From:	Bruce Jarnot <jarnotb@api.org>
Sent:	Thursday, February 15, 2007 8:58 PM (GMT)
To:	BenzConsort-TC@listserve.api.org; BenzConsort-OC@listserve.api.org
Cc:	Russell White <whiter@api.org>; Howard Feldman <Feldman@api.org>; John Wagner <Wagner@api.org>; Bruce Jarnot <jarnotb@api.org>
Subject:	BHRC-TC/-OC... 2H06 CC & DP/ME Progress Reports
Attach:	CC Progress Report 02-15-2007.pdf; DP ME Progress Report Jan-2007.pdf; Benzene exposure in shoemaking industry in China.pdf

Benzene Health Research Consortium (BHRC) Technical & Oversight Committee members –

Attached are pdf copies of Progress Reports for Case Control (CC) and Disease Progression / Molecular Epidemiology (DP/ME) studies for the second half of 2006 (2H06), which I received today from Drs. Wong and Irons.

Also attached is a pdf copy of an article published in *Regulatory Toxicology and Pharmacology* (46, 149–156) during this same period, authored by Laiming Wang, Yimei Zhou, Youxin Liang, Otto Wong, Thomas Armstrong, A. Robert Schnatter, Qiangen Wu, Jinbin Fang, Xibiao Ye, Hua Fu, and Richard D. Irons, titled "Benzene exposure in the shoemaking industry in China, a literature survey, 1978–2004."

Best Regards - Bruce.

energy API
www.api.org
Bruce M Jarnot, PhD
1220 L St., NW, Rm 1170
Washington, DC 20005
phone: 202.682.8473
e-mail: jarnotb@api.org

Available online at www.sciencedirect.com

ScienceDirect

Regulatory Toxicology and Pharmacology 46 (2006) 149–156

Regulatory Toxicology and Pharmacology

www.elsevier.com/locate/yrtph

Benzene exposure in the shoemaking industry in China, a literature survey, 1978–2004

Laiming Wang [a], Yimei Zhou [b], Youxin Liang [a,*], Otto Wong [c,d,e], Thomas Armstrong [b], A. Robert Schnatter [b], Qiangen Wu [a], Jinbin Fang [a], Xibiao Ye [a], Hua Fu [a], Richard D. Irons [f,g]

[a] *Fudan University School of Public Health, Shanghai, China*
[b] *ExxonMobil Biomedical Sciences, Inc., Annandale, NJ, USA*
[c] *Applied Health Sciences, San Mateo, CA, USA*
[d] *Tulane University, New Orleans, LA, USA*
[e] *Chinese University of Hong Kong, Hong Kong, China*
[f] *Sino-US Joint Clinical and Molecular Laboratory (JCML), Institutes of Biomedical Sciences and Department of Pathology, Fudan University, Shanghai, China*
[g] *Department of Pharmaceutical Sciences, School of Pharmacy and Department of Pathology, School of Medicine, University of Colorado Denver and Health Sciences Centre, Denver, CO 20262 USA*

Received 19 April 2006

Abstract

This article presents a summary of benzene exposure levels in the shoemaking industry in China reported in the Chinese medical literature between 1978 and 2004. A comprehensive search identified 182 papers reporting such exposure data. These papers could be classified into two categories: benzene poisoning case reports and industrial hygiene surveys. From each paper, the following information was abstracted whenever available: location and year of occurrence, occupation and/or task involved, benzene content in adhesives/solvents, work environment, working conditions, working hours, diagnosis, and air monitoring data of benzene. A total of 333 benzene measurements (88 averages, 116 minimums, 129 maximums) in the shoemaking industry were reported in the 182 papers identified. The data were analyzed in terms of geographical location, time period, type of ownership (state, township, or foreign), type of report (benzene poisoning reports vs. industrial hygiene surveys), and job title (work activity) or process. The reported data covered a wide range; some measurements were in excess of 4500 mg/m^3. Thirty-five percent of the reported benzene concentrations were below 40 mg/m^3, which was the national occupational exposure limit (OEL) for benzene between 1979 and 2001. The remaining 65% measurements, which exceeded the national OEL in effect at the time, and were distributed as follows: 40–100 mg/m^3, 11%; 100–300 mg/m^3, 21%; 300–500 mg/m^3, 13%; and 500+ mg/m^3, 20%. However, only 24% of the reported measurements after 2002 were below 6 mg/m^3, i.e., Permissible Concentration-Time Weighted Average (PC-TWA) and 10 mg/m^3, i.e., Permissible Concentration-Short Term Exposure Limit (PC-STEL), the newly amended benzene OELs in effect after May 2002. The data demonstrated that the majority of the facilities in the shoemaking industry reported in the literature were not in compliance of the OEL for benzene in effect at the time. Overall, the data show a clear downward trend of benzene exposure levels over the years, particularly after the introduction of the new lower OEL in 2002. Even though substantially lower when compared to levels in the past, current benzene exposure measurements from the literature review suggest that many facilities in the shoemaking industry in China have benzene concentrations that are still above the new OEL. The reported data, stratified by job, year and survey reason, can be used as part of the information and analysis for developing a job-exposure matrix in retrospective exposure assessment and thus may be part of the information used in developing historical exposure estimates in epidemiologic studies of shoe workers.

* Corresponding author. Fax: +86 21 64043069.
E-mail address: yxliang@shmu.edu.cn (Y. Liang).

0273-2300/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.yrtph.2006.06.009

Keywords: Shoemaking; China; Benzene; Adhesives; Glues; Solvents; Benzene poisoning; Occupational exposure limit; Retrospective exposure assessment; Job-exposure matrix

1. Introduction

Shoemaking is one of the most economically important industries in China, producing approximately 7 billion pairs of shoes each year in the 2000s. It is estimated that there are 38,000 enterprises for the shoemaking industry in China with approximately 2 million shoe workers employed (Huang, 2000). Shoemaking consists of cutting, fitting, sewing and gluing various parts together. A number of occupational hazards are associated with the shoemaking industry. Shoe workers in China are potentially exposed to a variety of toxic chemicals that are present in adhesives, glues and solvents; such as benzene, toluene, xylene, methyl ethyl ketone, acetone, *n*-hexane, gasoline, and other organic solvents. Of particular health concern are adhesives or solvents that contain a high concentration of benzene. In addition, the general conditions in many workplaces in the shoe industry in China have been or still are unsatisfactory; often with no or inadequate ventilation and little or no personal protection. The Chinese medical literature is replete with reports of benzene overexposure and benzene poisoning cases (Wong, 2002, 2003a). In this literature survey, we summarize and present benzene exposure data in the shoemaking industry reported in the Chinese medical literature in the last three decades. The reported data represent documented historical benzene exposure levels in the workplaces in the shoemaking industry. These data are useful to demonstrate the impact of regulatory polices of occupational benzene exposure and to provide insights of historical benzene exposure levels associated with benzene-related hematopoietic diseases in China.

2. Materials and methods

Primarily, there are two types of articles in the literature that report workplace benzene exposure levels: benzene poisoning case reports and systematic industrial hygiene surveys. A comprehensive online search was performed to identify reports of both types of articles. The online search included the following two databases: Chinese Biomedical Literature Database (1978–1993) and China National Knowledge Infrastructure (1994–2004). Key words used in the search included the Chinese equivalents of the following technical terms: shoemaking, benzene exposure, benzene poisoning, and occupational health. In addition to technical terms, several commonly used trade names of benzene-containing adhesives/solvents were also included (Chinese names: Ludingjiao, Tiannashui, Xiangjiaoshui). In addition to the online search, a supplemental manual search was also conducted, particularly for information describing the production technology and the history of chemical compositions of adhesives, glues and solvents used in the shoemaking industry. The titles and, whenever warranted, the abstracts of all articles published during 1978–2004 in 25 major Chinese occupational medical journals were reviewed. The online and manual searches resulted in 182 papers of benzene poisoning cases or industrial hygiene surveys published in 25 journals from 1978 to 2004.

From each paper, the following information was abstracted whenever available: location and year of occurrence, occupation and/or task involved, benzene content in adhesives/solvents, work environment, working conditions, working hours, diagnosis, and air monitoring data of benzene. A paper might provide one or more sets of benzene measurements with each set representing one or more benzene exposure levels by work locations or job titles (work activity). In the 182 papers identified, benzene measurements were reported as individual samples or in aggregate as averages, minimums, and/or maximums. Arithmetic means were calculated for the reported exposure data: arithmetic means of reported averages, arithmetic means of reported minimums, and arithmetic means of reported maximums. The data were analyzed in terms of geographical location, time period, type of ownership (state, township, or foreign), type of report (benzene poisoning reports vs. industrial hygiene surveys), and job title (work activity) or process. From the 1950s to the 1970s, the occupational exposure limit (OEL) for benzene in China was 50 mg/m^3 as a maximum allowable concentration (MAC). The regulatory limit was lowered to 40 mg/m^3 (also as a MAC) in 1979, which remained in effect through 2001. In 2002, with the implementation of the new *Occupational Diseases Prevention and Control Act*, a new benzene OEL was introduced: 10 mg/m^3 as permissible concentration of 15 min short-term exposure limit (PC-STEL) and 6 mg/m^3 as permissible concentration of 8-h time-weighted average (PC-TWA) (Liang et al., 2005). Thus, the reported benzene data from 2002 to 2004 may provide the first indication of the immediate impact of the new OEL on benzene exposure in the shoemaking industry.

3. Results

The collected data from the 182 papers covered 26 provinces, municipalities and autonomous regions; representing 84% of the 31 administrative regions in the country. However, the majority of the 182 papers (>80%) were reported from the most developed industrial areas in the coastal regions of eastern China; including Fujian, Zhejian, Shandong, Guangdong provinces and Shanghai municipality (Fig. 1). This distribution by geographical location was to be expected, as these areas are heavily industrialized and many shoemaking facilities are mostly located along coastal China.

One of the factors determining benzene air concentration is the benzene content in solvents used. It is estimated

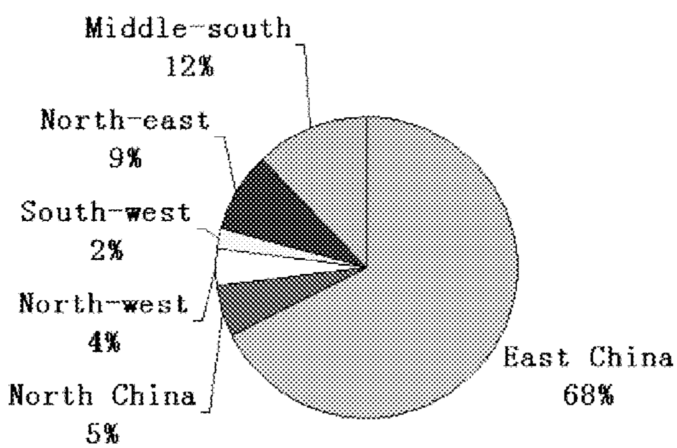

Fig. 1. Geographical distribution of published papers reporting benzene exposure levels in the shoemaking industry in China.

that solvents constitute approximately 75–80% (by weight) of most adhesives used in the shoemaking industry in China. Of the 182 papers included in the literature survey, 28 reported benzene content in the solvents used. The reported benzene content in solvents ranged from 27% to 96% (average of 83%). Assuming on the average typical adhesives contain 80% solvents, the average benzene content in adhesives would be approximately 66%. However, it has been reported that, in some cases, pure benzene was used during the 1980s. Furthermore, benzene is present in many "non-benzene-based" solvents or adhesives. For example, many toluene-based industrial products, including toluene-based adhesives, that were manufactured in China contained about 10% benzene; with some as high as 20–30% of benzene as an impurity in the toluene (Chen and Chan, 1999).

A total of 333 benzene measurements (88 averages, 116 minimums, 129 maximums) in the shoemaking industry were reported in the 182 papers identified. The reported data covered a wide range; some measurements were in excess of 4500 mg/m^3. Based on the 333 measurements, the overall arithmetic mean, median and geometric mean were 422.4 mg/m^3, 145.2 mg/m^3 and 108.7 mg/m^3, respectively. Thirty-five percent of the reported benzene concentrations (averages, minimums or maximums) were below 40 mg/m^3, which was the national occupational exposure limit (OEL) for benzene between 1979 and 2001. The remaining 65% of the measurements which exceeded the national OEL in effect at the time were distributed as follows: 40–100 mg/m^3, 11%; 100–300 mg/m^3, 21%; 300–500 mg/m^3, 13%; and 500+ mg/m^3, 20%. The data reported in the literature thus suggest that most facilities in the shoemaking industry were not in compliance of the MAC OEL for benzene in effect at the time.

The 182 papers reporting benzene exposure measurements were published between 1978 and 2004. As shown in Fig. 2, few papers were published before the 1990s. Starting in the early 1990s, with the increased development of the shoemaking industry and the improvement in occupational health services, an increasing number of papers were published in the medical journals. Of the 182 papers with benzene data, year of air monitoring or sampling was specified in 177 papers. The temporal trend of reported

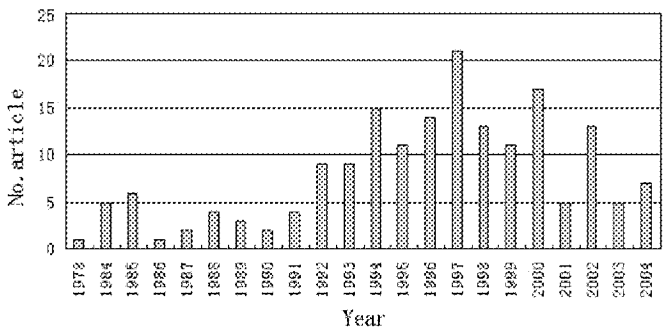

Fig. 2. Number of published papers reporting benzene exposure levels in the shoemaking industry in China by year.

benzene exposure levels in the shoemaking industry is presented graphically in Figs. 3, a and b. Measurements taken in the 1970s and/or1980s were quite high, with results well above 400 mg/m^3 (the arithmetic mean of averages) and 2000 mg/m^3 (the arithmetic mean of maximums). Even as recently as the early 1990s, reported maximum levels were close to or higher than 1000 mg/m^3.

Overall, Fig. 3 indicates a tendency of declining benzene exposure in terms of all three exposure variables: averages, minimums and maximums. The entire time span covered by the literature survey (1978–2004) was divided into the following three time periods according to the growth of the industry and regulatory events:

A. 1978–1990: Opening policy and the beginning of economic growth,
B. 1991–2001: Further industrial development and growth, and
C. 2002–2004: Post 2002 Occupational Diseases Prevention and Control Act and the introduction of the new OEL for benzene.

Table 1,a and b show reported benzene concentrations in the shoemaking industry in China by the three time periods above. The arithmetic means of averages, minimums and maximums were the lowest for 2002–2004, and those for 1978–1990 were the highest. The arithmetic mean of the reported averages for 1978–1990 was 405.3 mg/m^3, more than 10 times the maximum allowable concentration (MAC) of 40 mg/m^3 in effect at the time. Although the reported averages were much lower after the introduction of the new OEL in 2002, the arithmetic mean of the reported averages (69.7 mg/m^3) during the interval 2002–2004 was still seven times the new STEL of 10 mg/m^3 and more than 11-fold of the new TWA of 6 mg/m^3.

An analysis of variance indicated that the differences of arithmetic means of the reported averages for the three time periods were statistically significant ($F = 8.471$, $p < 0.05$). Although the arithmetic means of both minimums and maximums were also different for the three time periods, the differences were not statistically significant at the 5% level.

The reported benzene data were stratified by type of report: benzene poisoning cases vs. industrial hygiene surveys Table 2. Both maximum and average benzene levels reported in benzene poisoning cases were significantly higher than those reported in industrial hygiene surveys. The arithmetic means for the reported maximums and averages in benzene poisoning reports (1358 and 470 mg/m^3, respectively) were more than twice those reported in industrial hygiene surveys (533 and 161 mg/m^3, respectively). As most benzene poisoning cases appear to arise from high-exposure work environments; it is not surprising therefore those exposure measurements in such specific environments tend to be much higher than others.

Information identifying the type of ownership of the industrial enterprises was provided in 84 papers. For

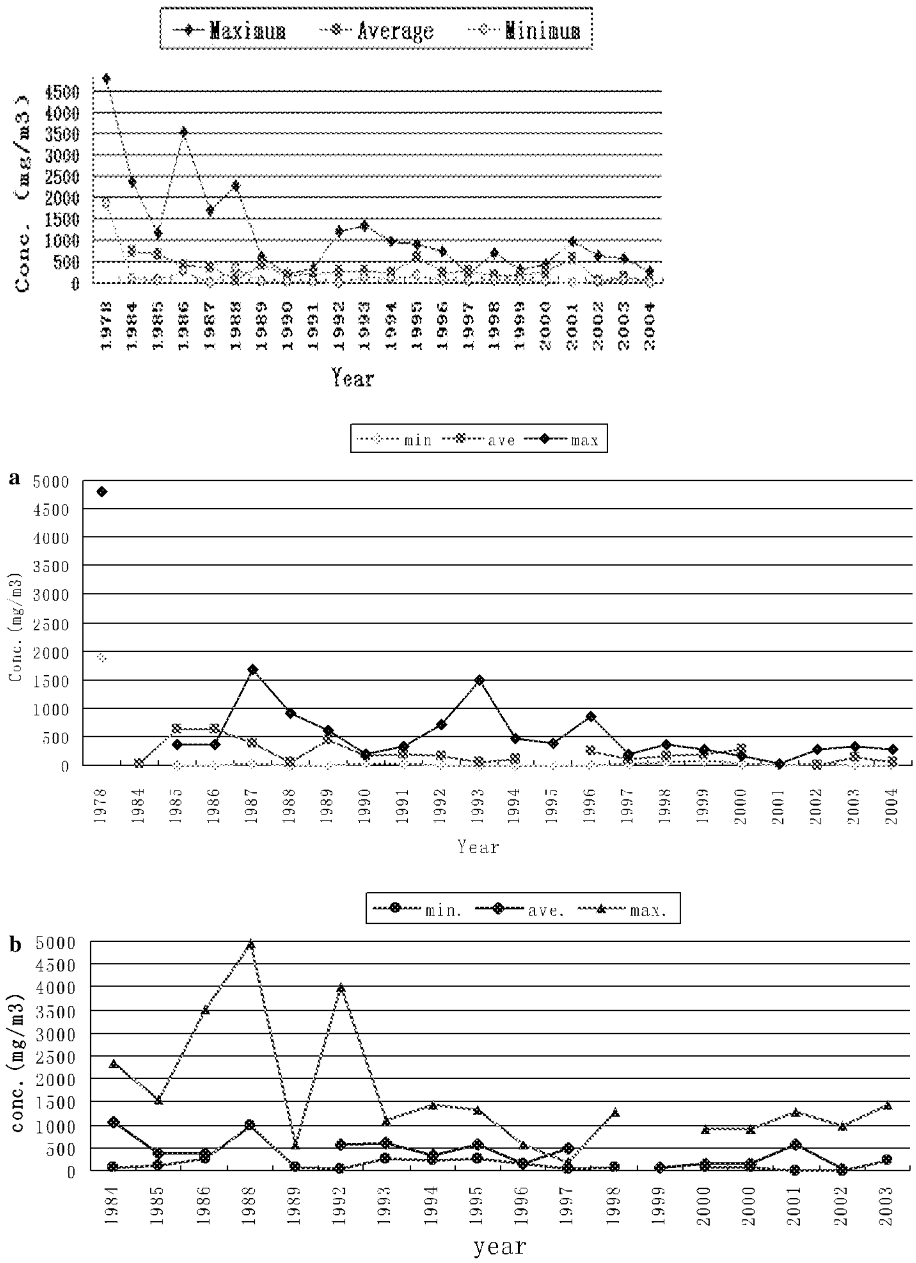

Fig. 3. Temporal trend of reported benzene levels in the shoemaking industry in China by year (based on overall data). (a) Temporal trend of reported benzene levels in the shoemaking industry in China by year in IH survey reports. (b) Temporal trend of reported benzene levels in the shoemaking industry in China by year in Case report (Panel a shows a similar temporal trend as was shown by the overall data; Panel b shows a similar trend as for Fig. 3, but is not as certain because of the lack of data for certain time periods.).

Table 1
Arithmetic means of reported benzene concentrations (mg/m^3) at workplaces by time periods (based on overall data)

Time periods	No. paper	Minimum		Average[a]		Maximum	
		No. paper	Mean	No. paper	Mean	No. paper	Mean
1978–1990 (A)	24	17	339.4	12	405.3	18	2074
1991–2001 (B)	129	81	63.0	62	293.1	91	730.1
2002–2004 (C)	24	16	31.0	12	69.7	18	490.7
Total	177	114		86		127	

[a] A vs. B, $p > 0.05$; A vs. C, $p < 0.05$; B vs. C, $p < 0.05$.

Table 1a
Arithmetic means of reported benzene concentrations (mg/m^3) at workplaces by time periods in IH survey reports

Time periods	No. paper	Minimum		Average[a]		Maximum	
		No. paper	Mean	No. paper	Mean	No. paper	Mean
1978–1990 (A)	15	9	218.5	8	302.2	10	1194.6
1991–2001 (B)	79	55	26.7	39	181.3	58	480.8
2002–2004 (C)	19	11	12.9	10	64	13	295.1
Total	113	75		57		81	

[a] A vs. B, $p > 0.05$; A vs. C, $p < 0.05$; B vs. C, $p < 0.05$.

Table 1b
Arithmetic means of reported benzene concentrations (mg/m^3) at workplaces by time periods in case reports[a]

Time periods	No. paper	Minimum		Average		Maximum	
		No. paper	Mean	No. paper	Mean	No. paper	Mean
1978–1990 (A)	9	8	229	5	663.9	8	2411.4
1991–2001 (B)	48	26	155.8	22	464	33	1144.4
2002–2004 (C)	5	5	59.1	2	129.2	5	1086.4
Total	62	39	—	29	—	46	—

[a] No statistical differences were shown among any compared group.

Table 2
Comparison of benzene levels (mg/m^3) in benzene poisoning case reports and industrial hygiene surveys

Benzene levels	Source	No.	Arithmetic mean	Range	Median	P_{25}	P_{75}	t-test for means	p
Maximum	Case report	46	1358	82–4968	1002	277	2084	4.88	<0.01
	Ind hyg survey	83	533	2.5–4800	339	89	582		
Average	Case report	29	470	13–1496	370	167	668	4.36	<0.01
	Ind hyg survey	57	161	2–1000	93	37	222		
Minimum	Case report	39	85	0*–995	30	3	54	0.76	>0.01
	Ind hyg survey	77	80	0*–1840	11	2	52		

* In most samples, "0" denotes benzene levels below detection limit.

Table 3
Comparison of benzene levels by ownership of enterprises

Type of ownership	Comparison	Total			IH survey			Case report		
		Average (mg/m^3)	Aver difference	p	Average (mg/m^3)	Aver difference	p	Average (mg/m^3)	Aver difference	p
Foreign-invested (A)	A vs. B	131.38	352.29	<0.05	137.56	112.66	>0.05	73.7	576.4	<0.05
Town-/village-owned (B)	A vs. C	488.67	336.51	<0.05	243.96	336.59	>0.05	650.1		
State-owned (C)	B vs. C	467.89	15.78	>0.05	467.89	223.93	>0.05	NA		

analysis, three broad categories of ownership were used: state, township or village, and foreign investors. Table 3 compares reported benzene levels by category of ownership. The average for reported benzene levels was much lower in foreign-owned facilities when compared with the averages in state-owned or township-owned enterprises. However, even for foreign-owned enterprises, the arithmetic mean of reported averages (131.38 mg/m^3) was more than threefold of the OEL for benzene in effect at the time (40 mg/m^3).

There were 1054 cases of benzene poisoning in the shoemaking industry reported in the literature between 1978 and 2004. Typically, in these case reports a description of the work environment was presented along with benzene measurements. The following two examples are typical of benzene poisoning case reports in the Chinese medical literature. In 1995 Yang reported two cases of benzene poisoning at a small workshop making slippers in the province of Zhejiang (Yang, 1995). The adhesive used was a mixture of chloroprene and benzene (1:4). The work area was actually a makeshift workshop inside a farmer's residence, with little or no ventilation. Four heating lamps were used to enhance drying after the application of adhesive. Two women were diagnosed with benzene poisoning after working there 10 h a day for 4 months. Benzene levels measured at the workshop ranged from 302.4 to 1383.8 mg/m^3

Table 4
Comparison of benzene poisoning case by job titles (25–75% intervals added)

Work activity	No. case	Arithmetic mean (mg/m^3)	Median	P_{25}	P_{75}	Range (mg/m^3)
Uppers and soles fitting	418	897	476	277	1143	5–3117
Soles making	395	1155	478	278	1384	103–4010
Uppers making	139	290	229	99	512	88–560
Temporary uppers embedding	102	774	574	427	1290	278–1530
Total	1054					

(average of 731.3 mg/m^3). A similar episode of benzene poisoning in a small shoe workshop in Suzhou was reported by Tao in 2000 (Tao, 2000). The small workshop was described as a room inside a farmer's residence. There was no ventilation system and the windows were often closed. A mixture of chloroprene and benzene (1:4) was used as adhesive. Two charcoal-heated stoves were used for drying. Air benzene concentrations were recorded above 1000 mg/m^3.

The distribution of benzene poisoning cases by job category is presented in Table 4. The largest number of cases (418) occurred among workers who assembled the upper parts and the soles of shoes, and the arithmetic mean of the reported averages was 897 mg/m^3. Among workers making soles, there were 395 benzene poisoning cases, and the arithmetic mean of the reported average exposures was 1155 mg/m^3. By comparison, workers in "temporary uppers embedding" and "uppers making" had fewer poisoning cases and the exposure associated with "uppers making" was lower (arithmetic mean of 290 mg/m^3).

The number of work hours varies as well. According to the published reports, many workers in the shoemaking industry worked long hours, far exceeding 40 h a week in many instances, even though "8 work hours per day and 5 work days a week" was specified by the State Council PR China in May 1995. The published reports indicated that many employees frequently worked between 10 and 14 h a day and some worked as many as 20 h a day to meet deadlines of "rush orders" Table 5. According to 52 of the 182 published reports, most workers in the shoemaking industry spent 11–14 h working per day, with 6 and 7 day workweeks not uncommon. The impact of routinely prolonged work hours is an important aspect to properly consider in exposure assessment studies.

Finally, an attempt was made to stratify exposure data by job title (work activity) and time period Table 6. Exposure data in this format, (particularly those from the industrial hygiene survey reports) can provide reference for historical exposure estimates used in, for example, epidemiologic studies of workers in the shoemaking industry. The discussion section below includes a review of some of the limitations on the use of the data for Job Exposure Matrix (JEM) application. As expected, Table 6 indicates that both job task (work activity) and time period are important parameters in characterizing historical exposures. In terms of maximum exposure, measurements in the early time period 1978–1990 were the highest (~1500 mg/m^3). However, the middle time period 1991–2001 was associated with the highest average exposures. For example, "temporary uppers embedding" in 1991–2001 entailed the highest average exposure (mean of 534.6 mg/m^3) and "soles making" in the same time period the second highest average exposure (466.6 mg/m^3). The table also identifies gaps in the exposure data. For example, there are no sufficient data available for "temporary uppers embedding" in 2002–2004. As indicated before, Table 6 shows that exposures in the shoemaking industry have declined significantly during the most recent period, but still remained above the current OEL.

Table 5
Work hour for some work activities of shoe making workers

Work activity	Work hours per day		
	Minimum	Maximum	Average
Uppers and soles fitting	7	16	11.5
Soles making	8	20	12.9
Temporary uppers embedding	10	17	14.0
Uppers making	9	14	11.7

4. Discussion and conclusion

The Chinese medical literature is a unique and important source of historical exposure information in workplaces in China. The reported data represent documented exposure levels in the workplaces in the shoemaking industry. The data indicate that benzene exposure levels from both the benzene poisoning case reports and the industrial hygiene survey reports for the shoemaking industry in China were quite high, particularly before the passage of the *Occupational Diseases Prevention and Control Act* and the introduction of the new OEL for benzene in 2002. The literature survey indicates that benzene levels in excess of 1000 mg/m^3 were not uncommon in shoemaking facilities in China, with some were as high as 4500 mg/m^3 under certain extreme circumstances. Sixty-five percent of the reported benzene measurements were above the OEL of 40 mg/m^3 in effect at the time, with 20% in excess of 500 mg/m^3. In addition, shoe workers typically worked 11–14 h a day and some even worked as long as 20 h daily. High benzene exposures, coupled with long working hours, have resulted in many acute and chronic benzene poisoning cases in the shoemaking industry in China.

The exposure data may be useful in developing historical exposure estimates in epidemiologic studies of shoe workers. Exposure data (especially from the industrial hygiene survey reports) once stratified by job title and year of exposure, as in Table 6, can be used in constructing a

Table 6
Comparison of benzene levels (arithmetic mean, median, mg/m^3) for some work activities by time period

Work activity	1978–1990						1991–2001						2002–2004					
	Min		Ave		Max		Min		Ave		Max		Min		Ave		Max	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Fitting uppers with soles	34.7	NA	313.6	230.1	1575.3	1354	68.3	10	371.6	223.5	778.0	460	7.4	NA	25.1	NA	27.6	NA
Soles making	NA	NA	66.9	66.9	1609.9	957	110.2	31.2	466.6	366.5	709.3	477.5	NA	NA	73.6	NA	NA	NA
Temporary uppers embedding	NA	NA	370	NA	1530.0	NA	88.16	4.1	534.6	495	1038.2	670.2	NA	NA	NA	NA	NA	NA
Uppers making	NA	NA	NA	NA	NA	NA	80.0	NA	NA	NA	324.4	NA	19.9	NA	NA	NA	169.1	NA

NA, not available.

job-exposure matrix in retrospective exposure assessment. When applying these data to retrospective exposure assessment, the nature and the limitations of the reported data must be taken into consideration. Some of such considerations include:

- Based on dominant sampling methods, most of the data represent 1 minute grab samples from the work environment. If also given data on where and for how long workers perform tasks, the measurements might be used to construct a task-time weighted average to estimate full shift exposures.
- Some benzene poisoning investigation reports may represent re-creation of conditions that may or may not match well with the actual routine conditions. Since most reports are mute on the survey strategy, this is hard to determine.
- The surveys were undertaken by a range of investigators, for a range of reasons which were seldom mentioned in the reports. Biases introduced by the survey rationale and by possible alterations in the normal working environment limit the direct applicability of such diverse data to an epidemiologic study and job-exposure matrix.
- It is unknown if the submittal and publication process biases toward reporting only higher level measurements. It has often been suggested that the occupational epidemiology literature is subject to a bias where more positive than negative or equivocal studies are published.

Overall, the data indicate exposure levels associated with benzene poisoning cases were generally higher than those reported in industrial hygiene surveys by a factor of more than two. Most benzene measurements were reported in aggregate as averages, and as minimums or maximums individually. Many of the data were reported without any measure of variability or sampling interval. The majority of measurements were area samples. Limitations notwithstanding, these data can provide valuable information on historical benzene exposures in the shoemaking industry in China.

There were three common sampling and analytical methods used for benzene measurements in China. The earliest employed an impinger with solvent through which the air was bubbled, followed by a colorimetric analysis. The next method employed glass syringe grab sampling, with gas chromatographic analysis. This glass syringe method may be the one used for most of the data reported in the reviewed literature, but such details are often not included in the reports. The last method uses a single section charcoal tube with a twenty minute sampling period at a nominal flow rate of 200 ml/min, also with gas chromatographic analysis. Investigation of the comparability of the methods is underway, but is not ready for summary in this current report.

The data also reflect temporal trend of exposure levels in relation to the growth of the industry, the type of glues or solvents used and regulatory events (new laws or OELs).

However, due to the limited number of early-era publications, the early data are limited in number. Knowledge of factors specific to the industry sector needs to be considered to help interpret the trend data. For example, the shoemaking industry in China has evolved from manual sewing processes with small production capacity in the 1950s and 1960s to large-scale assembly line facilities of the 1990s and 2000s. Although the gluing process of shoemaking started as early as the 1930s in industrialized countries, the technology was not adopted in China until the late 1960s. Since then the gluing process has developed gradually and has been widely used in the shoemaking industry. Among the solvents commonly used in the shoemaking industry in China, benzene ranked first, followed closely by toluene and xylene. A number of factors contributed to the popularity of the use of benzene in the industry; including its low price, strong solvation capacity and rapid vaporization. These factors resulted in lower cost, higher work efficiency and better quality of the products for the industry.

Because of the awareness of the toxic effects of benzene and the increasingly more stringent regulatory occupational exposure standards, the use of benzene in the industry in China has declined steadily over the years. Benzene-based adhesives are now banned in China and the national standard for benzene in adhesives is regulated to be less than 0.5% (State General Administration, 2003). Toluene-based or other less toxic solvent-based glues or adhesives have been used to replace benzene-based glues. At the same time, control measures at workplaces have also contributed to the further reduction of benzene exposure. Fig. 3 clearly demonstrates the downward trend of benzene exposure in the shoemaking industry in the last two decades that include the township industries which account for about 70% of the overall measurements.

An important milestone in occupational health in China is the passage of the *Occupational Diseases Prevention and Control Act* in 2002. The *2002 Act* is one of the most significant and comprehensive legislatures in occupational health in China (Wong, 2003b). Along with the *2002 Act*, new or revised OELs were introduced. The OEL for benzene was reduced substantially. Although it may still be too early to see the full impact of the new reduced OEL, early insights are encouraging. Table 1 shows that benzene exposure levels reported in 2002–2004 (mean of 69.7 mg/m^3) were substantially lower than that of proceeding years 1991–2001 (mean of 293.1 mg/m^3). However, the data indicate that the current benzene exposure levels are still high, exceeding the current OEL by several fold.

Although benzene-based solvents are now banned in China and, unlike in the past, pure benzene is no longer used commercially, many Chinese workers are still exposed to relatively high levels of benzene. Today, the most commonly used Chinese-made adhesives are toluene-based, and the toluene may contain 10% or more benzene as one of the "impurities". According to a national survey, benzene was detected in the air of 76% of workplaces which used toluene- or xylene-based solvents (Yin et al., 1994). Legislative and enforcement actions may be necessary to deal with the issue of benzene contamination in toluene- or xylene-based solvents.

In summary, current benzene exposures in the shoemaking industry in China, even though substantially lower when compared to levels in the past, are still at concentrations greater than the new OEL (PC-TWA or PC-STEL) at many facilities (Liang et al., 2003). However, additional efforts to construct full-shift exposure estimates, or verify the sample applicability to evaluating a STEL need to be undertaken before drawing conclusions about compliance to the new OEL for benzene.

The significant number of references drawn upon precludes listing them all in this report. Copies of the list are available from the corresponding author on request.

Acknowledgments

We are grateful to the Benzene Health Research Consortium for sponsoring the Shanghai Health Study; to Dr. Jerry Rice at Georgetown University for reviewing the manuscript; and to Professor Xipeng Jin at Fudan University School of Public Health, Professor Shixing Yang at Shanghai Municipal Institute of Public Health Supervision for advising literature survey; and other team workers for the literature search.

References

Chen, M.S., Chan, A., 1999. China's "market economics in command": Footwear workers' health in jeopardy. International Journal of Health Services 29 (4), 793–811.

Huang, P., 2000. Advances in adhesives used in the shoe industry (in Chinese). Guangdong Chemical Engineering 1, 13–16.

Liang, Y.X., Su, Z., Wu, W.A., Lu, B.Q., Fu, W.Z., Yang, L., Gu, J.Y., 2003. New trends in the development of occupational exposure limits for airborne chemicals in China. Regulatory Toxicology and Pharmacology 38, 112–123.

Liang, Y.X., Wong, O., Armstrong, T., Ye, X.B., Miao, L.Z., Zhou, Y.M., Wu, Q.E., Qian, H.J., Fu, H., 2005. An overview of published benzene exposure data by industry in China, 1960–2003. Chemico-Biological Interactions 153–154, 55–64.

State General Administration, 2003. PR China for Quality Supervision and Inspection and Quarantine. National Standards for Adhesives used in Footwear and Suitcase Manufacturing (GB 19340-2003). China Standard Publisher, Beijing.

Tao, G.Y., 2000. Some thoughts and reflections of benzene poisoning. Occupation and Health 16 (8), 67–68 (in Chinese).

Wong, O., 2002. Investigations of benzene exposure, benzene poisoning and malignancies in China. Regulatory Toxicology and Pharmacology 35 (1), 126–135.

Wong, O., 2003a. Letter from Shanghai. Occupational and Environmental Medicine 60 (3), 223.

Wong, O., 2003b. Regulation of occupational exposures in China. Regulatory Toxicology and Pharmacology 38, 109–111.

Yang, F., 1995. A report of two cases of benzene poisoning and aplastic anemia. Occupational Medicine 22 (2), 26–27 (in Chinese).

Yin, S.N., Li, G.L. (Eds.). The explanation of the development of the diagnostic criteria and management principles for occupational benzene poisoning (in Chinese). In: Toxicological and Epidemiological Studies on Benzene in China. Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, Beijing, 1994.

PROGRESS REPORT

January 2007

Shanghai Health Study

Richard D. Irons*

I. ANALYSIS OF DISEASE PROGRESSION FOR APLASTIC ANEMIA, MYELODYSPLASTIC SYNDROME, ACUTE MYELOGENOUS LEUKEMIA AND BENZENE POISONING IN SHANGHAI, CHINA

II. EXPOSURE ASSESSMENT AND DATA ANALYSIS

III. MOLECULAR EPIDEMIOLOGY OF BENZENE-EXPOSED WORKERS IN SHANGHAI, CHINA.

*With input and major contributions from numerous Project Staff.

I. JCML

A. Case Contact

Between August 8, 2003 and December 31, 2006, the laboratory processed 3008 new cases. Figure 1 illustrates the rate of case contact per month between June 2005 and December 2006.

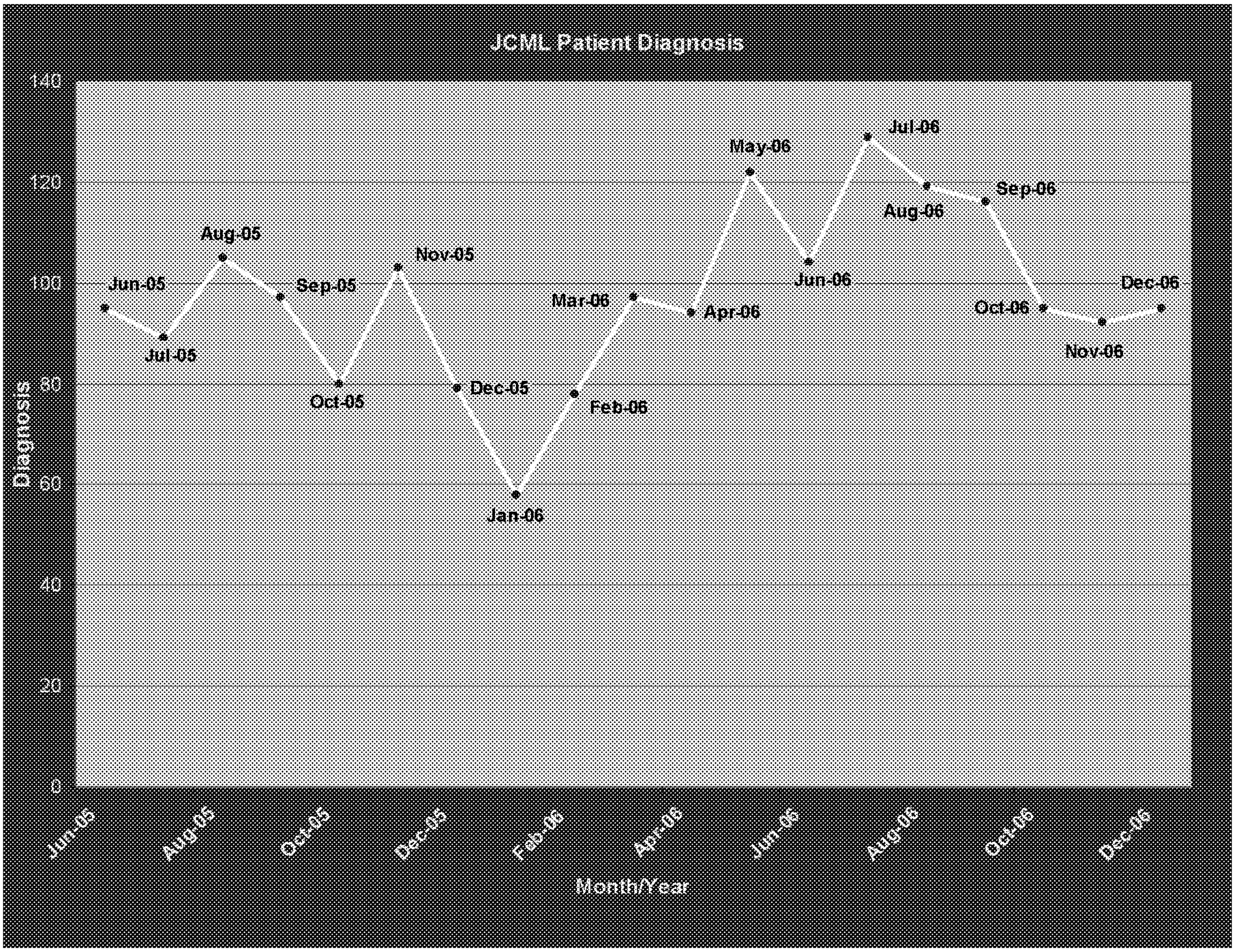

Figure 1. History of JCML Caseload by Month since June 2005

SHELL-MCCLURG-053575

B. Review of Classification and Diagnostic Criteria

The diagnostic standard used by the laboratory to diagnose patients is the World Health Organization (WHO) classification published in 2001, which is based on state-of-the-art technology and requires analysis of histopathologic, immunophenotypic and genetic features. Importantly, WHO is also an epidemiologic classification scheme and will be the scheme used to define and classify all cases in this project.

The International Classification of Disease, Ninth Edition, (ICD-9) is an older, different classification scheme first published in 1977 that was used for most epidemiology studies conducted between 1977-2001. ICD-9 is only a classification scheme and does not provide criteria for disease diagnosis. Studies using the ICD-9 classification system are based on diagnoses that 1) were obtained using histopathologic criteria alone, and 2) vary from study to study, period of time and place. As a result, direct conversion of the ICD-9 classification to WHO is not feasible.

At the beginning of this project, numerical goals for case accrual were selected in order to be comparable in size to previous study results that used the ICD-9 classification. However, all diagnoses and classification criteria used in this study employ the full set of diagnostic and technical tools required for WHO. Estimates of ICD-9 numbers presented in progress reports represent a cursory look back by study pathologists at the older classification criteria and are intended solely for use in assessing study progress on a numerical basis compared to previous studies. Estimated number of cases based on the ICD-9 criteria realized in December 2006 versus those predicted in June 2006, are presented in Table 1 for assessing study progress and do not represent a study result. Some other selected outcomes based on the WHO classification are presented in Table 2, but do not represent a comprehensive list of study results (cases listed in Table 1 are not duplicated in Table 2).

Table 1. Current versus Projected Case Goals Based on ICD-9 criteria (See text above).

Classification	Study Goals	Projected Case Accrual* (12/31/06)	Actual Case Accrual (12/31/06)
AML	500	424	423
NHL	500	433	214**
MDS	350	480	519
AA	250	137	131
BID***	50	36	54

*Projected as of 6/30/06

**Number of NHL's with confirmed documentation. (Total number of NHL's diagnosed: 410).

***Benzene-induced dysplasia, Irons et al (2006) Leukemia Research 30: 769-775.

C. Follow-up

Patients initially diagnosed in the disease progression study are contacted at 6-month intervals and asked to return for follow-up evaluation. As of the end of December 2006, a total of 239 follow up cases have been evaluated by the laboratory. This represents an increase of 80 follow up cases since September 2006, indicating an increased rate of follow-up accrual as we approach the end of the project. However, follow-up accrual remains short of the goal of 635 projected in the original proposal.

Table 2. Case Accrual for Other Selected Outcomes.

Additional Cases	Case Accrual (12/31/06)
AML (WHO)	207
Other Lymphoid Neoplasms (WHO)	213*
Cytopenias	117
CML	83
Nutritional Deficiencies	242

* Number of other lymphoid neoplasms with confirmed documentation. (Total number of other lymphoid neoplasms diagnosed: 230).

D. Quality Assurance/Quality Control

1. IC/EA documentation

In late August 2006, a discrepancy was discovered between the number of accrued cases and the number of exposure questionnaires received. By October it was determined that this coincided with the inability to document informed consents for a subset of 416 case subjects referred by one of the major participating hospitals. Informed consent was routinely obtained from patients presenting at the hospital for collection of diagnostic material. However, we were unable to confirm that written informed consents were obtained specifically for our study. In November a series of meetings were held between SOPH, JCML personnel and hospital staff to identify the problem and formulate a plan for correction and remediation. Despite general agreement on a plan, nothing of substance was achieved during December. Subsequently, a contract was executed directly between the Institutes of Biomedical Sciences /Fudan University and the hospital to implement a corrective plan of action and to prevent future occurrences. To date, hospital clinical staff have contacted a total of 115 cases for which IC could not be documented. Informed consents have been signed, questionnaires have been administered and new controls assigned by 33 of these cases. An additional 34 subjects have been contacted and appointments are pending, and 11 patients have declined further participation. Efforts continue to contact and recruit additional cases with outstanding documentation (See Tables 1 & 2).

2. In-house IC validation

During the last quarter JCML has embarked on a separate in-house physical validation of informed consents for all study subjects. To date, documentation has been confirmed for cases and controls presenting between August 8, 2003 and February 28, 2006. Excluding the outstanding cases discussed above, 5 out of 2059 case files failed validation. Validation of documentation for the remaining 2006 case files is in progress and has been implemented as a routine procedure for the duration of the study.

3. Validation of study diagnoses

A QA program for confirmation of clinical diagnosis and nosologic assignment of disease classification (i.e. Study Diagnosis) has been ongoing since the beginning of the study (August 2003) and is independent of diagnostic review. As of December 2006, 2823 out of 3008 cases have been diagnosed and WHO case assignment independently confirmed. This step is linked to 1) verification of database entry and 2) the development and validation of query strategies that link study diagnoses to individual clinical and research laboratory data sets. This QA process is a prerequisite for populating the tables that form the basis for export of study data for analysis. To date, the logic for 12 query strategies involving up to 3000 entry fields per case has been validated.

II. Exposure Assessment

A. Sector Analyses and Literature Review

A meeting of the IH steering group with Drs. Cherrie and Herrick was held in October 2006 with bi-monthly telephone conferences scheduled beginning in December. To date, the initial focus has centered on CC/DP study processes, with the first meeting involving a detailed review of the shoe sector and the development of plans for optimizing data use. The group decided to obtain additional information available in the Chinese and Western literature on solvent and glue composition. The Western literature review focuses on pre-1960's data, especially for earlier years, before rigorous control of benzene exposure in Europe and North America. This is applicable to many aspects of pre-1990's Chinese operations. A report on Chinese glues and adhesives is scheduled for completion at the end of March and will include information on glue compositions for a broad range of industries in addition to the shoe sector.

Additional industry sector reports for commonly seen industry and task combinations are in preparation to provide exposure-related details for the CC/DP study. Reports on paint making and paint use are nearly complete, while additional reports on shoe making/leather goods manufacturing, and printing are scheduled. ME factory inspections, surveys and analyses of the rubber industry provide a wealth of information for IH analysis in the CC/DP study.

B. Exposure Simulations

Simulations for painting and small part degreasing have been completed. These employed traditional work methods, and materials similar to those used before recent reductions in benzene use. These studies included determining the ventilation rates, material composition and materials use rates that are key variables in modeling exposure for scenarios where relevant exposure data are not available from field investigations or the literature. Results of these simulations provide direct data for commonly seen tasks in CC/DP subject work histories.

C. Questionnaire Administration and Analysis

The CC/DP exposure assessment process, which has been described in previous reports, is again outlined in Figure 2. Individual subject EA is a dynamic and iterative process with cases undergoing continuing review. Therefore, statistics that describe progress for individual subject EA represent a "snapshot" in time and are not cumulative, i.e. the status of each case is subject to change. Consequently, EA progress cannot be directly reconciled with diagnostic case accrual (which is cumulative). To date, 7200 EA questionnaires have been collected, 6802 entered into the database, 6628 have been validated and 6462 have had preliminary EA completed. The difference between total cases + controls (~9000) and EA collected generally reflects EA questionnaires in process, some excluded cases, and shortfalls in documentation previously described.

D. Translations

From August 2003 until June 2006, a total of 3235 questionnaire files out of approximately 6500 were translated by the SOPH. In July 2006, JCML assumed responsibility for translations, and over the last 6 months a total of 2300 translations have been performed resulting in 2000 currently outstanding files. Assuming a case plus control accrual rate of 2400-3000 in 2007, we are on track to complete translations coincident with completion of EA.

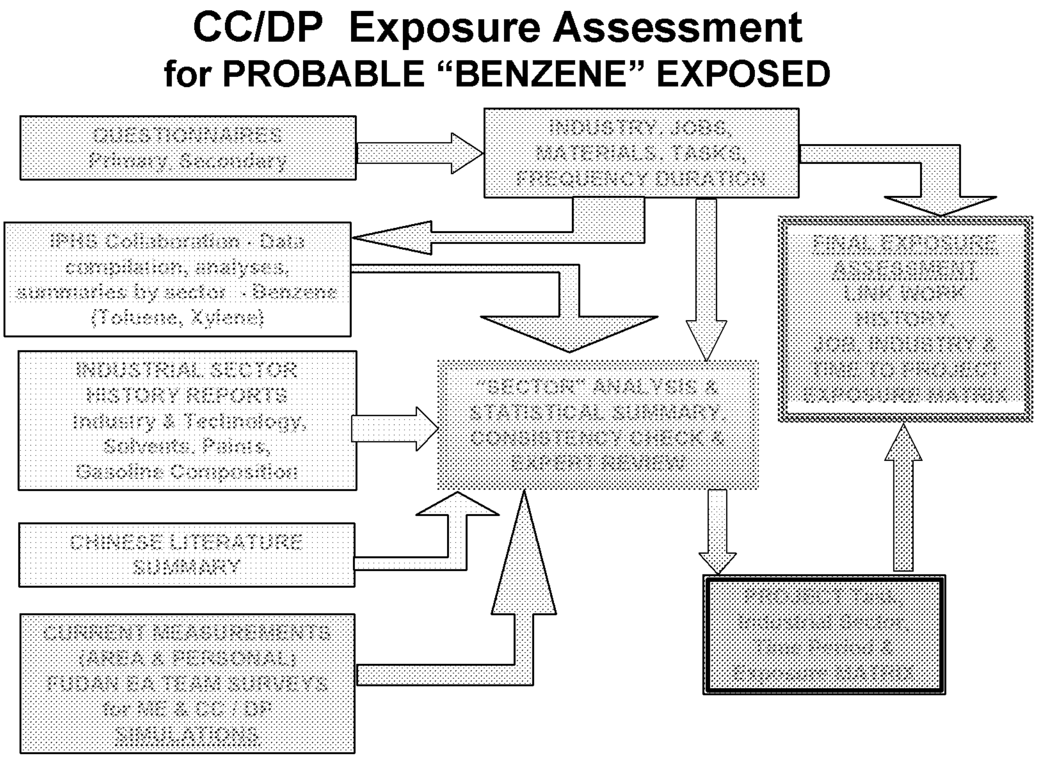

Figure 2. CC/DP Exposure Assessment for Probable "Benzene" Exposed.

III. ME

A. Phase I

In light of other activities, no progress on Phase 1 has been made since the August 2006 report. However, a review of Phase I data is slated for early March. This will include analysis of existing exposure data on potential Phase 1 factories and categorization of each factory as follows: (a) exposure data inadequate and cannot be remediated in a reasonable time, (b) exposure data inadequate and remediation plan developed, (c) exposure data adequate for analysis.

B. Phase II

To date, 890 individual subjects have been recruited to the Phase II study from 5 factories representing the rubber, pharmaceutical, asbestos/rubber composites and shoe manufacturing industries. A subset of these workers have been evaluated up to three times under different working conditions in order to obtain an accurate profile of their exposure. During 2006, a total of 583 urinary and blood metabolite samples were collected spanning exposure ranges from <1 ppm to >40 ppm. Blood CBC, benzene metabolites, polymorphism and exposure datasets are being organized and preliminary analysis is in progress. In order to round out and complete the exposure range, additional factory sampling and subject recruitment will be conducted this spring.

AML and NHL Case-control Study
Shanghai Health Study

Progress Report
Activities through December 2006

Prepared by:
Otto Wong, Sc.D.
Applied Health Sciences, Inc.
Post Office Box 2078
San Mateo, CA 94401
USA

Tel: 1 (650) 347-7898 USA
Fax: 1 (650) 344-6887 USA
ottowong@aol.com
ottowong@shmu.edu.cn

15 February 2007

♦♦♦♦♦♦♦♦

Status of Patient Enrollment

Currently, there are 33 hospitals in Shanghai participating in the Shanghai Health Study (SHS); consisting of 17 municipal hospitals, 13 district hospitals, 2 occupational disease hospitals and one private hospital. These hospitals contribute patients to all three research studies in the SHS. The hospitals, however, vary greatly in size. Twelve hospitals have not contributed any patients during the time period June-December 2006. Some of these hospitals are relatively small, but one of them (No. 2 Medical University Hospital) is a large hospital and should have a large population of patients. Therefore, case ascertainment at some hospitals might not be complete.

In terms of the case-control study, according to the numbers provided by Dr. Richard Irons on 13 February 2007, the cumulative numbers of patients diagnosed with AML and NHL (based on ICD-9 definition) as of 31 December 2006 were as follows:

- 423 AML patients
- 410 "NHL" patients (214 or 52% with interviews)

Using the broader WHO definition, the additional cumulative numbers of AML and lymphoid neoplasm patients as of 31 December 2006 were:

- 207 AML patients
- 230 other lymphoid neoplasm patients (213 with interviews)

The numbers of AML and NHL/lymphoid neoplasm patients reported above must be interpreted with caution. The numbers represent patients diagnosed with AML or NHL/lymphoid neoplasm at the participating hospitals. These numbers do not represent the numbers of AML or NHL/lymphoid neoplasm patients with questionnaire information. Many patients, especially those diagnosed with NHL (ICD-9), do not have questionnaire information. As indicated above, only approximately half of the NHL patients were interviewed.

I first noticed that some NHL patients did not have questionnaire information when I examined the "test datasets" of AML and NHL patients provided to us by Gail Jorgensen of ExxonMobil in July 2006, shortly before the Houston meeting on 1-2 August 2006. Of the 150 NHL patients in the test dataset, only 61 patients (41%) had questionnaire information. The other 59% NHL patients did not have any questionnaire information, and, therefore, would eventually have to be excluded from the case-control study. This problem, which would have a major impact on the case-control study, was reported to the Scientific Review Panel at the August 2006 meeting in Houston and also reported in our semi-annual progress report dated 9 August 2006, which was distributed to both panel members and sponsors. At the time of the August meeting, I did not know the reason for the missing questionnaires.

During my September trip to Shanghai, I investigated the problem of NHL patients without questionnaires. I talked to a number of people (Pei Xiaodan, Guo Xiao, Xie Junfang, Wang Yiying, Chen Gian, and Fu Hua) and was surprised to learn that from January 2006 to early September 2006, fewer than 10 patients at the Tumor Hospital were interviewed, even though the number of patients diagnosed with NHL during the same time period was much greater. The majority of NHL patients in the SHS were patients at the Tumor Hospital. It appeared that the Clinical Coordinators at the Tumor Hospital did not make arrangement for the NHL patients to be interviewed after the patients' laboratory reports (diagnosis) were sent to the hospital.

Xie Junfang is the person at Fudan whom the participating hospitals notify with new cases and controls. Xie Junfang, in turn, notifies Guo Xiao at Fudan who actually sends out interviewers to hospitals. Xie Junfang keeps a spreadsheet of all NHL patients as well as a list of NHL patients with interviews.

The following is a summary of NHL patients with and without questionnaires by year.

Year	Total no. of NHL patients	NHL patients with questionnaires	Row percentage
2003	39	26	67%
2004	93	53	57%
2005	137	48	35%
2006 (up to mid-September)	98	9	9%
Total	367	136	37%

The distribution of NHL patients with questionnaires by hospital is as follows:

Hospital	No. of NHL patients with questionnaires	Column percentage
Tumor Hospital	91	67%
Huadong Hospital	16	12%
Tongi Hospital	9	7%
Jiangding Hospital	3	2%
Zhabei Hospital	1	1%
Shuguang Hospital	6	4%
Changning Hospital	1	1%
Changhai Hospital	1	1%
No. 5 Renmin Hospital	5	4%
Ruijin Hospital	2	1%
Huangpu Hospital	1	1%
Total	136	100%

Approximately two-thirds of the NHL patients with questionnaires are from the Tumor Hospital. It appears that many NHL patients at the Tumor Hospital were not interviewed, because the Clinical Coordinators at the Tumor Hospital did not notify Xie Junfang of cases and controls for interview.

The problem of NHL patients without an interview or questionnaire has a major impact on the case-control study and on the overall SHS as a whole. The only information we have on these NHL patients consists of their names, hospitals and approximate dates of admission. These patients, without detailed questionnaire information, will not be included in our analysis.

As many of the patients diagnosed with NHL (approximately 61%) were patients at the Tumor Hospital, it was important to take immediate actions not only to capture all newly diagnosed patients from now on but also to recapture as many missing patients as possible at the Tumor Hospital. In October a retired nurse from the Tumor Hospital, Lu Yunhua (陆云花), was hired to deal with patient accrual at the Tumor Hospital. I met with Lu Yunhua several times in October and November. In addition to newly diagnosed NHL patients, she also tried to recapture some of the previously diagnosed patients who were not interviewed. Below is a summary of Lu's work in November and December 2006 (based on information provided to Wang Yiying by Lu).

(A) Newly diagnosed patients:

No. of patients registered	No. contacted by Lu	No. agreed to participate	No. refused to participated	No. actually interviewed
27	26	14	12	12

(B) Previously diagnosed patients who had not been interviewed:

No. of patients searched for contact info	No. with phone number or other info	No. of contacts attempted by Lu	No. successfully contacted	No. agreed to participate	No. actually interviewed
205	167	149	34	24	16

It appeared that only a small number of the "missing" NHL patients could be recaptured, although it may take a couple more months before a definite estimate can be made. In any event, to make up for the missing patients, Dr. Richard Irons proposed that patient accrual be extended to the end of 2007.

Power Calculation

The original target sample size was 500. For NHL, even if the end of case accrual be extended to the end of 2007, the actual sample size may still fall short of the original target. The sample size of NHL patients will likely be between 300 and 400, depending on the level of success in enrolling both newly diagnosed patients and previously diagnosed patients who were not interviewed. The following table shows the smallest risk ratios that analyses based on different sample sizes will be able to detect. This table is useful in estimating the statistical power of the overall analysis of the entire study as well as detailed analyses of subgroups (such as diagnostic subtypes). As can be seen, the smallest detectable risk ratios depend on the exposure rate in the controls. Currently, I do not have a good estimate for that, but it should be around 2% or 3%. The statistical parameters in the power calculation are as follows:

- Control-to-case ratio = 2:1,
- Alpha = 0.05,

- Power = 0.80, and
- One-sided test.

Exposure rate in controls	Minimum detectable risk ratios						
	25 cases	50 cases	100 cases	200 cases	300 cases	400 cases	500 cases*
5%	6.72	4.34	3.04	2.29	2.01	1.85	1.74
4%	7.72	4.87	3.34	2.47	2.14	1.96	1.84
3%	9.34	5.74	3.82	2.76	2.35	2.13	1.99
2%	12.54	7.42	4.74	3.27	2.73	2.44	2.25
1%	21.96	12.25	7.28	4.67	3.74	3.24	2.95

* Original target sample size.

Exposure Assessment

Under the direction of Dr. Thomas Armstrong, the exposure assessment team continues to develop exposure data/estimates using the "sector analysis" approach. The analysis for two commonly encountered industries (shoe and rubber) has been completed. A more thorough discussion of exposure assessment will be provided by Dr. Armstrong in a separate report.

Exposure data from other sources are also being collected, including published literature. According to Professor Liang, who heads the literature review task, preliminary exposure data for the following occupations/industries have been completed: shoemakers, painters, paint manufacturers, printers, dyers, and rubber workers. These literature data will supplement the Shanghai Municipal IPHS database and district IPHS data in the development of job-exposure matrix (JEM).

The report of benzene exposure in the shoe industry based on the Chinese medical literature has been completed and a shortened version has been published in a special issue of *Regulatory Toxicology and Pharmacology* entitled "The Development and Regulation of Occupational Exposure Limits in Asia," which was published in November 2006. The title of the paper is "Benzene exposure in the shoemaking industry in China, a literature survey, 1978-2004" (Wang L, Zhou Y, Liang Y, Wong O, Armstrong T, Schnatter AR, Wu Q, Fang J, Ye X, Fu H and Irons R; *Regul Toxicol Pharmacol* 2006;149-156). A copy of the paper is attached.

A similar report of benzene exposure in another two industries, paint manufacturing and painting, has been completed. The report in draft form is now being reviewed internally. After the internal review, the report will be forwarded to the Scientific Review Panel for approval for journal submission.

QA/QC

Pei Xiaodan, who is responsible for QA/QC, has been providing monthly reports on a regular basis. These monthly reports include accuracy checks of the following items: primary and secondary questionnaires, data entry and initial exposure assessment.

QA/QC of questionnaires taken between July and December 2006 indicated that 96% of primary questionnaires sampled for review were "qualified" (i.e., no problems were found), which was an improvement over the last time period. During the same time period, for patients with selected occupations of interest, 99% of their secondary questionnaires were "qualified."

Once the questionnaires are completed, the information is entered into the SHS database at Fudan. The overall data entry error from July to December 2006 was 3%, which is acceptable.

During my trips to Shanghai in September, October and November, I conducted three *ad hoc* QA checks of samples of both primary and secondary questionnaires taken in the last six months. I identified only a few (less than 10) minor mistakes in these questionnaires (with literally thousands of items/entries) per QA check. These results reinforce/validate the routine QA/QC checks by Pei Xiaodan.

Epidemiology Review of Risk Factors of AML and NHL

In anticipation of analysis planning and report writing, we have started reviewing epidemiologic studies of AML and NHL in relation to occupational and environmental risk factors. We are particularly interested in studies that provide information on subtypes of AML and NHL. We have collected the abstracts of more than 300 potentially relevant papers. We are currently reviewing the abstracts and retrieving selected papers. Wang Yiying at Fudan is assisting me in this review.

Project Management and Timeline

Communication with the Fudan team in Shanghai remains a high priority item. In addition to email and telephone calls, I made 3 trips to Shanghai in the second half of 2006.

Professor Fu and his staff remain as my primary contact in Shanghai for the case-control study. Professor Fu's group continues to monitor and update me the progress of the study when I am not in Shanghai. His group also provides the necessary support when I work on the study in Shanghai.

As discussed above, Dr. Irons proposed that the end of patient accrual be extended to the end of 2007. My current understanding is that the proposed extension will be accepted. Given the new end date for case accrual, final diagnoses, control selection, and interviews will most likely be completed around the end of the first quarter of 2008. Exposure assessment of newly enrolled patients (cases and controls) will be conducted in the first and second quarters of 2008. Assuming that both diagnostic and exposure data for all patients will be finalized and available by June 2008, we will be performing epidemiologic analyses of the final data in the third quarter of 2008.

To facilitate data transfer/linkage and to develop plans for statistical analyses, however, we need relatively large and representative samples of exposure estimates and diagnoses of study subjects by mid-2007 (see the timeline table below). These samples would allow us to develop plans for data transfer/linkage and to test-run analysis programs.

The timeline of the case-control study depends heavily on the timing when diagnostic and exposure data (both test data samples and final complete data sets) are provided to us. The delay of any one event in the timeline will likely affect the others. The revised timeline below for the case-control study is based on our current understanding and assumptions.

Revised timeline of the case-control study

Tasks	Date
Test data sets to AHS*	June 2007
QA/QC of test data sets	July-September 2007
Development of analytical programs/plans	October 2007-March 2008
End of patient accrual*	December 2007
Final diagnoses of all patients completed*	March 2008
Interviews of all patients completed*	March/April 2008
Questionnaire data entry completed*	May 2008
Exposure assessment completed*	June 2008
Final QA/QC and data editing	July-August 2008
Complete final data to AHS*	End of June 2008
Statistical/epidemiological analysis	August-September 2008
Preparation of draft report	September-October 2008
Presentation of study results	October 2008
Discussion with SRP	October-November 2008
Preparation of final report	October-December 2008

* Activities not under our control.