

Percutaneous penetration *via* hand eczema is the major accelerating factor for systemic absorption of toluene and xylene during car spray painting

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Background: For absorption of organic solvents, the respiratory tract is well known as the major site, but percutaneous absorption might be critical in some workplaces.

Objectives: The aim of the study is to determine whether the skin, if disordered, is 1 of the major routes of organic solvent absorption.

Patients/Methods: 72 male workers who painted the car body in the booth of a Japanese car company were participated in this study. The severity of hand eczema, urinary metabolites of organic solvents and the concentration of airborne organic solvents were measured.

Results: The correlation coefficient between the skin severity index and the urinary concentration of hippuric acid or methylhippuric acid was statistically significant. There was no significant correlation between their urinary values and the air concentration of mixed organic solvents.

Conclusions: The skin is a more critical absorption route for organic solvents than the respiratory tract in some occupational settings. Hand eczema is a common disease and has a possibility to be a critical absorption route of organic solvents.

Key words: hand eczema; hippuric acid; methylhippuric acid; toluene; xylene. © Blackwell Munksgaard, 2007.

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It is well known that exposure to a low or moderate concentration of organic solvents may cause various symptoms such as headache and dizziness (1, 2). The health risk is assessed by biological monitoring of exposure through the evaluation of the internal dose. The threshold limit values (TLVs) are guidelines designed for use by industrial hygienists in making decisions regarding safe levels of exposure to various chemical substances and physical agents found in the workplace. Toluene and xylene are used in various workplaces, in particular industrial settings. When toluene and xylene are absorbed into the body, they are discharged in urine after several steps of chemical changes (3, 4). Urinary hippuric acid and methylhippuric acid are the most frequently used biomarkers in the biological monitoring of occupational exposure to toluene and xylene (5). There have been data of urinary hippuric acid in 3,947

workers and of methylhippuric acid in 1,523 workers in Japan (5). The results can be classified into 3 levels, and the category 3 represents the urinary levels of metabolites of organic solvents higher than the classified American Conference of Governmental Industrial Hygienists (ACGIH) recommendations of TLVs and the biological exposure indices issued in 1988–1989.

In addition to the respiratory intake, the percutaneous absorption is expected to be an important factor of the biological exposure to organic solvents, but the skin has not been estimated as a critical route to determine the TLVs. Only a couple of chemicals are known to be absorbed through the skin, as represented by *N,N*-dimethylformamide (6). While normal skin may be resistant to absorption of organic solvents (7), it is possible that pathological or injured skin allows the solvents to penetrate the skin. In this respect, hand eczema

is thought to be the most critical skin disorder, because its incidence is very high (8) and the hand is easily exposed to the solvents (9). Moreover, hand eczema often occurs in patients with atopic dermatitis or atopic backgrounds (10, 11). A recent finding has suggested that a high incidence of mutation of filaggrin is seen in atopic patients (12). Because filaggrin deeply participates in the skin barrier function, individuals with the disordered barrier are prone to have atopic dermatitis as a result of feasible skin penetration of exogenous substances.

To investigate the influence of hand eczema on the absorption of organic solvents, we monitored the levels of urinary hippuric acid and methylhippuric acid in relation to the severity of hand eczema in spray painters of an automobile plant.

Materials and Methods

72 male workers who painted car body for 8 hrs a day in the painting booth of a Japanese car company located in Kosai City, Japan, were enrolled in this study. They worked in 7 different, 65×6 m-wide booths equipped with general ventilation system. All the workers wore Tyvek dust-proof overalls, gas masks that are suitable for Japanese Industrial Standards, and nylon electrostatic gloves. The concentrations of organic solvents in air were lower than their respective TLVs of ACGIH recommendation in all painting booths. For biological monitoring of toluene and xylene, urine hippuric acid and methylhippuric acid were measured, respectively. Urine samples were collected on the last day of the working week. To avoid the influence of benzoic acid, aspirins or food preservatives are prohibited for 1 week. The concentrations of hippuric acid and methylhippuric acid were measured by high performance liquid chromatography (Enshu Medical Laboratory, Hamamatsu, Japan). The lowest detection levels of these metabolites were 0.01 g/l. Urine hippuric acid (mean $\pm$ SD = 0.3375 ± 0.3283 g/l) and methylhippuric acid (mean $\pm$ SD = 0.0436 ± 0.0346 g/l) levels belonged to the category 1 or 2 in all the workers, and thus satisfied the ACGIH issued recommendations. Samples of air were collected with a 1 l vacuumed glass sampling tube. The levels of toluene and xylene were quantified by gas chromatography and mass spectrometry (Department of Experiment and Analysis, Suzuki Motor Company, Hamamatsu, Japan).

The severity of hand eczema was evaluated by a dermatologist in dryness, erythema, scaling, dyshidrosis, fissuring, and lichenification using

simple visual scoring: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. The skin severity index was represented by the sum of these values (13). To explore the association of the urinary metabolites of organic solvents with the skin severity index, Spearman's correlation coefficients were used. All statistical analyses were performed with JMP V5.0.1TM.

Results

As shown in Fig. 1, the urine hippuric acid level of 72 spray painters (mean $\pm$ SD = 0.3375 ± 0.283 g/l) was significantly higher than that of healthy 41 male workers who had not used organic solvents (mean $\pm$ SD = 0.1671 ± 0.2243 g/l) ($P = 0.0038$). The urine methylhippuric acid level of 41 normal subjects was under the lowest detection level. The skin severity index in the workers ranged from 0 to 6 points. The correlation coefficient between the skin severity index and the urinary concentration of hippuric acid or methylhippuric acid was statistically significant (Fig. 2). In particular, a high correlation coefficient (0.6099) was observed in hippuric acid. It was noted that workers without any hand eczema (the skin severity index, 0) exhibited extremely low levels of urinary hippuric acid, except for 1 worker. All the workers wore a gas mask that was regularly maintained, and the

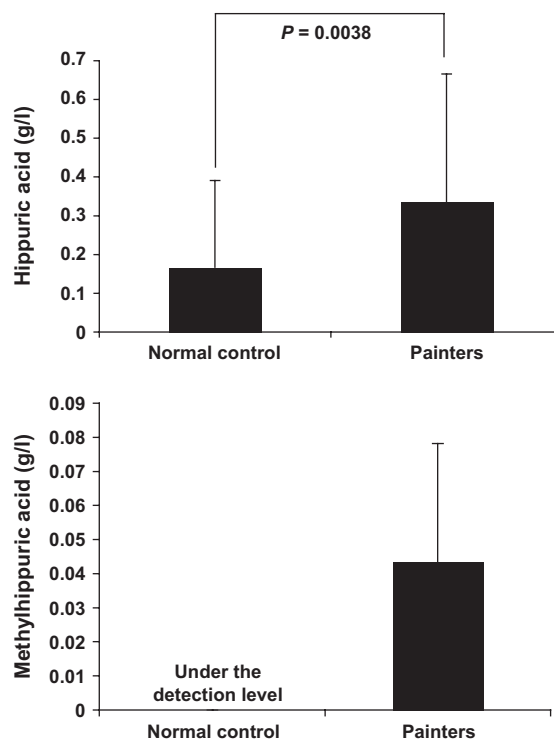


Fig. 1. Urinary metabolites of toluene and xylene of 72 spray painters are significantly higher than those of 41 normal subjects who have not been used organic solvents.

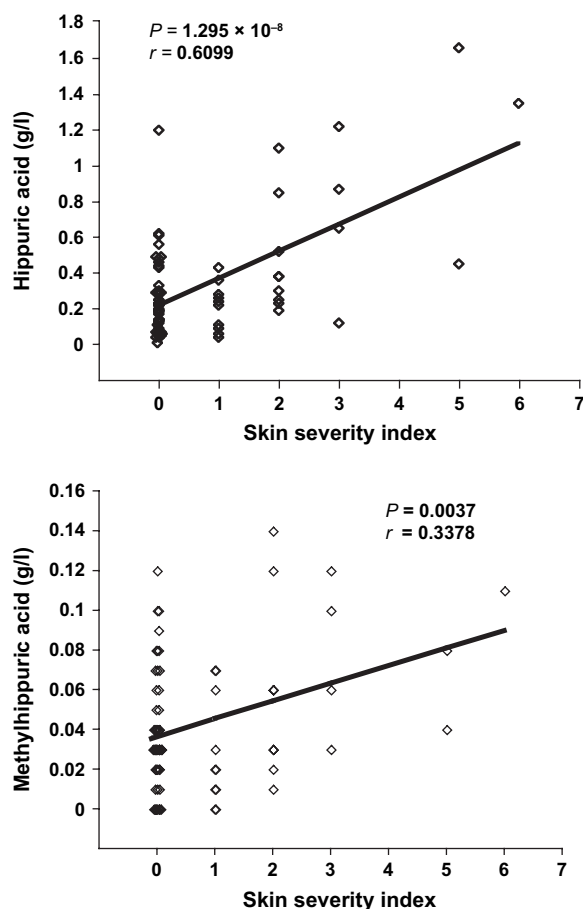


Fig. 2. Positive correlation between urinary hippuric acid (top) or methylhippuric acid (bottom) and skin severity index of hand eczema.

air exchange was efficiently performed in the 7 booths. To further exclude the possible absorption through the respiratory tract, we also examined the relationship between the urinary concentration of hippuric acid or methylhippuric acid, and the air concentration of toluene and xylene, respectively. Figure 3 shows these correlations in 7 different booths. There was no significant correlation between the air levels of toluene and xylene and urine concentrations of hippuric acid and methylhippuric acid, respectively, confirming that the respiratory absorption of organic solvents did not contribute to the urinary levels in this workplace. These data indicate that the concentrations of urinary hippuric acid and methylhippuric acid depend on the severity of hand eczema.

Discussion

Our study clearly showed that workers with hand eczema have high urinary levels of hippuric acid and methylhippuric acid when occupationally exposed to organic solvents. Although the respiratory tract has been estimated as the major

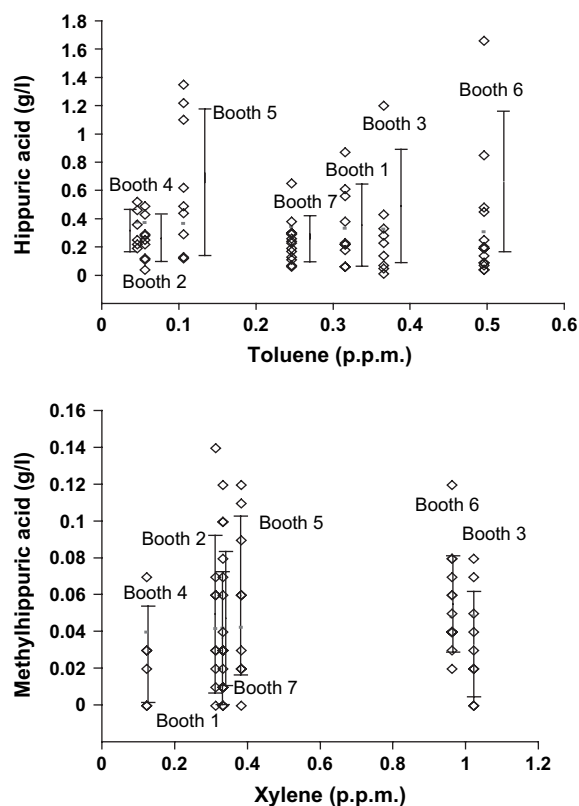


Fig. 3. Absence of correlation between urinary hippuric acid and toluene concentration in air (top) or methylhippuric acid and xylene concentration in air (bottom). The concentrations of toluene and xylene in air were measured in the 7 different booths and correlated with the concentrations of urinary hippuric and methylhippuric acids of the workers in each booths. Error bar represents the mean $\pm$ SD of urinary hippuric acid or methylhippuric acid levels of painters in each booths.

absorption system of the solvents (3, 4), we found that the urinary concentration of hippuric acid or methylhippuric acid did not depend on the air concentration of mixed organic solvents in our occupational settings. Thus, the skin is 1 of the crucial absorption routes for organic solvents.

Skin protection items such as protective gloves and barrier creams are necessary for prevention from the irritation by or penetration of organic solvents (13). The workers in our study wore nylon electrostatic gloves, but they could not protect the penetration of organic solvents. The workers also used emollients for skin care with insufficient protection. Our findings indicate that the skin protection from organic solvents is difficult. The actual advantage of barrier creams over emollients for skin protection is still debated (13).

Hand eczema is a common disease and induced by organic solvents themselves as well as atopic background (10, 11). Given that organic solvents can disrupt the skin barrier by removing ceramide of the stratum corneum (14), the induced acute

barrier disruption may further exaggerate the percutaneous absorption of the solvents. It should be kept in mind that the absorption *via* eczematous skin is the important mechanism underlying systemic absorption of organic solvents when workers deal with the solvents by hands.

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