

Assessment of dermal exposure to benzene and toluene in shoe manufacturing by activated carbon cloth patches

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Objectives: The aim of this investigation was to use activated carbon cloth (ACC) patches to study the probability and extent of dermal exposure to benzene and toluene in a shoe factory. **Methods:** Inhalation and dermal exposure loading were measured simultaneously in 70 subjects on multiple days resulting in 113 observations. Dermal exposure loading was assessed by ACC patches attached to likely exposed skin areas (e.g. the palm of the hand and abdomen). A control patch at the chest and an organic vapor monitor (OVM) were used to adjust the hand and abdomen patches for the contribution from the air through passive absorption of benzene and toluene on the ACC patches. Systemic exposure was assessed by quantification of unmetabolized benzene (UBz) and toluene (UTol) in urine. **Results:** Mean air concentrations for the study population were 1.5 and 7.5 ppm for benzene and toluene, respectively. Iterative regression analyses between the control patch, OVM and the dermal patches showed that only a small proportion of the ACC patches at the hand had likely benzene ($n = 4$; mean $133 \mu\text{g cm}^{-2} \text{h}^{-1}$) or toluene ($n = 5$; mean $256 \mu\text{g cm}^{-2} \text{h}^{-1}$) contamination. Positive patches were exclusively observed among subjects performing the task of gluing. Significant dermal exposure loading to the abdomen was detected only for toluene ($n = 2$; mean $235 \mu\text{g cm}^{-2} \text{h}^{-1}$). No relation was found between having a positive hand or abdomen ACC patch and UBz or UTol levels. In contrast a strong association was found between air levels of benzene ($p = 0.0016$) and toluene ($p < 0.0001$) and their respective urinary levels. **Conclusions:** ACC patches are shown to be a useful technique for quantifying the probability of dermal exposure to organic solvents and to provide estimates of the potential contribution of the dermal pathway to systemic exposure. Using ACC patches we show that dermal exposure to benzene and toluene in a shoe manufacturing factory is probably rare, and when it occurred exposures were relatively low and did not significantly contribute to systemic exposure.

Introduction

Exposure to benzene occurs worldwide to workers in the oil, shipping, automobile repair, shoe manufacturing and other industries. Inhalation is generally believed to be the major route of benzene exposure in most occupational settings but it has been hypothesized that under certain exposure scenarios, mostly including immersion of hands in benzene, the dermal route contributes significantly or even overwhelms the benzene intake by inhalation.¹

Quantification of dermal exposure to volatile organics such as benzene has been challenging and has often been assessed indirectly through biomonitoring of urinary metabolites. Although this could be adequate for estimating systemic exposure, it does not produce readily interpretable data on the importance of different pathways of exposure (e.g. inhalation, dermal). Activated carbon cloth (ACC) patches to identify potential dermal exposure loading from organic compounds were first described by Cohen and Popendorf.² More recently their application has been shown in the petrochemical industry, carpentry workshops and in the fiberglass reinforced plastics industry to measure a variety of organic compounds (i.e. benzene, toluene, monoterpenes and styrene).^{2–6} We describe here the results of a dermal exposure survey among shoe manufacturing workers in Tianjin, China employing ACC patches. The study was designed to evaluate the possible contribution of the dermal exposure route to systemic benzene and toluene exposure. For this purpose we simultaneously measured inhalation and dermal exposure loading to benzene and toluene and their respective unmetabolized parent compounds in urine.

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Material and method

Study subjects and sampling

Dermal, inhalation, and urine measurements were collected from 70 subjects employed in a large shoe factory (>500 employees) in Tianjin, China. About half of the workers ($n = 36$) were repeatedly measured for two or three days within a two-week time period. In total 113 measurements were collected. Subjects were part of a cross-sectional survey to evaluate the impact of low levels of benzene exposure on hematologic, cytogenetic and molecular endpoints, as previously described.^{7,8} Subjects were selected to represent the different tasks and operations in shoe manufacturing (e.g. cutting, modeling, fitting, finishing, packing, supervision). 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 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'). Exposure to benzene and toluene in this process comes from the use of glues containing benzene and/or toluene.⁸ Subjects involved in gluing were assumed to have the highest probability of exposure although other jobs could have potential dermal exposure due to handling of glued materials. All gluing activities were performed manually. No personal protective equipment (e.g. masks, gloves) was used.

Personal air sampling employed 3MTM 3500 organic vapor monitors (OVM). Dermal exposure loading was assessed by ACC patches (Charcoal Cloth International, Newcastle, UK). ACC patches were composed of two layers of activated carbon filaments ($\sim 400 \text{ g m}^{-2}$) pouched between a layer of cotton and non-woven cloth and were worn on the palm of the dominant hand ($3.5 \times 3.5 \text{ cm}^2$) and under the clothing at the abdomen ($3.5 \times 7.0 \text{ cm}^2$). Patches were attached by medical tape which was screened for possible benzene and/or toluene contents. These sampling locations were chosen based on detailed task observations, discussions with workers of the most probable exposed skin areas, and where they could be worn without interfering with normal work practices. As the ACC patches also absorb organic vapors from the air through passive diffusion a 'control' patch ($3.5 \times 3.5 \text{ cm}^2$) was worn at the chest directly next to the OVM. As there is a negligible likelihood, within the studied setting, for direct contact between the chest patch and the source (e.g. glues), aerosols or droplets, the benzene and toluene contents of this patch can be directly attributed to absorption of the vapor phase. Air and dermal measurements were collected for approximately the last 3–4 h of the work shift as dermal samplers could not be worn during lunchtime.

Prior to chemical analyses a $\diamond 28.5 \text{ mm}$ segment was punched out of the ACC patch. Analyses of the OVM and ACC for benzene and toluene were conducted by gas chromatography (GC) with a flame ionization detector (FID) according to NIOSH method 1501.⁹ The limit of detection (LOD) for inhalation exposure was 0.20 ppm and 0.30 ppm, for respectively, benzene and toluene and 1.2 and $1.6 \mu\text{g cm}^{-2} \text{ h}^{-1}$ for dermal exposure loading, respectively.

Urinary benzene (UBz) and toluene (UTol) have been shown to be sensitive markers for low benzene and toluene exposure, respectively.^{10–12} Levels of UBz and UTol in spot urine samples collected at the end of the work shift¹³ were determined according to the method of Waidyanatha *et al.*,¹⁴ with minor modifications.¹³ Briefly, in a 2 ml vial containing 0.5 ml of urine *ca.* 0.5 g of NaCl was added and 1 μl of 5 $\text{ng } \mu\text{l}^{-1}$ [²H₆]benzene and [²H₈]toluene in methanol as internal standard. The vial was immediately sealed with a PTFE/silicone septum and the analytes were extracted with a 30 μm polydimethylsiloxane fiber from urine headspace at 40 °C for 15 min. Samples were analyzed by gas chromatography-mass spectrometry (GC-MS) in electron impact (EI) mode. Quantification was based on peak areas relative to the corresponding isotopically labeled internal standards.

Statistical analyses

All concentrations below the LOD [Inhalation: benzene ($n = 29$); toluene ($n = 4$); Dermal: benzene chest ($n = 2$), hand ($n = 1$), abdomen ($n = 10$); toluene chest ($n = 7$), hand ($n = 3$), abdomen ($n = 9$)] were assigned a value of $\text{LOD}/\sqrt{2}$ before statistical analyses.¹⁵

Spearman correlation coefficients were obtained for pairs of measurements of benzene and toluene in air and the corresponding ACC patches. Dermal patches with significant benzene and/or toluene contamination that could not be attributed to absorption of organic vapors from the air were identified by iterative linear regression analyses between levels of benzene or toluene on the chest 'control' patch and on the dermal patch at the hand or abdomen (e.g. uncorrected dermal contamination levels). In these analyses extreme outliers, as identified by a Studentized residual >4 and correspondingly high Cook's D , were marked as samples with potential dermal exposure.¹⁶ The cut-point was based on regression analyses between the OVM sampler and chest sampler that identified no Studentized R greater than ± 4 . As such it can be assumed that Studentized residual larger than 4 are more than likely not due to random measurement error but due to a contribution from another source than the air. Analyses were repeated without the earlier identified positive samples until no extreme outliers could be detected. Consequently, the above analyses were repeated using the OVM as the reference to examine if the identified outliers were potentially caused by measurement error in the chest 'control' patch. Samples that were found positive in both analyses were regarded as 'likely positive'. Samples that were deemed positive in either of the analyses were regarded as 'possibly positive'. Subsequently, the positive patches (e.g. likely and possibly) were corrected for the contribution from the air by using the obtained regression equation between the 'negative' dermal patches and the 'control' chest patch to estimate the contribution of benzene and toluene on the patch based on the corresponding air concentration. The difference between the estimated contamination and measured contamination level is regarded as the amount of dermal exposure loading.

Associations between UBz and UTol and inhalation and dermal exposure loading of benzene and toluene were

investigated by means of a mixed-effects model. The model framework can be described by the following equation.

$$Y_{ij} = \sum(\text{Fixed effects})_{ij} + \chi_i + \varepsilon_{ij},$$

where Y_{ij} is the natural logarithm of UBz or UTol measured on the j th day of the i th worker; χ_i is the random effect of the i th worker and ε_{ij} is the random error. The model assumes that all χ_i and ε_{ij} are mutually independent and normally distributed with zero means. Fixed effects tested in the models were the natural logarithm of the breathing zone benzene or toluene concentration (ppm) and dermal exposure to benzene or toluene at the hand (yes/no) or abdomen (yes/no) in the i th subject on the j th day. Analyses were corrected for age and urinary cotinine levels as additional fixed effects in the model.

All statistical analyses were performed using SAS V9.0 at a significance level (two-tailed) of 0.05.

Results

Mean air concentrations for the study population were 1.52 (SD 2.82) and 7.49 (SD 11.60) ppm, for benzene and toluene, respectively. Uncorrected dermal contamination levels were highest for the hand followed by the chest and were lowest for the abdomen (Table 1). Spearman correlations between air concentrations and uncorrected contamination levels of dermal patches were relatively high ($r_s > 0.7$ and $r_s > 0.8$ for benzene and toluene, respectively) (Table 1). Spearman correlations between contamination levels of the three skin locations were also generally above 0.8. The high correlations among the dermal patches and the corresponding air concentrations indicate a common exposure source.

The differential levels of contamination between dermal chest patches with those of the hand and abdomen were used to identify potential benzene and/or toluene contamination by iterative linear regression analyses. For the hand and abdomen this procedure resulted in four and three patches with potential benzene exposure, respectively, and nine and four patches with potential toluene exposure, respectively. Analyses were repeated by using the OVM concentration as the reference. These analyses confirmed that, indeed, four and five of the hand patches and two and four of the abdomen patches had likely benzene and/or toluene contamination, respectively. Scatter plots of the above analyses indicating the identified positive dermal samples (likely and possibly) and regression equations excluding the positive dermal samples are presented in Fig. 1 by dermal sample location and exposure. It is clear

from these plots that dermal contamination at the hands and abdomen occurred predominantly during activities that were associated with higher air concentrations. The regression equation between the benzene and toluene contamination levels at the chest patch and at the hand for the 'negative' samples revealed that the association was close to $x = y$. This was not the case for the association between benzene and toluene at the chest and abdomen patch where the exposure under the clothing tended to be 50% to 60% lower than the corresponding chest patch.

Table 2 presents the average benzene and toluene dermal exposure loading, corrected for the corresponding air levels for the positive dermal samples based on the equations presented in Fig. 1. Dermal exposure loading for benzene were lower overall than those for toluene. All positive hand patches for both benzene and toluene were related to gluing activities. Only two of the positive abdomen positive patches ($n = 4$) for toluene were associated with gluing activities. However, these were the two highest contamination levels (321 and 149 $\mu\text{g cm}^{-2} \text{ h}^{-1}$), while the positive non-gluing ($n = 2$) associated samples had much lower levels (36 and 32 $\mu\text{g cm}^{-2} \text{ h}^{-1}$).

Levels of UBz were significantly correlated with benzene air levels ($p = 0.0016$), but not with dermal exposure at the hand or abdomen (Table 3). Similarly, UTol was strongly associated with toluene air levels ($p < 0.0001$) but again no association was observed with dermal contamination at the hand or abdomen. The results did not change when both likely and possibly positive dermal samples were considered positive. As dermal contamination appeared to be related to gluing activities we repeated the above multivariate analyses with performing the task of gluing ($n = 25$) as a nominal variable in the model instead of the positive dermal exposure indicators. No association was observed between performing the task of gluing and elevated levels of UBz or UTol, independent of the concurrent air concentration (data not shown).

Discussion

In this paper a dermal exposure survey of a shoe manufacturing facility using ACC patches is described. The survey was nested within a comprehensive exposure assessment to accurately quantify the exposure profiles of subjects enrolled in a cross-sectional study of low levels of benzene (< 1 ppm).^{7,8} Subjects were selected based on tasks performed and covered all tasks generally encountered in shoe manufacturing.

Table 1 Spearman correlation between air concentrations (ppm) and uncorrected dermal contamination levels at the chest, hand and abdomen ($\mu\text{g cm}^{-2} \text{ h}^{-1}$) for benzene and toluene ($n = 113$)

Location	Uncorrected dermal contamination/ $\mu\text{g cm}^{-2} \text{ h}^{-1}$				Spearman correlation coefficients air with dermal ^a	
	Benzene		Toluene		Benzene	Toluene
	AM (SD) ^b	Median	AM (SD)	Median		
Chest	7.2 (8.7)	3.5	17.6 (26.5)	9.6	0.70	0.85
Hand	13.8 (35.6)	4.3	33.2 (75.1)	12.2	0.73	0.84
Abdomen	4.1 (4.4)	2.3	12.1 (34.0)	4.9	0.75	0.74

^a $P < 0.0001$ for all correlations coefficient presented. ^b Arithmetic mean (AM) and standard deviation (SD).

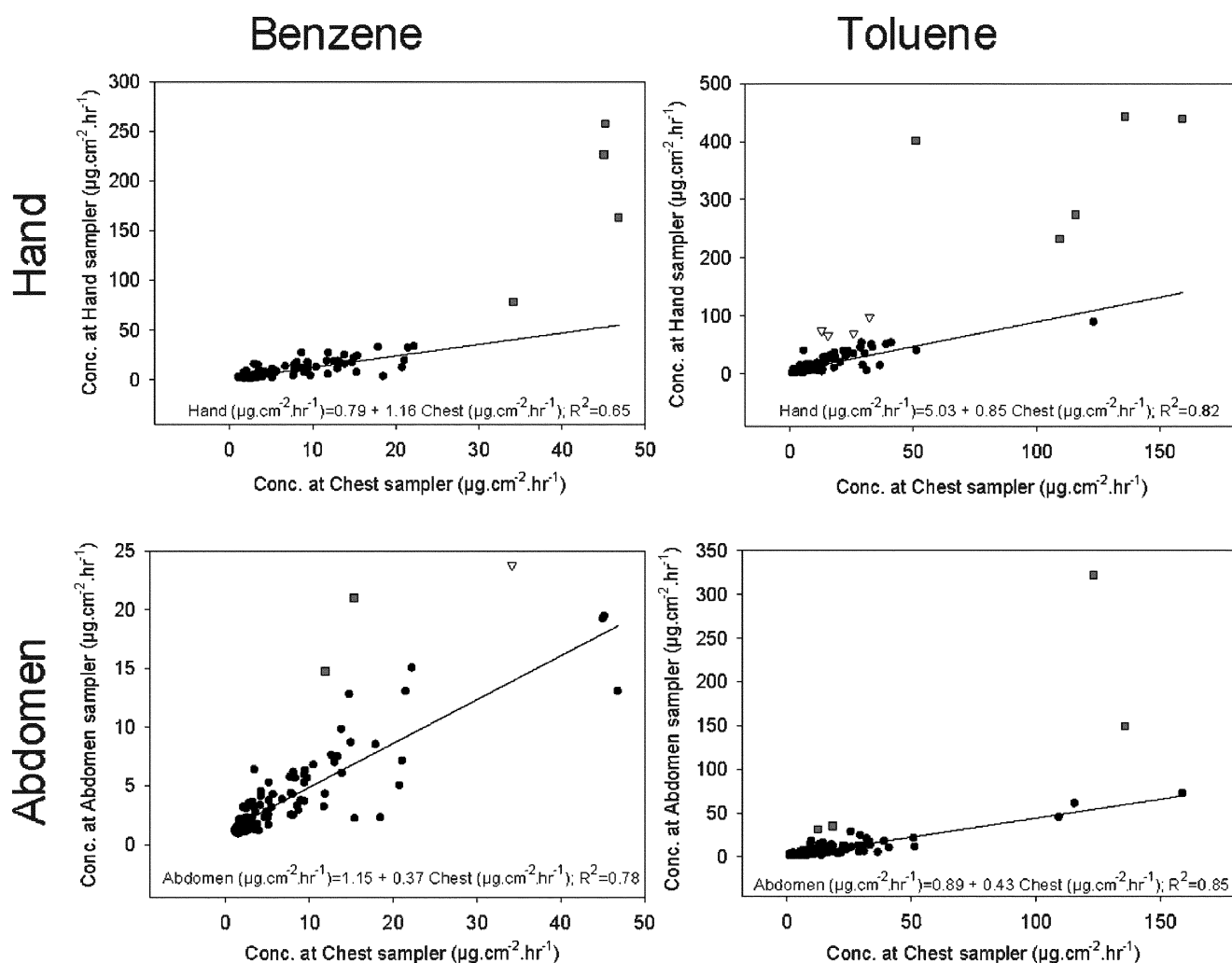


Fig. 1 Scatter plots of benzene contamination levels at chest sampler and at hand or abdomen sampler for benzene and toluene. Solid squares, open triangles and solid circles indicate 'likely positive', 'possibly positive', and 'negative' dermal samplers, respectively. Linear regression equation and R^2 are presented in the respective figures.

Dermal exposure to benzene and toluene was assessed by using ACC patches that can be a valuable tool for assessing dermal exposure to volatile chemicals.^{2–3,6} One potential shortcoming of ACC patches is that they might become saturated in extreme exposure scenarios.⁴ Our patches have been tested previously in laboratory tests and found to have no indication of saturation till at least ~ 14 mg of benzene. The

highest level measured on any patch in this study was less than 11 mg. Furthermore, based on the average exposure levels of other hydrocarbons (see Vermeulen *et al.*, 2004⁸) it can be estimated that average levels of total hydrocarbon levels were less than 2 mg. Therefore such saturation of the patches under these field circumstances seems unlikely. However, a more impending limitation in the applicability of charcoal-cloth

Table 2 Average benzene and toluene dermal exposure loading for 'likely positive' samples corrected for concurrent air concentration

		# Subjects (%) ^a	# Samples (%) ^b	Gluing ^c	AM ^d / μg $\text{cm}^{-2} \text{h}^{-1}$	SD ^e	Min/ μg $\text{cm}^{-2} \text{h}^{-1}$	Max/ μg $\text{cm}^{-2} \text{h}^{-1}$
Benzene	Hand	3 (4.3%)	4 (3.5%)	4	132	74	38	205
	Abdomen	2 (2.9%)	2 (1.8%)	0	12	4	9	14
Toluene	Hand	5 (7.1%)	5 (4.4%)	5	256	97	135	353
	Abdomen	4 (5.7%)	4 (3.5%)	2	102	114	25	268

^a A total of 70 subjects were measured. ^b A total of 113 samples were collected. ^c Number samples where the performed task was gluing.

^d Corrected for concurrent air concentrations based on observed relations between the contamination level at the chest 'control' patch and hand or abdomen patch as presented in Fig. 1. ^e Standard deviation.

Table 3 Association between urinary benzene and toluene measures and external exposure measures^a

Determinants	Ln(urinary benzene/nmol l ⁻¹)		Ln(urinary toluene/nmol l ⁻¹)	
	β (SE)	<i>P</i> value	β (SE)	<i>P</i> value
Intercept	4.55 (1.55)	0.0046	2.64 (0.67)	0.0002
Ln(air concentration (ppm))	0.44 (0.13)	0.0016	0.56 (0.07)	<0.0001
Hand exposure ^b	-0.25 (0.94)	0.79	0.35 (0.39)	0.37
Abdomen exposure ^c	-0.50 (1.07)	0.64	0.29 (0.39)	0.45

^a Models corrected for urinary cotinine levels (ng mg⁻¹ creatinine) and age. β , regression coefficient; SE, standard error; *P*, probability. ^b Compared to no hand exposure. ^c Compared to no abdomen exposure.

patches is that they not only measure dermal exposure to droplets and aerosols, but also absorb organic vapors through passive diffusion, necessitating a correction for ambient levels of the volatile compounds. In this study we describe a novel method to identify and correct positive dermal patches for the contribution from the air by iterative least-square regression analyses. In these analyses the amount of benzene and toluene collected by the chest patch and the OVM monitor were used to identify positive dermal samples at the hand and abdomen.

The identification of the positive samples depends on the cut-point used to define the maximum Studentized residuals. We based this cut-point on the regression analyses between the OVM sampler and chest sampler that identified no Studentized *R* greater than ± 4 . As such it can be assumed that Studentized residuals larger than 4 are more than likely not due to random measurement error but due to a contribution from another source than the air (*e.g.* dermal contamination). Alternatively, we calculated the minimal contribution that would occur if a single drop of glue, containing the least amount of benzene or toluene used in this study, were to be deposited on the dermal sampler. If we assume that (1) a drop has a volume of 0.06 ml, (2) that the minimal percentage of the benzene and toluene is 1% and 3%,⁸ respectively, and that the ACC patches have a 100% absorption efficiency, a dermal exposure loading of approximately 20 and 65 $\mu\text{g cm}^{-2} \text{h}^{-1}$ for benzene and toluene, respectively, would be expected above the contribution from the air (see Table 2). Applying these criteria to our data we would identify the same positive hand samples for both benzene and toluene. For the abdomen, only the two highest toluene levels and none of the benzene levels fulfill these criteria. We therefore conclude that the low contamination levels for both benzene and toluene at the abdomen identified in the iterative regression analyses are most likely false positive results due to measurement error in either the abdomen or control patch. This is further supported by additional regression analyses using log-transformed dermal exposure levels. These analyses were performed due to indications of heteroscedasticity in the regression analyses. However, log-transformation does not only result in equal variance of the errors but also reduces the influence of extreme values, which is the focus of these particular analyses. Nevertheless, based on influence parameters (Studentized *R* and Cook's *D*) three of the four previously identified positive hand patches and none of the abdomen patches were still identified as positive for benzene. For toluene only one of the five hand patches and two (*i.e.* the two highest) of the abdomen patches remained positive for toluene. However, the two positive

patches at the abdomen for toluene should still be treated with caution as the positive results could either be through the contact with glues or because of the subject adjusting their clothing allowing more vapor to come into contact with the ACC patch.

ACC patches have been shown to be perfect sinks with a 100% absorption efficiency and will thus not reflect the process of evaporation or run off that would take place in most normal exposure scenarios involving volatile substances^{3,4}. As such estimated dermal exposure loading based on the positive dermal samples are an overestimation of actual dermal exposure. On the other hand, due to the likely non-uniform spatial distribution of dermal exposure and the limited area covered by the dermal patches it could be that dermal contamination was missed. We addressed this concern by not only relating the identified positive dermal patches to urinary benzene and toluene levels but also by assuming that subjects actively involved in gluing would have a higher chance for dermal exposure. Note, all positive dermal samples were associated with gluing. No association was found between either the positive dermal samples or gluing as a task and urinary benzene, further indicating that dermal exposure did not contribute to the systemic exposure. In contrast, a strong association was found between benzene and toluene in air and urine indicating that inhalation was the predominant and most important route of exposure.

This seems also plausible from the measured air and dermal contamination levels for benzene and toluene. If we assume that for benzene and toluene 99% [note, EPA assumes a minimal uptake of 0.05% to a maximal uptake of 0.1%¹⁷] and 95%, respectively, of the material evaporates from the skin before it can be absorbed and that the measured contamination levels at the hands (132 and 256 $\mu\text{g cm}^{-2} \text{h}^{-1}$, respectively) are loaded evenly onto 10% of the skin surface of the palm of both hands (36 cm²) and that the exposure is constant over the 8 hours we can estimate that the amount likely to be absorbed will be approximately $\sim 0.5 \text{ mg}$ [$132 \times 0.01 \times 36 \times 8$] and 4 mg, for benzene and toluene, respectively. Assuming a breathing volume of 10 m³, an air concentration of 14 ppm and 52 ppm (*e.g.* average benzene or toluene air concentration for subjects where dermal contamination to benzene or toluene was detected) and 50% and 80% retention in the lung for benzene¹⁸ and toluene,¹⁹ respectively, the uptake would be around 70 mg [$14 \times 10 \times 0.5$] and 416 mg for benzene and toluene, respectively. Using these data it can be estimated that for the subjects with dermal exposure to the hand (<5% of the study population) the contribution to the

systemic exposure would be less than 1% for both benzene and toluene. Significant dermal exposure to the abdomen was only detected for toluene ($n = 2$; mean = $235 \mu\text{g cm}^{-2} \text{h}^{-1}$). Using the same assumptions of evaporation, 10% dermal exposure surface (171 cm^2), exposure evenly distributed over 8 hours and a concurrent air concentration of 33 ppm, we can estimate that the contribution would be 16 mg ($\sim 9\%$ of inhalation). These estimates are more than likely an overestimation as from workplace observations it is unlikely that the workers in this factory would have had a constant exposure over the 8 h working day to 10% of their hands or especially their abdomen.

In conclusion, dermal exposure to benzene and toluene was detected on the hands of a small proportion of the population ($< 5\%$) and was exclusively observed among subjects performing the task of gluing. Furthermore, dermal exposure levels for both benzene and toluene were low and did not seem to contribute to the systemic exposures of these compounds. We conclude that dermal exposure to benzene and toluene did not play an important role in the studied shoe factory. If these results can be extrapolated to other shoe manufacturing facilities depends on the source strength and the amount of skin contact with the glue. However, based on the results of this study it seems that dermal exposure in shoe manufacturing is generally limited. ACC patches offer a useful technique to quantify dermal exposure to benzene and toluene. However, as ACC patches do not take into account the run-off and other losses of contaminants the actual values should be treated as a measure of potential exposure. Alternative methods have been developed that try to mimic these processes by having a permeable membrane in combination with an absorption layer that would measure the mass of a contaminant likely to be adsorbed by the skin. However, these techniques are still under development and have not yet been able to accurately mimic the permeability of the skin.⁴

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