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Detailed Exposure Assessment for a Molecular Epidemiology Study of Benzene in Two Shoe Factories in China

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Objectives: We carried out a detailed exposure assessment of benzene and toluene in two shoe factories in Tianjin, China. Our goal was to identify workers with a broad range of benzene exposures, for an epidemiologic study relating exposure to early biologic effects.

Methods: A comprehensive exposure survey program was initiated. Over a period of 16 months, 2783 personal solvent exposure samples were collected in two workplaces from 250 workers. Mixed-effects models were used to identify factors affecting exposure. Principal component analyses (PCA) and subsequent regression analyses on the scores of the identified principal components were used to relate potential co-exposures to various exposure sources present in the workplace.

Results: The mean benzene exposure level was 21.86 p.p.m. (10th–90th percentiles 5.23–50.63 p.p.m.) in the smaller shoe factory (factory A) and 3.46 p.p.m. (10th–90th percentiles 0.20–7.00 p.p.m.) in the larger shoe factory (factory B). Within-factory exposure levels differed among job titles and were higher for subjects directly involved in handling glues. In contrast, mean toluene levels were relatively similar in the two factories (factory A, 9.52 p.p.m.; factory B, 15.88 p.p.m.). A seasonal trend was identified for both benzene and toluene in factory B. This could be explained in part by changes in air movement and ventilation patterns occurring during the year. A seasonal trend was not present in the smaller shoe factory, where general ventilation was absent. Supplemental analysis showed that exposure levels to other hydrocarbons were low (≤5 p.p.m.), less than 5% of their respective ACGIH threshold limit values, and generally comparable in the two factories. PCA showed that co-exposures in factory B could largely be explained by glue sources that were used in distinct areas in the workplace.

Conclusions: We demonstrated the occurrence of a broad range of benzene exposure levels in two shoe manufacturing factories in Tianjin, China. Benzene and toluene exposures were determined in part by the degree of contact with glues, the benzene and toluene content of each glue, air movement and ventilation patterns. The availability of long-term monthly personal monitoring data provides an excellent opportunity to estimate individual exposures at different times during the 1 yr period of observation.

Keywords: benzene; China; exposure assessment; glues; molecular epidemiology; principal component analysis; shoe manufacturing; toluene

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INTRODUCTION

By 1981, the evidence linking benzene exposure with increased risk of acute non-lymphocytic leukemia (ANLL) was considered sufficient to classify benzene as a Group I carcinogen (IARC, 1982). Subsequent studies have confirmed that benzene causes ANLL (Aksoy, 1985; McCraw *et al.*, 1985; Bond *et al.*, 1986; Rinsky *et al.*, 1987; Wong, 1987; Yin *et al.*, 1987, 1996; Austin *et al.*, 1988; Swaen and Meijers, 1989) and myelodysplastic syndrome (MDS) (Hayes *et al.*, 1997) and may play a role in other leukemias, non-Hodgkin's lymphoma and lung cancer (Savitz and Andrews, 1997). Despite extensive research, questions remain regarding the mechanisms by which benzene exerts its effects, the influence of inter-individual variation in benzene metabolism and the risk benzene presents at low doses.

In a retrospective cohort study of 74 828 workers exposed to benzene and 35 805 unexposed workers in China, Hayes *et al.* (1997) reported an excess risk of ANLL and MDS at occupational exposures below 10 p.p.m., providing some of the strongest evidence to date that benzene poses health risks in this exposure range. In addition, we previously documented hematotoxicity (Rothman *et al.*, 1996) and elevated levels of specific classes of chromosomal aberrations that are relevant for hematological malignancies (Smith *et al.*, 1998; Zhang *et al.*, 1998) in workers exposed to a wide range of benzene concentrations in Shanghai, China. To follow up these findings, we conducted another molecular epidemiology study to evaluate hematological, cytogenetic and molecular end-points in workers exposed to benzene, with a particular focus on exposures below 10 p.p.m.. As hematological and other end-points in this study are related to exposures in the more recent past (weeks to months) (Rothman *et al.*, 1996), the exposure survey was primarily designed to assess individual exposures to benzene and toluene over a 16 month period of observation.

This paper describes the two Chinese factories selected for the molecular epidemiology investigation and presents results of the extensive monitoring survey to characterize personal exposures to benzene, toluene and other organic hydrocarbons at work and in the workers' homes.

MATERIALS AND METHODS

Factories and subjects

Our goal was to study at least 200 workers exposed to benzene, particularly at levels below 10 p.p.m. Eligible factories had to be in the same industry and geographical area and not to have used genotoxic or hematotoxic chemicals other than benzene. The workforce needed to have been very stable, to have worked for at least 5 yr in the same factory and to have had little or no task rotation. Two shoe factories in Tianjin, China were selected based on the above criteria. Factory A is a small facility consisting of one workshop with 58 production workers producing ~70 000 'uppers' for luxury shoes per year (Table 1). The production process is characterized by a low level of mechanization and so requires a skilled labor force. No general ventilation is present (with only doors able to be opened) and no personal protective equipment (PPE) is used. Factory B is a large shoe manufacturing facility consisting of five workshops with about 560 workers producing ~1 400 000 shoes per year. The level of mechanization is higher than in factory A, with shoe components transported on conveyor systems to machines and work positions. All gluing activities are performed manually. Drying ovens are equipped with local exhaust ventilation systems while ceiling and wall fans provide air movement and general ventilation in the workshops. No PPE is used.

The shoe production process of both factories can be divided into five main production functions: (i) 'cutting', (ii) 'modeling', (iii) 'fitting', (iv) 'finishing' and (v) 'packing'. In 'cutting', leather or other shoe materials are sorted and prepared, then cut out either by hand or with automatic presses. In 'modeling', the different components of the 'uppers' are sewn or

Table 1. Overview of the two shoe factories

	Factory A	Factory B
Product	Luxury shoes (only upper part of shoe)	Safety shoes
Number of production workers	58	560
Shoe production (number/yr)	~70000	~1400000
Number of glues used	2	7[a]
Glue use (kg/yr)	~18000	~220000
Number of workers actively using glues	~30	~115
Ventilation	None	Ceiling and wall fans; local exhaust ventilation on drying ovens
Total workplace volume (m^3)	7100, 1 workshop	33 800, 5 workshops
PPE use	None	None

[a]Seven glues are used on a regular basis and account for almost all glue used in the factory (>90%).

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glued together. In 'fitting', the uppers and the heels, inner soles and outer soles are glued and sewn together. Shoes are cleaned, waxed and polished ('finishing') and, finally, inspected and packaged ('packing'). Subjects were enrolled in the study through random selection, based on the expected range of exposures defined by their job titles and preliminary exposure data. Thirty-seven workers from factory A (64% of the workforce) were enrolled in the study. In factory B, 213 workers were enrolled (38% of the workforce). The study was approved by Institutional Review Boards at the NCI and the National Institute of Occupational Health and Poison Control, China CDC, Beijing. All recruited study subjects were informed of the nature of the study, the potential benefits and potential risks and provided written informed consent.

Information on the production process and work practices was obtained during several walk-through surveys and interviews with workers and management. Data on the amounts of glues used were abstracted from factory records.

Glue analyses

Bulk samples of glues used in factory B were collected in June 2001. No bulk samples of glues used in factory A could be obtained, as permission for collection of source samples could not be obtained from management. Samples were collected in gas-tight tubes, sealed and stored in a protective container. Bulk samples were analyzed for benzene and toluene content via static headspace gas chromatography (GC-MS) by US Environmental Protection Agency (EPA) method 8260. The percentages of benzene and toluene in the headspace of the glue were estimated as the ratio between the peak areas of benzene or toluene divided by the sum of all peak areas.

Personal exposure sampling

Workplace sampling. Personal sampling employed 3M™ organic vapor monitors (OVMs), which were attached to the worker's lapel over the full work shift. After collection, the monitors were individually sealed and transported to the laboratory of the National Institute of Occupational Health and Poison Control, China CDC, Beijing, for analysis of benzene and toluene. In ~15% of the samples a duplicate monitor was worn on the other lapel, which was sent to a commercial laboratory in the USA for analysis. Measurements in factory A were carried out on one random day each month between March and June 2000. Biological samples were collected from the 37 participating workers in June. In May 2001, air sampling was repeated for nine of these workers who provided a repeat biological sample the same month. Exposure measurements in factory B were carried out on 1–2 days per month between March 2000 and June 2001. In June 2000, exposure was measured only for workers who provided a biological sample in the pilot phase of the study (n = 20). Samples were collected and processed by the same personnel working in the same laboratories and using essentially the same protocols throughout the duration of the study. In total, 2783 exposure measurements (not including duplicate monitors) were collected, providing data on 250 workers (number of samples per subject: median 12, range 2–15).

Home sampling. Personal exposure measurements to benzene and toluene during non-working hours were taken once during the winter (December 2000) and once or twice during the spring (March/April 2001) using OVMs. Samplers were placed on the workers' lapels at the end of the work shift with instructions to wear them until they returned to work the next day (14–16 h). The sampler was to be placed next to the bed at night. Duplicate monitors were worn for ~18% of the measurements. In total, 595 solvent exposure measurements (not including duplicate monitors) were collected.

Analyses. Analyses of the monitors for benzene and toluene were conducted by GC-FID according to NIOSH method 1501 (NIOSH, 1994). The limit of detection (LOD) was 0.20 p.p.m. for benzene and 0.30 p.p.m. for toluene. A subset of duplicate OVMs from the workplace (n = 66), collected between March and June 2001, were analyzed for other organic hydrocarbons (n = 29) according to OSHA method 7 (OSHA, 2001) (GC-FID) to identify potential exposures to 1,1,1-trichloroethane, 1,2,4-trimethylbenzene, 1,2-dichloroethane, 1,4 dioxane, acetone, benzene, butyl acetate, chlorobenzene, cyclohexanone, decane, ethyl acetate, ethyl benzene, heptane, hexane, isooctane, methyl ethyl ketone (MEK), methyl isobutyl ketone (MIBK), methylene chloride (DCM), octane, pentane, propyl acetate, styrene, tetrachloroethylene, tetrahydrofuran, toluene, trichloroethylene, *m*-xylene, *o*-xylene and *p*-xylene. For the analyses of other hydrocarbons, OVMs were selected to represent all workplace activities and glue sources, in order to identify potential co-exposures to organic hydrocarbons.

Statistical analyses

There was a very high correlation between the logged air levels of benzene in the monitors analyzed at the CDC in China and in the duplicate monitors analyzed at the commercial laboratory in the USA (Pearson r = 0.93). In addition, the slope of the least squares regression line (forced through the origin) between the two sets of measurements was close to unity (slope = 1.10). Similar results were obtained from the analysis of the duplicate monitors for

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toluene ($r = 0.95$, slope = 0.99). These results indicate good agreement between measurements of benzene and toluene by the two laboratories. Subsequently, the results will be based on the analyses performed by the China CDC.

Workplace measurements that had an effective sampling duration of <240 min were excluded from the analyses (n = 152, 5.2%). All concentrations below the LOD [n = 370 (13.3%) for benzene and n = 238 (8.6%) for toluene] were replaced with values equal to the LOD divided by $\sqrt{2}$ (Hornung and Reed, 1990). Exposure levels are summarized as averages (AM), geometric means (GM) and geometric standard deviations (GSD) and the 10th and 90th percentile of the exposure distributions.

Normal probability plots indicated that exposures by factory could best be described by log-normal distributions. Therefore, natural logarithms of exposure concentrations were used in the statistical analyses. To evaluate determinants of exposure in factory B, mixed-effects models were constructed (model 1). Potential exposure determinants (e.g. season, ventilation, amount of benzene and toluene used per day and distance to exposure source) were treated as fixed effects, whereas the worker and error were treated as random effects.

$$Y_{ij} = \mu + \beta_1 + \beta_2 + \ldots + \beta_k + \chi_i + \varepsilon_{ij} \qquad (1)$$

where Y_{ij} is the natural logarithm of the exposure concentration measured on the jth day for the ith worker, μ is the true underlying mean of log-transformed exposure averaged over all strata, β_1, β_2,..., β_k are fixed effects of k exposure determinants, χ_i is the random effect for the ith worker and ε_{ij} is the random error (within-worker day-to-day variation).

The model assumes that all χ_i and ε_{ij} are mutually independent and normally distributed with 0 means and variances ${}_{BW}\sigma_y^2$ and ${}_{WW}\sigma_y^2$, representing between- and within-worker variability, respectively. These variances are estimated as between-worker (${}_{BW}S_y^2$) and day-to-day (${}_{WW}S_y^2$) covariance components.

To quantify the contribution of the fixed effects to the ${}_{BW}S_y^2$ and ${}_{WW}S_y^2$ covariance components, we compared the values of the covariance components obtained under model 1 with those from a mixed-effects model without the inclusion of fixed effects (e.g. one-way random effects model).

To examine whether the interrelationships between the different hydrocarbons could be attributed to distinct exposure sources present in the workplace, principal component analyses (with VARIMAX rotation) were performed (Fisher and van Belle, 1993). Only principal components (PCs) with eigenvalues > 1 were considered significant (i.e. explaining more multiple correlation than a single hydrocarbon concentration). Numerical indices representing each PC were generated as principal component scores and were used as dependent variables in subsequent regression analyses with handling of particular glues as independent variables. All analyses were carried out using SAS version 8.0 software (SAS Institute, Cary, NC).

RESULTS

Glues

Factory A used two glues in the production process (total use ~18 000 kg/yr) (Table 2). Glue A was used in 'fitting' and 'finishing', while glue B was used in

Table 2. Amount of specific glues used per year in the two shoe factories and their estimated benzene and toluene contents based on headspace analyses of collected bulk samples

Description	Amount (kg/yr)[a] (% of total use)	Benzene (%)	Toluene (%)	No. of study subjects using glue[b]
Factory A				
A Treatment glue	14443 (81.1)	NQ[c]	NQ	10
B Gasoline glue	3360 (18.9)	NQ	NQ	7
Factory B				
C Latex glue	68749 (31.4)	0.6	23	9
D Resin glue	47209 (21.5)	1	36	15
E Gasoline glue	37091 (16.9)	2	10	8
F Benzene glue	9770 (4.5)	34	3	6
G Treatment glue 1	7818 (3.6)	NQ	NQ	6[d]
H Treatment glue 2	7213 (3.2)	2	39	6[d]
I Treatment glue 3	4830 (2.2)	1	46	6[d]

[a]Based on glue use data from May 2000 to May 2001.
[b]Number of subjects enrolled in the exposure study handling a specific glue. Does not reflect the total number of workers handling a specific glue in the factories.
[c]Not quantified as no sample of glue was obtained during the walk-through surveys.
[d]Six workers used treatment glues, but the specific type of treatment glue or combination was not specified.

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'modeling'. In total, 17 study subjects were involved in gluing activities. In factory B, seven glues were used on a regular basis, accounting for almost all of the glue used per year (~220 000 kg/yr). Glues C and E were used in 'modeling', glues D, G, H and I were predominantly used in 'fitting' and glue F was used solely in 'packing'. In total, 43 study subjects from factory B were involved in gluing activities. Estimated benzene content of the glues ranged from 0.6 to 34%, with all but one glue having benzene levels ≤2%. Estimated toluene content ranged from 3 to 46%, with glues used in 'fitting' having a somewhat higher toluene content.

Workplace sampling: benzene and toluene

The average benzene exposure level in factory A was 21.86 p.p.m., ranging from 9.04 p.p.m. among workers in 'modeling' to >20 p.p.m. among workers who worked in 'finishing' or worked directly with glues (Table 3). As there was no physical separation between the operations in factory A, workers who did not handle any glues were still exposed on average to ~10 p.p.m. benzene. Toluene exposure levels showed a similar pattern, but were about half of those for benzene. Overall, benzene and toluene exposure levels were highly correlated ($r = 0.91$, $P < 0.0001$).

The average benzene level in factory B was 3.46 p.p.m., ranging from 0.45 p.p.m. in cutting to 24.18 p.p.m. for subjects who glued packaging materials. Average toluene exposure levels ranged from 1.49 p.p.m. in 'cutting' to 58.83 p.p.m. for subjects involved in gluing of the outer sole. Workers directly involved in gluing had higher benzene and/or toluene exposure levels (depending on the particular glue used) than subjects within the same job titles who did not handle glues. Due to different sources and physical separation between 'cutting' (workshop 1), 'modeling' (workshops 2 and 3), 'fitting', 'finishing' and 'packing' processes (workshops 4 and 5), the overall correlation between benzene and toluene was lower ($r = 0.46$, $P < 0.0001$) than in factory A.

Benzene and toluene exposure levels in factory A did not show a clear seasonal trend over the follow-up period. In contrast, exposure levels in factory B showed a clear seasonal pattern with the lowest exposures during the summer months, followed by the fall and spring and higher exposures during the winter months (Fig. 1). Mixed-effects modeling, with season as the fixed effect, showed that the different seasons explained 17 and 24% of the day-to-day variance ($_{WW}S_y^2$) for benzene and toluene, respectively. The use of ceiling and wall fans and opening of windows largely coincided with the different seasons and changes in ambient temperatures and therefore these factors could not be used as fixed effects in one single model. As the model fit criterion, Akaike's information criterion, favored the model with the use of fans and opening of windows as the fixed effect and, as these are more 'objective' determinants of exposure, the final model presented is based on these parameters (Table 4). Benzene and toluene exposure increased with the amount of benzene or toluene used per day at the nearest glue source. Direct handling of glues (distance = 0 m) resulted in the highest exposures, which decreased with increasing distance from the source for subjects that did not directly handle glues. The use of ceiling and wall fans reduced benzene and toluene exposure by 43 [$100 \times (1 - \exp^{-0.57})$] and 47%, respectively. Opening the windows in addition to the use of fans resulted in total reductions of 78 and 84% for benzene and toluene exposure, respectively, compared with no general ventilation. The mixed-effects model explained ~52% of the between-worker variance ($_{BW}S_y^2$) for both benzene and toluene exposure and explained slightly more of the day-to-day variance for toluene (27%) than for benzene (21%). The explained day-to-day variance in benzene and toluene exposures could largely be attributed to changes in air movement and ventilation (95 and 71%, respectively) with absolute effects similar to the observed seasonal effects, corroborating the conclusion that the observed seasonal pattern was largely due to changes in air movement and ventilation patterns (data not shown).

Workplace sampling: co-exposures to organic hydrocarbons

In total, 11 different hydrocarbons were detected in the selected samples from factory A, of which nine were detected in >25% of the samples (Table 5). Benzene, toluene, pentane, ethyl benzene, hexane and *m*-xylene were detected in all samples, followed by *p*-xylene (83.3%), 1,1,1-trichloroethane (83.3%) and heptane (66.7%). In factory B, 16 different hydrocarbons were detected in the selected samples, of which eight could be detected in over 25% of the samples. Only toluene was detected in all samples, followed by benzene (93.3%), pentane (81.7%), hexane (75.0%), MEK (71.7%), ethyl acetate (61.7%), acetone (60.0%) and heptane (36.7%). Exposure levels of hydrocarbons other than benzene and toluene were low in both factories (generally <5 p.p.m.) and were less than 5% of the current ACGIH threshold limit value (TLV). None of the individual measurements exceeded the respective TLV, except those for benzene.

Principal component (PC) analysis of multiple correlations among levels of hydrocarbons measured in factory B revealed that four sources of variability accounted for 78% of the multiple correlations among the measured compounds (Table 6). The first PC was positively associated with pentane, hexane, heptane, 1,1,1-trichloroethane and octane; the second PC with toluene, MEK, ethyl acetate, 1,2-dichloroethane and acetone; the third PC with *m*-xylene, MIBK, ethyl benzene and DCM; the fourth PC with

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Table 3. Exposure to benzene and toluene per factory summarized for different production processes and direct handling of glues

	Glue[a]	*K* (%)[b]	*N*	Benzene (p.p.m.)					Toluene (p.p.m.)				
				AM	GM	GSD	10th percentile	90th percentile	AM	GM	GSD	10th percentile	90th percentile
Factory A		37 (68%)	116	21.86	14.40	2.31	5.23	50.63	9.52	7.10	2.03	3.07	17.04
1 Cutting		14 (100%)	41	10.96	10.24	1.45	6.53	16.26	5.35	4.95	1.49	3.15	8.13
2 Modeling	B	6 (27%)	18	9.04	7.75	1.75	4.45	18.69	4.42	4.22	1.37	2.80	6.40
3 Fitting	A	14 (100%)	47	29.31	21.34	2.34	7.06	65.17	12.54	10.38	1.92	3.78	24.62
4 Finishing	A	3 (75%)	10	54.64	28.03	3.30	7.62	179.60	21.61	13.31	2.75	4.60	57.90
Factory B		213 (38%)	2667	3.46	1.28	3.64	0.20	7.00	15.88	6.65	4.35	0.60	38.42
1 Cutting		30 (60%)	427	0.45	0.34	2.05	0.17	1.15	1.49	0.98	2.39	0.35	3.44
2 Modeling		59 (32%)	735	2.74	1.71	2.81	0.38	6.04	6.37	3.38	3.23	0.40	11.36
2a Gluing	C, E	9 (20%)	114	5.35	3.21	3.00	0.63	12.46	10.67	4.06	3.75	0.49	15.68
2b Other		50 (36%)	621	2.26	1.52	2.66	0.30	4.69	5.58	3.27	3.13	0.40	11.24
3 Fitting		90 (38%)	1096	2.19	1.12	2.98	0.26	4.68	26.29	16.34	2.75	4.89	57.88
Heel/ inner sole													
3a Gluing	C, D, E	15 (43%)	186	3.61	1.38	3.91	0.20	9.78	29.30	16.23	3.20	3.41	66.91
3b Other		35 (34%)	434	1.70	0.99	2.83	0.18	3.81	15.49	11.18	2.39	3.80	30.88
Outer sole													
3c Gluing	D, G, H, I	13[c] (50%)	147	1.53	1.00	2.49	0.31	3.35	58.83	41.29	2.71	17.36	117.49
3d Other		29[c] (41%)	329	2.33	1.24	2.81	0.34	4.57	24.30	17.89	2.20	7.35	45.59
4 Finishing		20 (30%)	241	8.35	2.91	3.33	0.65	11.69	18.96	14.46	2.16	5.81	40.84
5 Packing		14 (58%)	168	15.55	7.60	3.47	1.43	43.06	21.81	15.54	2.32	4.75	44.44
5a Gluing	F	6 (75%)	72	24.18	11.96	3.38	1.99	63.12	23.02	15.90	2.39	4.51	46.55
5b Packing		8 (50%)	96	9.08	5.42	2.92	1.36	20.48	20.91	15.28	2.28	4.79	43.93

K, number of workers; *N*, number of measurements; AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation.
[a]See Table 2 for description.
[b]Percentage of workforce.
[c]One worker changed job within this section and therefore the total number of workers in the sub-categories does not equal the total number of workers in the production function 'Fitting'.

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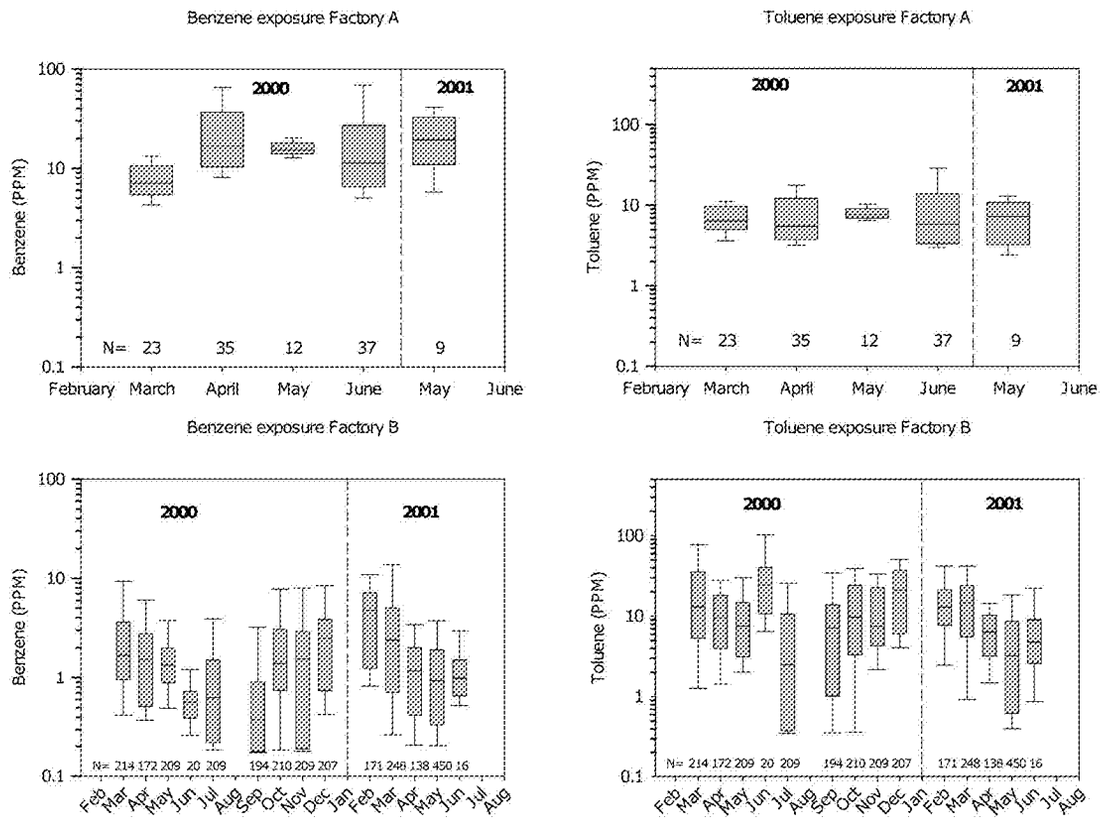


Fig. 1. Monthly benzene and toluene exposure distributions by factory (box plots). The line within the box marks the median; the lower and upper boundaries of the box indicate the 25th and 75th percentiles. Whiskers above and below the box indicate the 10th and 90th percentiles. *N* is the number of successful measurements collected in that particular month.

benzene. Subsequent regression analyses, using the scores of the PCs as dependent variables, revealed that PC1, PC2 and PC4 were strongly related to certain glues (Table 7). However, no relationship was found between PC3 and any documented glue source. Analyses with job titles and other production characteristics did not reveal any clear association with the identified PC (not shown), although all positive samples were detected in a subset of samples from subjects fitting the outer sole.

Home sampling: benzene and toluene

Personal monitoring of subject exposures to benzene and toluene during non-working hours revealed no detectable levels of these substances outside the workplace in either winter or spring. This result was confirmed in duplicate monitors analyzed at the US laboratory (n = 105), which had somewhat lower limits of detection for benzene (LOD = 0.03 p.p.m.) and toluene (LOD = 0.16 p.p.m.). This indicates that home exposures did not contribute significantly to benzene and toluene exposures among these workers.

DISCUSSION

We assessed benzene, toluene and other solvent exposures in two shoe factories in China. Benzene and toluene exposures were estimated from passive air monitors analyzed at the Chinese CDC laboratory. Previous studies utilizing the same laboratory had implemented detailed quality control procedures to ensure high quality analyses (Qu *et al.*, 2002). In this study, results from the CDC correlated well with duplicate analyses performed at a commercial laboratory in the USA.

Benzene exposure levels in the smaller shoe factory (factory A) were substantially higher than those in the larger shoe factory (factory B). However, benzene exposure distributions did overlap between the low exposed job titles of factory A and high exposed job titles in factory B. Since 'fitting' and 'finishing' processes in factory A showed the highest benzene exposure levels, it seems likely that the treatment glue used in factory A contained a significant amount of benzene. Due to the high source strength, poor ventilation, close vicinity and absence of any physical separation of the processes in factory A, all

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Table 4. Determinants of exposure to benzene and toluene (fixed effects) in factory B: results of mixed-effects models with worker as random effect and compound symmetry covariance structure

Determinant of exposure	ln(benzene) (p.p.m.) (N = 2667, k = 213)[a]			ln(toluene) (p.p.m.) (N = 2667, k = 213)[a]		
	β[b]	SE[c]	$P(b \neq 0)$[d]	β[b]	SE[c]	$P(b \neq 0)$[d]
Intercept	–0.17	0.10	0.09	–0.11	0.14	0.42
Amount (kg/day)[e]	0.12	0.012	<0.0001	0.03	0.002	<0.0001
Distance (m)[f]						
0	1.17	0.14	<0.0001	2.28	0.17	<0.0001
1–3	1.02	0.15	<0.0001	2.18	0.19	<0.0001
3–9	0.70	0.12	<0.0001	1.92	0.15	<0.0001
Ventilation[g]						
Fans	–0.57	0.04	<0.0001	–0.63	0.04	<0.0001
Fans and windows	–1.50	0.05	<0.0001	–1.84	0.06	<0.0001
Covariance components[h]	Estimate	SE	R^2 [i]	Estimate	SE	R^2 [i]
Between-worker (${}_{BW}S_y^2$)	0.36	0.04	52.9%	0.62	0.07	51.5%
Within-worker (${}_{WW}S_y^2$)	0.70	0.02	21.0%	0.62	0.02	26.7%

[a]N, number of measurements; k, number of workers.
[b]Regression coefficient for fixed effect. For dichotomous variables, exp[b] yields a factor by which the background exposure level should be multiplied to calculate the estimated GM.
[c]Standard error of β or estimate of covariance component.
[d]t-test for the fixed effect.
[e]Amount of benzene or toluene used per day for nearest glue source (kg/day). Estimates based on the percentage of benzene or toluene in the nearest glue source (Table 2) × the estimated daily use of the particular glue in kilograms based on monthly estimates of glue use. For glue G the amounts of benzene and toluene were assumed to be 1.5% and 42.5%, respectively (average of glues H and I).
[f]Compared with >9 m from glue source; 0 m was assigned to subjects actively handling the glues.
[g]Compared with conditions without running fans and closed windows.
[h]Covariance components derived from the model with fixed effects (e.g. amount, distance and ventilation).
[i]Percent of covariance component explained (R^2), relative to model without fixed effects (e.g. one-way random effects model).

workers in this facility were exposed to relatively high benzene levels (~10 p.p.m.).

There was more variability in benzene and toluene exposure levels in factory B than in factory A, both between workers (benzene, ${}_{BW}S_y^2 = 0.77$ versus 0.10; toluene, ${}_{BW}S_y^2 = 1.27$ versus 0.14) and within workers (benzene, ${}_{WW}S_y^2 = 0.88$ versus 0.60; toluene, ${}_{WW}S_y^2 = 0.85$ versus 0.36). The observed difference in day-to-day variance between the two factories was not influenced by the shorter observation period for factory A, as ${}_{WW}S_y^2$ for the exact same observation period in factory B was essentially the same (${}_{WW}S_y^2 = 0.89$) as ${}_{WW}S_y^2$ for the full observation period. The temporal variation in factory B was partly due to differences in air movement and general ventilation during the year. Only crude measures of air movement and general ventilation (i.e. fan use and open windows) could be used in the model. Measurements of the actual ventilation or of outdoor wind speed and direction, which could have had a significant role in the effectiveness of the general ventilation on a given day, were not available. However, the strong repetitive nature of the seasonal trend over the 16 month time period clearly indicates an important influence of seasonal differences in air movement and general ventilation patterns, as was confirmed with mixed-effects modeling using season as a covariate.

Differences in benzene exposure between job titles in factory B could be ascribed largely to the use of different glues in various stages of the production process and the proximity of workers to these sources. In the beginning of the production process ('cutting') no glues were used and benzene levels in this part of the factory were generally <1 p.p.m. Workers in 'modeling' and 'fitting' who were not actively involved in gluing procedures were generally exposed to benzene levels between 1 and 5 p.p.m. Workers in 'modeling' and 'fitting' who also performed gluing activities were exposed to benzene levels up to 10 p.p.m. Even higher benzene exposures occurred among workers who handled benzene glue in 'packing' or worked in close proximity to this activity ('finishing').

Although benzene and toluene were clearly the dominant exposures, vapors of 18 other hydrocarbons were detected in selected personal samples from the two factories. Exposure levels were generally low (≤5 p.p.m.) for these other hydrocarbons, representing less than 5% of their respective ACGIH TLVs. We used principal component analysis to link the presence of different hydrocarbons to specific glues used in factory B, where most hydrocarbon data were obtained. As specific combinations of glues were used within particular production processes (see Table 3), the principal component analyses clustered

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Table 5. Detected hydrocarbon exposure levels (p.p.m.) in selected personal OVM monitors (n = 66)

Hydrocarbon	TLV[a]	N positive (% positive)	AM	GM	GSD	Ratio AM:TLV (%)
Factory A (N = 6)						
Benzene	0.5	6 (100%)	42.3	37.3	1.79	8460
Toluene	50	6 (100%)	17.8	15.4	1.83	35.6
Pentane	600	6 (100%)	9.5	8.8	1.52	1.6
Ethyl benzene	100	6 (100%)	3.7	3.3	1.66	3.7
Hexane	500	6 (100%)	3.2	2.8	1.92	0.6
m-Xylene	100	6 (100%)	2.0	1.6	2.21	2.0
m-Xylene	100	5 (83.3%)	0.8	0.7	1.79	0.8
1,1,1-Trichloroethane	350[b]	5 (83.3%)	0.5	0.4	1.73	0.1
Heptane	400	4 (66.7%)	0.5	0.5	1.76	0.1
Octane	300	1 (16.7%)	0.3	0.3		0.1
Chlorobenzene	10	1 (16.7%)	0.5	0.5		5.0
Factory B (N = 60)						
Benzene	0.5	56 (93.3%)	4.6	1.1	4.84	920
Toluene	50	60 (100%)	10.7	5.5	3.52	21.4
Pentane	600	49 (81.7%)	9.9	1.8	5.71	1.7
Hexane	500	45 (75.0%)	3.5	1.0	4.30	0.7
Methyl ethyl ketone	200	43 (71.7%)	6.2	2.2	3.24	3.1
Ethyl acetate	400	37 (61.7%)	2.3	1.1	2.99	0.6
Acetone	500	36 (60.0%)	3.0	1.5	3.14	0.6
Heptane	400	22 (36.7%)	0.7	0.4	2.62	0.2
1,1,1-Trichloroethane	350[b]	11 (18.3%)	0.2	0.2	1.80	0.1
1,2-Dichloroethane	50[b]	11 (18.3%)	0.5	0.3	2.09	1.0
Octane	300	9 (15.0%)	0.3	0.2	1.72	0.1
m-Xylene	100	6 (10.0%)	0.3	0.2	1.43	0.3
Iso-octane	300	5 (8.3%)	0.2	0.2	1.35	0.1
Methyl isobutyl ketone	100[b]	3 (5.0%)	1.1	1.1	1.31	1.1
Ethyl benzene	100	3 (5.0%)	0.3	0.2	1.59	0.3
Methylene chloride	50	3 (5.0%)	0.2	0.2	1.43	0.4

N, number of samples with detectable levels; AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation.
[a]Threshold limit value (TLV) based on the ACGIH criteria for chemical substances (ACGIH, 2002).
[b]In the absence of TLVs, the recommended exposure limits (REL) based on the NIOSH pocket guide to chemical hazards (NIOSH, 2003) are indicated.

glues that were used in these processes. Interestingly, one principal component (PC3) could not be linked to the use of specific glues or other production characteristics. Given the low exposure levels of the hydrocarbons associated with this PC and the apparently sporadic occurrence of these hydrocarbons, this exposure is most likely associated with a source that was not used routinely in the shoe production process, possible a specialty glue or an adhesive remover.

Because the identified glues were used in different parts of the production process, it is unlikely that hydrocarbon exposures associated with these glues would confound possible relationships between benzene exposure and particular biological end-points. This conclusion is further supported by the fact that exposures to hydrocarbons other than toluene were generally very low and are not suspected of being hematotoxic or genotoxic or of influencing benzene metabolism at these levels. Finally, the identification of these distinct sources of co-exposures does facilitate the quantitative estimation of co-exposures for all study subjects, as the location of each study subject in relation to the major exposure sources (e.g. glues) is known and as glue formulations appeared to be constant over time, based on the observed ratios between benzene and toluene over the observation period (data not shown).

Toluene has been shown to competitively inhibit benzene metabolism and therefore might alter the dose–response relationships between benzene and biological end-points (Medinsky *et al.*, 1994). The correlation between benzene and toluene was high for factory A (r = 0.91) and was modest for factory B

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Table 6. Results of principal component analysis of multiple correlations among personal exposures to hydrocarbons (transformed by the natural logarithm) measured in factory B[a] (numbers in bold signify eigenvector ≥ 0.70)

Hydrocarbons	Eigenvector			
	First PC (PC1)	Second PC (PC2)	Third PC (PC3)	Fourth PC (PC4)
Benzene	0.28	0.08	–0.06	**0.82**
Toluene	–0.006	**0.89**	0.12	0.26
Pentane	**0.88**	–0.27	0.009	0.22
Hexane	**0.90**	–0.25	0.04	0.25
Methyl ethyl ketone	–0.26	**0.90**	0.16	0.06
Ethyl acetate	–0.12	**0.94**	0.02	–0.02
Acetone	–0.18	**0.72**	0.32	0.07
Heptane	**0.95**	–0.10	0.09	0.16
1,1,1–Trichloroethane	**0.91**	–0.01	0.30	0.05
1,2–Dichloroethane	–0.06	**0.81**	0.14	–0.23
Octane	**0.90**	0.001	0.31	–0.09
m–Xylene	0.28	0.01	**0.80**	0.44
Iso–octane	0.06	0.48	0.53	–0.23
Methyl isobutyl ketone	0.14	0.35	**0.82**	–0.20
Ethyl benzene	0.31	–0.003	**0.70**	0.47
Methylene chloride	0.02	0.23	**0.70**	0.002
Eigenvalue (variance explained)	4.56 (26.8%)	4.22 (24.8%)	3.79 (22.3%)	1.48 (4.38%)

[a]VARIMAX rotation was used, only PCs with eigenvalues > 1 are shown.

Table 7. Determinants of the scores of the four principal components derived from personal hydrocarbon exposure measurements in factory B

Glues[a]	*N*	Score PC1			Score PC2			Score PC3			Score PC4		
		β	SE	*P*	β	SE	*P*	β	SE	*P*	β	SE	*P*
Intercept		–0.19	0.12	0.12	–0.32	0.11	0.007	0.05	0.16	0.77	–0.24	0.12	0.05
Latex glue	4	1.93	0.4	<0.0001	–0.15	0.38	0.70	–0.08	0.54	0.88	0.73	0.40	0.07
Resin glue	6	–0.18	0.33	0.59	1.44	0.32	<0.0001	–0.13	0.45	0.77	0.27	0.33	0.41
Gasoline glue	4	2.71	0.55	<0.0001	0.06	0.52	0.91	–0.84	0.75	0.26	–0.32	0.55	0.56
Benzene glue	2	0.04	0.40	0.91	0.23	0.38	0.54	0.21	0.54	0.70	2.69	0.40	<0.0001
Treatment glue	4	–0.26	0.40	0.52	2.46	0.38	<0.0001	–0.24	0.54	0.66	–0.10	0.40	0.81
Explained variance (R^2)		0.48			0.53			0.03			0.48		

[a]Personal exposure samples of subjects not directly handling glues (n = 40) was used as a reference.

(r = 0.46). When all measurements were combined (n = 2783) the correlation between benzene and toluene among the total study population was 0.44. Given this modest level of correlation, it should be possible to determine if any observed dose–response relationship between benzene and a particular biological endpoint is modified by toluene exposure.

No exposure to benzene and toluene was detected during non-working hours. The lowest exposure level that could possibly have been detected was 0.03 p.p.m. for benzene and 0.16 p.p.m. for toluene (for a sampling duration of 14–16 h). Although these detection limits were much greater than air concentrations of benzene and toluene that have been reported indoors and outdoors in Asia (Guo *et al.*, 2003), they indicate that sources outside the workplace should not significantly add to the occupational exposures of workers in these factories. Future analyses of urinary benzene and its metabolites and benzene-related protein adducts in blood should further corroborate this finding and, in conjunction with questionnaire data, should shed light on the contribution of environmental and active tobacco smoking on internal benzene exposure levels.

As the study factories were selected based on several *a priori* eligibility criteria, it is unclear how representative these two shoe factories are of the contemporary Chinese shoe manufacturing industry. However, this study showed that benzene exposure levels are still rather high in at least some parts of the

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Chinese shoe manufacturing industry. It is noteworthy that 53% of the benzene measurements in factory A were above the Chinese exposure limit at the time of surveying (then 12.3 p.p.m., currently 1.9 p.p.m.), while 4% of the measurements in factory B were above the exposure limit. Given the known health risks of benzene at high levels of exposure, it is imperative that control measures be implemented in these two shoe factories. Based on measurement results collected during this survey, we made specific recommendations to improve the work environment. Since the survey was completed, factory B has installed local exhaust ventilation on almost all workstations where glues are used. In addition, the high benzene-containing glue has been replaced with a glue that has a lower benzene content.

A dose-dependent decline in peripheral blood cells is a well-known indicator of benzene exposure (Rothman *et al.*, 1996; Qu *et al.*, 2002). Preliminary analyses of the hematological data, collected as part of the hematological, cytogenetic and molecular endpoints in this study, showed a clear dose-dependent decline between the benzene exposure levels described here and peripheral white blood cells (Lan *et al.*, 2003). This observation seems to be consistent with a recently published study on hematological effects among Chinese workers with a broad range of benzene exposures (Qu *et al.*, 2002) and are an additional indication that exposures were assessed accurately.

In summary, we identified two shoe factories in the same geographical region of China that had very stable workforces. Over the course of the 16 month survey, there was essentially no task rotation in either workplace. We demonstrated the presence of a broad range of benzene and toluene exposure levels in personal air samples among these workers and identified production processes with distinct exposure patterns. Benzene and toluene exposure levels could be largely explained by the amount of benzene and toluene handled per day, the average distance to the nearest exposure source and air movement and ventilation patterns. Preliminary analyses of dermal exposure data collected as part of the current study indicate that this route of exposure did not contribute substantially to the total benzene and toluene doses received (unpublished data). Exposures to other measured hydrocarbons were quite low in both workplaces and were generally attributable to distinct glues. Overall, these data support the appropriateness of combining exposure and biological end-point data from the two factories, which, from an exposure perspective, differ primarily with regard to benzene exposure levels. The availability of long-term monthly personal monitoring data provides an excellent opportunity to estimate individual exposures at different times during the 1 yr period of observation and enables us to define subgroups of individuals who experienced relatively low levels of benzene exposure throughout the year.

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