rates were 81.1/100,000 for men and 60.8/100,000 for women.

Studies have identified a large number of potential risk factors of NHL: inherited immunodeficiency diseases, acquired immunodeficiency diseases, autoimmune diseases, viruses (e.g., Epstein-Barr virus), certain drugs, chemotherapy and radiation therapy, ionizing radiation, chronic infectious diseases, tuberculosis, malaria, diabetes, previous cancer, rheumatoid arthritis, Sjogren's syndrome, kidney calculus, duodenal ulcer, pneumonia, scarlet fever, herpes zoster, eczema dermatitis, cysts, family history of cancer, smoking or tobacco consumption, agricultural work, farming or living on a farm, forestry, and employment in the meat industry.[2-14]

In this paper, we will present an overview of the epidemiology of benzene exposure and NHL. Further, we will also discuss an ongoing case-control study of NHL in Shanghai, China.

An Epidemiologic Overview

In 1979 Vianna and Polan reported the results of an investigation based on the linkage of deaths from lymphosarcoma and reticulosarcoma or Hodgkin's disease during 1950-1969 in New York State and the 1960 US census.[15] A total of 14 occupations were assumed to have occupational exposure to benzene or coal tar fractions. The largest groups were farmers and woodworkers. Other occupations included fishermen, brick and stone workers, and barbers. Populations at risk in these occupations were estimated from the 1960 census. Occupations listed on death certificates were used to identify New York residents in these occupations who died from lymphosarcoma or reticulosarcoma. According to Vianna and Polan,[15] an increased risk of lymphosarcoma or reticulosarcoma was found in these occupations, and, in particular, the highest risk was reported among fishermen. The Vianna and Polan investigation has been criticized by Enterline[16], Smith and Lickiss[17], and Wong.[18] The major criticism was that information on occupation derived from the US census and death certificates was not compatible, and the reported mortality excess might simply be an artifact.

Hayes et al.[19] reported a study of 74,828 Chinese workers who were exposed to benzene in a wide spectrum of industries with heterogeneous exposures (e.g., food, textile, paper products, agricultural chemicals, pharmaceutical, rubber and plastic, electrical equipment). The comparison group was a cohort of 35,805 Chinese workers who were not exposed to benzene or any other carcinogens. There were 17 NHL deaths among the benzene-exposed workers. Among the non-exposed workers, the number of NHL deaths was 3. The risk ratio (RR) was 3.0 (95% CI 0.9-10.5). Analysis by occupation reported the following RRs: "organic, insecticide and benzene production" (RR=7.8), paint and other coatings (RR=1.6), and shoe (RR=1.6). The group "organic, insecticide and benzene production," which had the highest risk, consisted of several heterogeneous industries/occupations with very different exposures. In particular, insecticide workers are exposed to a variety of chemicals not related to benzene, and studies have reported increased risk of NHL among agricultural chemical workers or farmers throughout the world. Thus, the result might have been confounded by chemicals other than benzene. Analysis by cumulative benzene exposure reported the following RRs: 1.0, 3.3, 1.1, and 3.5 for non-exposed, <40, 40-99, and 100+ ppm-years, respectively. The lack of a clear positive exposure-response relationship further argues against an association between benzene exposure and NHL. Quite appropriately, Hayes et al. did not conclude that the findings established a causal association between benzene exposure and NHL. Instead, they concluded that "the possible links with NHL are all provocative new observations."

Wong reported the mortality experience of a cohort study of 7,676 chemical workers in the US.[20,21] Most of these workers were exposed to benzene in the 1940s and 1950s, with some whose first exposure occurred in the 1920s and 1930s. Some of these workers were exposed to relatively high benzene levels in the past (in the range of 50 to 100 ppm). In the original study, no analysis specific to NHL was reported because of the NHL classification in the past and the grouping of diseases in vital statistics. A subsequent analysis indicated that there were 7 deaths from NHL among workers exposed to benzene, compared to 5.12 expected deaths based on the US general population.[22] The corresponding SMR was 1.37 (95% CI 0.55-2.82). Thus, there was no increased risk of NHL in this large cohort of workers exposed to benzene.

In the US there is another often-cited cohort study of workers exposed to benzene, consisting of 1,165 white men at two rubber hydrochloride plants in Ohio, where benzene exposures were reported to be very high (up to several hundred ppm).[23] In this cohort, a significant increase of leukemia mortality was reported. In particular, a remarkable risk of acute myeloid leukemia (AML) was found and a positive exposure-response relationship between cumulative exposure to benzene and AML was also reported.[24] In terms of NHL, however, based on the latest update, Rinsky et al. reported 5 NHL deaths, comparable to 5.01 expected (SMR=1.00, 95% CI 0.32-2.33).[25] Thus, there was no elevated risk of NHL in this cohort of workers who were exposed to extremely high levels of benzene and who were found to have experienced an elevated risk of AML.

Further supporting evidence that there is no association between benzene exposure and NHL comes from case-control studies, which have been summarized by Wong.[22] In a case-control study consisting of 501 NHL patients in North Carolina, Schumacher and Delzell reported 66 cases exposed to benzene.[26] The risk ratios for benzene exposure were 0.77 (95% CI 0.56-1.07) in whites and 0.94 (95% CI 0.47-1.87) in blacks. Ott et al.[27] conducted a detailed case-control study of lymphatic and hematopoietic tissue cancers among 29,139 Union Carbide employees in West Virginia. Based on 52 cases, the NHL risk ratio for exposure to benzene was reported as 1.0. In a case-control study consisting of 303 NHL cases in Boston, the risk ratio for benzene exposure was 1.2 (95% CI 0.5-2.6).[10] In a case-control study conducted by the US National Cancer Institute, the exposure histories of 622 NHL cases in Iowa and Minnesota were compared to those of 1,245 controls.[13] A total of 153 cases were reported to have been exposed to benzene. The risk ratio for benzene exposure was 1.1 (95% CI 0.9-1.4), indicating no increased risk.

Case-control studies from other countries also support the results of no association reported in the American studies. In a case-control study consisting of 215 NHL patients in Montreal, 26 cases reported exposure to benzene.[28] The relative risks were 0.7 for any exposure to benzene and 0.8 for substantial exposure to benzene. In another report based on the same data, Siemiatycki et al.[29] reported the following relative risks for a variety of petroleum-derived fuels or solvents: 0.8 for automotive gasoline, 0.4 for aviation gasoline, 0.8 for mineral spirits, 0.4 for kerosene, 0.7 for jet fuel, 1.1 for diesel fuel, and 0.7 for heating oil. In an Italian case-control study of 208 NHL cases, the risk ratio for exposure to benzene and solvents was reported as 1.14, with a 95% CI of 0.57-2.28.[3] In a case-control study of NHL conducted in the UK, the employment and medical histories of 158 cases were compared to those of their matched controls.[6,30] The risk ratio for benzene exposure was 0.49, with a 95% CI of 0.21-2.00.

The risk ratios reported in these case-control studies of NHL and benzene or benzene-containing solvents ranged from 0.49 to 1.2. Although exposure classification in some of these case-control studies might lack specificity, these investigations have consistently demonstrated that no association was found between exposure to benzene and NHL. Thus, these case-control studies confirm the results of cohort studies of workers exposed to benzene or benzene-containing petroleum products.

Finally, petroleum workers are exposed to benzene or benzene-containing petroleum products. As such, studies of these workers provide an opportunity for investigating the relationship between benzene and NHL. Wong and Raabe reviewed and summarized the results of 26 cohorts of petroleum workers in the US, the UK, Canada, Australia, Italy and Finland.[31] Data from these studies were reviewed individually as well as combined in a pooled analysis (meta-analysis). The combined multi-national cohort consisted of more than 308,000 petroleum workers (6.6 million person-years), and the observation period covered an interval of 60 years from 1937 to 1996. A total of 506 NHL deaths were observed, compared to 561.68 expected. The SMR was 0.90 and the 95% CI was 0.82-0.98. Stratified analyses were performed by type of facility or industrial process. Stratum-specific SMRs (95% CIs) were 0.96 (0.86-1.07) for US refinery workers, 1.12 (0.90-1.37) for non-US refinery workers, 0.64 (0.50-0.82) for product (gasoline) distribution workers, and 0.68 (0.47-0.95) for crude oil workers. When individual cohorts were stratified by length of observation, no pattern was detected. In general, occupational exposure levels prior to 1950 were much higher than thereafter. However, analysis of workers by hire date (<1950, ≥1950) revealed no difference in NHL mortality. Furthermore, none of the individual studies showed significant exposure-response relationship. In summary, results from individual studies as well as from the pooled analysis indicated that petroleum workers were not at an increased risk of NHL as a result of their exposure to benzene or other benzene-containing petroleum products in their work environment.

An Ongoing Case-control Study of NHL in Shanghai

To further investigate the relationship between NHL and exposure to benzene or other substances, we are currently conducting a case-control study of NHL in Shanghai. The study is one of the research projects of the Shanghai Health Study sponsored by the Benzene Health

Research Consortium. The Shanghai Health Study is a collaborative research program between the USA and China. Participants in the Shanghai Health Study include the following US and Chinese organizations:

- Applied Health Sciences,
- University of Colorado,
- ExxonMobil Biomedical Sciences,
- Fudan University School of Public Health, Shanghai,
- Shanghai Municipal Institute of Public Health Supervision,
- Shanghai District Institutes of Public Health Supervision,
- Shanghai Center for Disease Prevention and Control, and
- 29 hospitals in Shanghai.

The study design is that of a hospital-based case-control study. Cases are defined as patients who are aged 18 or older and diagnosed with NHL at one of the 29 participating hospitals in Shanghai between August 2003 and December 2006. The hospital diagnosis is verified or confirmed by a newly completed clinical laboratory at Fudan University, which has been built specifically for the Shanghai Health Study. The World Health Organization (WHO) definition of NHL is used for diagnosis. For each case, two individually matched controls are randomly selected from patients at the same hospitals, but free from any lymphatic or hematopoietic diseases. Matching criteria included: gender, age (within 5 years), and admission date.

To obtain relevant information from study participants, face-to-face interviews at the hospitals are conducted by trained interviewers from Fudan University School of Public Health. The case/control status is not made known to the interviewers. A 17-page primary questionnaire is used to obtain the following information:

- Demographics,
- Medical history,
- Family history,
- Medication history (both Western and Chinese traditional medicines),
- Employment and exposure history, and
- Non-occupational exposures (e.g., tobacco, alcohol, hobbies and farming).

Certain occupations of interest will trigger secondary questionnaires that are more detailed and industry- or occupation-specific. Some examples of these occupations are shoe worker, farmer, mechanic, machinist, electrician, assembly worker, health care worker, textile worker, laborer, manager and supervisor. The secondary questionnaires range from 4 to 9 pages. A typical secondary questionnaire asks for the following information:

- Industry and occupational title,
- Description of tasks,
- Substances handled,
- Frequency and duration of exposure,
- Workplace environment, and
- Use of personal protection equipment.

The employment histories are reviewed by the "Exposure Assessment" Committee at Fudan University, whose members are blinded to the case/control status. Jobs held by study subjects are assessed for exposure to benzene, with considerations of several relevant parameters. These parameters include industry, factory, work location, job title, tasks, and time. Primary sources of benzene exposure information include the following:

- Shanghai Municipal Institute of Public Health Supervision (IPHS) database (computerized),
- Records of exposure measurements at Shanghai District IPHS,
- Monitoring data maintained at the factories,
- Facility histories (e.g., raw materials, engineering changes, work practice changes) maintained at the factories,
- New ad hoc monitoring data at the factories, and
- Exposure data in the Chinese medical journals.

The Shanghai Municipal IPHS database consists of more than 50,000 benzene measurements taken at factories in Shanghai since the 1950s. Each measurement record includes the following items: date of sampling, industry code, occupational code, hazard (chemical) code, name and address code of the factory, sampling location at the factory, and individual and average values of benzene measurements. The names and the addresses of the factories from the questionnaires provide the necessary linkage between benzene measurements in the database and individual study subjects. Table 1 shows an example of a measurement record in the Shanghai Municipal IPHS database.

The Shanghai Municipal IPHS database is based on benzene measurements reported by Shanghai District IPHS. Unfortunately, the reporting may not be always complete, and it is sometimes necessary to search records maintained at Shanghai District IPHS for records of factories where the study subjects worked.

In some situations it is helpful to visit factories where the study subjects worked or, if the factories no longer exist, similar factories. Such visits are arranged by the Shanghai Municipal IPHS and accompanied by its personnel. Some factories may have maintained historical benzene measurements. If appropriate or necessary, new benzene air samples are collected. Other relevant records kept at the factories such as changes in work practice and ventilation are also reviewed.

Another source for benzene exposure information is the Chinese medical journals. Generally speaking, two types of articles provide benzene exposure data: industrial hygiene surveys and benzene poisoning case reports. Even though the facilities described in these articles are not the actual factories where the study subjects worked, the exposure data are useful in providing possible range of exposure for similar jobs, factories or industries.

Table 2 provides an example of data reported in an industrial hygiene survey.[32] The air samples were collected at a refining unit inside a coal tar plant. The authors stated that major renovations had been taking place at the plant since 1980, which is reflected in much lower exposure measurements reported in 1983 and 1995 (Table 2). To put the values in Table 2 in perspective, it should be noted that the occupational exposure limit for benzene in China before 2002 was 40 mg/m^3.

The Chinese occupational medical journals are replete with reports of cases of benzene poisoning and leukemia in workers exposed to benzene. The majority of cases occurred among shoe workers, bag workers and painters. Some of these workers were exposed to extremely high levels of benzene, particularly at small workshops. For example, Zhao et al.[33] reported a cluster of benzene poisoning cases among workers at small township-owned leather bag workshops in a small town in Hebei Province. In a survey of 6482 leather bag workers (4906 females and 1576 males) conducted in 2001 and 2002, 33 benzene poisoning cases (27 females and 6 males) were reported, including 23 aplastic anemia, 5 pancytopenia, 2 myelodysplastic syndrome, and 1 acute myeloid leukemia. Duration of exposure ranged from 3 to 23 months (average=10.8). Subsequently, 9 patients died. The interval between diagnosis and death ranged from 1 to 8 months (average=3.1). The ages of the workers ranged from 16 to 22 (average=17). The workshops were converted rooms inside residential houses, ranging from 30 to 80 m^3 and with inadequate or no ventilation. Of the some 20 adhesives used at the workshops, the benzene content in seven exceeded 30%. Working hours were usually exceedingly long, 12 to 17 hours. Benzene measurements as high as 2,040 mg/m^3 were reported. Furthermore, high measurements of toluene (up to 949 mg/m^3) and n-hexane (up to 85,800 mg/m^3) were also reported at the workshops (Table 3).

As stated earlier, case and control enrollment in our case-control study in Shanghai started in August 2003. A preliminary estimate projects that by December 2006, we will have approximately 400 to 450 NHL cases and twice as many controls. Some of the occupations or industries reported among accrued study subjects (cases and controls) with potential exposure to benzene include shoe workers, painters, mechanics or machinists, and printers. The earliest exposure was in 1941, and the occupations with the highest exposure were brush painters and spray painters. The highest exposures exceeded 1000 mg/m^3. The most frequent occupations or industries of study subjects (cases and controls) exposed to other substances are farmers, textile workers, engineers, drivers, cooks or chefs, and military personnel.

Discussion and Concluding Remarks

The epidemiologic overview presented earlier shows that there is little epidemiologic evidence supporting an association between benzene exposure and NHL. The record-linkage investigation reported by Vianna and Polan[15] was a classic example of misleading results derived from linking health data to administrative databases that were not set up for research purposes.[16,18] Another investigation suggesting an increased risk of NHL among benzene-exposed workers was based on a cohort of Chinese workers in a variety of industries involving exposures to not only benzene but also other chemicals.[19] The group reported to have the highest risk was "organic, insecticide and benzene production," consisting of several heterogeneous industries/occupations with very different exposures. In particular, insecticide workers are exposed to a variety of chemicals not related to benzene, and studies have reported increased risk of NHL among agricultural chemical workers or farmers throughout the world.

No other cohort studies of benzene-exposed workers have reported an association between benzene exposure and NHL. In particular, the study of workers at rubber hydrochloride plants in Ohio did not report any increased risk of NHL, even though benzene exposure levels were extremely high.[23,25] In fact, a remarkable increase of AML was found among the same workers. For example, Wong reported an SMR of 98-fold among workers with a cumulative exposure of 400+ ppm-years in the study.[24] For NHL, however, there was no suggestion for any increase in the cohort. Based on the latest update, Rinsky et al.,[25] reported 5 NHL deaths with an SMR of 1.00. Similarly, as discussed earlier, other cohort studies and case-control studies provide ample evidence supporting the finding of Rinsky et al., that is, no increased risk of NHL in benzene-exposed workers.

Nevertheless, to further investigate the possible role of benzene in the etiology of NHL, we are conducting a hospital-based case-control study in Shanghai. The study has a number of advantages. First, Shanghai is the largest city in China and its large population (17 million) will allow a prospective accrual of NHL patients in a relatively short period of time. The prospective case accrual and the newly created clinical laboratory will ensure the quality and specificity of diagnosis. The WHO definition is used and NHL cases are classified by subtypes, which will reduce the heterogeneity of the disease and allow analysis by subtype. Although the study design is, strictly speaking, a hospital-based case-control study, because of the large number of hospitals (n=29) participating in the study, we are confident that case ascertainment is virtually complete. Employment histories are obtained through face-to-face interviews, using a two-tier approach. This two-tier approach utilizes secondary questionnaires for certain industries that are more detailed and more exposure-specific. Sources for benzene exposure include the Shanghai Municipal IPHS database, which consists of more than 50,000 benzene measurements taken at factories in Shanghai since the 1950s. The Shanghai Municipal IPHS database is supplemented by additional data maintained at Shanghai District IPHS, ad hoc benzene measurements at factories, and benzene levels reported for similar occupations/industries in the Chinese medial journals. Furthermore, our Exposure Assessment team includes local experts who are familiar with factories and industrial hygiene in Shanghai. One team member is a retired Shanghai Municipal IPHS employee, who had personally visited hundreds of factories in Shanghai during his long career of several decades before retirement.

All these valuable resources in our Shanghai study are quite unique, and they are seldom, if not rarely, available to community- or hospital-based case-control studies. We estimate that case ascertainment will be completed by 2006 and that the project (including analysis and report) by 2007. We hope that the results of the study will provide some additional insights into the relationship between benzene exposure and NHL.

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Table 1.

An exposure record in the Shanghai Municipal Institute of Public Health Supervision database of benzene measurements taken at factories in Shanghai

Date of sampling	1986-12-26
Industry code	341 (rubber products, including tires, hoses, shoes & bags)
Occupational code	741c (glue application workers)
Hazard code	0715 (benzene)
Name of the factory	XYZ Athletic Shoe factory*
Address code of the factory	310115
Sampling location	Breathing zone of glue application workers
Benzene measurements (mg/m^3)	391.28, 391.28, 330.39, 330.39 (average=360.84)

*To protect confidentiality, the real name of the shoe factory is not revealed in this table.

Table 2.

Benzene measurements (mg/m^3) at a refining unit inside a coal tar plant by work area and year

Work area	1973	1979	1983	1995
Distillation	18.1	31.1	9.33	1.80
Washing	104.2	157.2	17.75	5.20
Finished products	156.0	531.1	26.96	2.90
Chemical analysis	233.0	316.4	15.44	1.95

Note: Major renovations (primarily ventilation) since 1980.

Table 3.

Benzene poisoning cases and benzene levels among leather bag workers

Diagnosis	33 cases of benzene poisoning cases reported in leather bag workers
Age of workers	16-22 (average=17)
Gender of workers	27 females and 6 males
Workshops	Converted rooms in residential homes, 30-80 m^2, inadequate ventilation
Adhesives	Benzene content of 7 of the 20 adhesives used exceeded 30%
Working hours	12-17 hours a day
Benzene levels	Up to 2,040 mg/m^3
Toluene levels	Up to 949 mg/m^3
n-hexane levels	Up to 85,800 mg/m^3