Evaluation of the Suitability of Establishing Biological Exposure Indices of Styrene

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ABSTRACT

Background: This study was designed to provide logical backgrounds for the revision of biological exposure indices (BEIs) for styrene exposure in Korea. In order to investigate the correlation between airborne styrene and biological exposure indices, we measured urinary mandelic acid (MA) and phenylglyoxylic acid (PGA) in workers exposed to styrene occupationally, as well as airborne styrene at workplaces.

Methods: Surveys were conducted for 56 subjects. The concentrations of airborne styrene and urinary metabolites of styrene were measured in 36 workers who were occupationally exposed to styrene, and in 20 controls. Air samples were collected using personal air samplers and analyzed by gas chromatography. Urine samples were collected at the end of the shift and analyzed by high performance liquid chromatography.

Results: The geometric mean concentration of airborne styrene was 9.6 ppm. The concentrations of urinary MA, PGA, and MA + PGA in the exposure group were 267.7, 143.3, and 416.8 mg/g creatinine, respectively. The correlation coefficients for correlation between airborne styrene and MA, PGA, and MA + PGA were 0.714, 0.604, and 0.769, respectively. The sum of urinary MA and PGA corresponding to an exposure of 20 ppm styrene was 603 mg/g creatinine.

Conclusion: The correlation of the sum of urinary MA and PGA with airborne styrene was better than the correlation of each individual urinary determinant. It is considered appropriate to amend the concentration of urinary MA + PGA to 600 mg/g creatinine as a BEI, which corresponds to an airborne styrene concentration of 20 ppm in Korea.

1. Introduction

Styrene is a substance used in the manufacture of synthetic resins, plastics, and rubber [1]. The amount of styrene production in Republic of Korea gradually increased from 2.7 million ton in 2006 to 3.6 million ton in 2010, and the volume of consumption increased from 4.68 million ton in 2001 to 5.23 million ton in 2010. Most of the styrene was used to produce polystyrene and styrene polymer [2–5].

Styrene exposure is classified as closed system or open operation based on the process type. Closed-system exposure mainly includes production of the styrene monomer, copolymer resins, and styrene, whereas open-operation exposure includes reinforced plastics manufacture (ship, bathtub, shower cubicle, etc.), reinforced polyether resin manufacture, and fiberglass liquid resin coating. In the past, during closed-system operation, the average concentration of airborne styrene was usually less than 10 ppm, whereas it was 40–100 ppm in open operations [6–11]. Exposure concentration levels according to the type of industry and job of the open operation were as follows. Mean exposures of hull lamination, deck lamination, small parts lamination, and gel coating were found to be 78 ppm, 67 ppm, 44 ppm, and 48 ppm, respectively [7]. The time-weighted average of exposure in an entire boat production was estimated to be 40–50 ppm [9]. In a recent study, the concentration of airborne styrene was higher in open operations (7.1 ppm) than in closed system (5.6 ppm) [12].
Therefore, the target workplaces were selected as open systems in this study. Styrene is absorbed via the pulmonary and dermal routes [13–15]. The octanol/water partition coefficient ($K_{ow}$) of absorbed styrene is 2.95 (the log value), which shows that styrene is a lipophilic substance. Styrene is slowly excreted (half-life, 2–4 days) after accumulation in adipose tissues and causes toxicity after metabolization into styrene-7, 8-epoxide [16]. Excretion of styrene mainly occurs through the urine, but a small fraction (1%) occurs via a pulmonary route. Mandelic acid (MA) and phenylglyoxylic acid (PGA) are the major metabolites of styrene and are found in urine. Moreover, MA is metabolized into PGA [17].

The threshold limit value time-weighted average (TLV-TWA) is 20 ppm (85 mg/m$^3$) in Republic of Korea, Germany, and Japan. The biological exposure index (BEI) is evaluated as the total urinary metabolites (MA + PGA) in Germany and Japan and is set as 600 and 430 mg MA + PGA/g creatinine, respectively. Furthermore, the American Conference of Governmental Industrial Hygienists (ACGIH) recommends monitoring MA + PGA in urine as an indicator of exposure to styrene, and the value of 400 mg/g creatinine is recommended as a BEI, which corresponds to a TLV-TWA of 20 ppm. The previous BEI was 800 mg MA/g creatinine or 240 mg PGA/g creatinine until 2016 when the BEI was revised in Republic of Korea. As for the correlation between airborne styrene and MA/PGA concentrations in urine, some studies showed higher correlations when MA and PGA were combined for assessment (MA + PGA) than when they were assessed individually [18,19]. A study by the Occupational Safety and Health Research Institute (OSHRI, 2010) also suggested using the sum of MA and PGA (400 mg/g creatinine) when they were assessed individually [20,21]. Results of the study were explained to the participants, and written consents were obtained (No: Occupational Health Research-2013-11) of the OSHRI. The objective of the study was to examine the suitability of urinary MA + PGA as an indicator of exposure to styrene and to propose the BEI for the TLV of 20 ppm.

2. Materials and methods

2.1. Participants

The participants of this study were 36 workers from five manufacturing industries handling styrene from March 2013 to September 2013. Twenty office workers who were not occupationally exposed to styrene were selected as the nonexposure group for the study. The five manufacturing industries consisted of shipbuilding (1), manufacturing of ship components (1), and manufacturing of plastic products (3) as an open operation. The type of industry and process, major tasks and products, and number of workers divided by tasks are presented in Table 1.

2.2. Air sampling

Airborne styrene was collected using a personal sampling pump (LFS-113DC; Gilian, USA) and continuously measured for 6 hours at a flow rate of 0.1 L/min according to the KOSHA guidelines [A-70-2012] [22]. Subsequently, the activated charcoal tubes were sealed at both ends and transported, and the samples were analyzed within 3 days. In the meantime, they were stored in a 5 °C refrigerator.

Urine samples were collected from the workers at the end of shift. To minimize sample loss, they were transported in 20-ml glass vials inside an icebox, refrigerated, and analyzed within 3 days.

2.3. Sample analysis

Airborne styrene was pretreated according to the National Institute for Occupational Safety and Health method #1501 and analyzed by gas chromatography (456-GC; Bruker, Billerica, USA), attached to a flame ionization detector [23].

MA and PGA in urine were analyzed by high-performance liquid chromatography (Ultimate 3000; Dionex, Germering, Germany), attached to an ultraviolet detector according to the Standard of BEI and Analytical Method I (2010), developed by the OSHRI of the KOSHA [20].

2.4. Institutional review board

This study was approved by the Institutional Review Board (No: Occupational Health Research-2013-11) of the OSHRI. The objective of the study was explained to the participants, and written consents were obtained.

2.5. Survey

Characteristics such as gender, age, work period, smoking, drinking, and body mass index (BMI) of the participants were

| Classification | Exposed group (n = 36) | Nonexposed group (n = 20) |
|----------------|------------------------|--------------------------|
| Sex            |                        |                          |
| Male           | 30 (83.3)              | 10 (50.0)                |
| Female         | 6 (16.7)               | 10 (50.0)                |
| Age            |                        |                          |
| 20–29          | 9 (25.0)               | 10 (50.0)                |
| 30–39          | 9 (25.0)               | 6 (30.0)                 |
| 40–49          | 6 (16.7)               | 2 (10.0)                 |
| 50–59          | 4 (11.1)               | 1 (5.0)                  |
| ≥60            | 8 (22.2)               | 1 (5.0)                  |
| Smoking (cigarettes on sampling day, unit) | | |
| Non-smoking    | 28 (77.8)              | 14 (70.0)                |
| 1–10           | 1 (2.8)                | 2 (10.0)                 |
| ≥11            | 7 (19.4)               | 4 (20.0)                 |
| Drinking (the day before sampling) | | |
| Yes            | 14 (38.9)              | 3 (15.0)                 |
| No             | 21 (58.3)              | 16 (80.0)                |
| Nonresponse    | 1 (2.8)                | 1 (5.0)                  |
| Work period (months) | | |
| <25            | 17 (47.2)              | 2 (10.0)                 |
| ≥25            | 13 (36.1)              | 14 (70.0)                |
| Nonresponse    | 6 (16.7)               | 4 (20.0)                 |

Table 1

Characteristics of the five studied sites

| Type of industry (N) | Type of process | Major tasks | Products | Workers |
|----------------------|-----------------|-------------|----------|---------|
| Shipbuilding (1)     | Open            | Laminating  | Synthetic resin ships | 3 |
| Manufacture of ship components (1) | Open | Laminating | Panel | 5 |
| Manufacture of plastic products (3) | Open | Molding Coating | BMC Bathub | 7 |
|                      |                 | Laminating  | Refrigerating plant   | 14 |
|                      |                 | Cutting     | Bathub              | 1 |
|                      |                 | Combining of molds Mixing | Bathub | 4 |

BMC, bulk molding compound.
investigated in the form of face-to-face interviews to understand the characteristics of the study participants.

2.6. Statistical analysis

Data analysis was conducted using Microsoft Excel 2010 and SPSS 21.0 software (IBM Corp., Armonk, New York, USA). Airborne styrene, urinary MA, and MA+PGA concentrations were log-normally distributed, but the distribution of urinary PGA was found to be skewed according to the Shapiro–Wilk normality test. A Mann–Whitney U test was performed to compare the mean concentrations of airborne styrene and the urinary metabolites, and Pearson’s correlation analysis was performed using the natural logarithms (ln) of the values. A simple linear regression analysis was used to predict the concentration of total urinary metabolites (MA + PGA), and multiple regression analysis was performed to evaluate the effect of smoking, drinking, and BMI.

3. Results

3.1. Characteristics of participants

The exposure group consisted mainly of men (30, 83.3%), and the nonexposure group consisted of 10 men and 10 women. The average age of the participants was 42.6 years in the exposure group and 34.3 years in the nonexposure group. Twenty-eight (77.8%) individuals from the exposure group and 14 (70.0%) from the nonexposure group were nonsmokers, showing that there were more nonsmokers in both the groups. The percentage of the participants who did not drink on the day before the measurement was higher in both the groups (exposure group, 58.3%; nonexposure group, 80.0%), and the mean styrene exposure period was 47.5 ± 54.8 months in the exposure group (Table 2).

3.2. Concentrations of airborne styrene and urinary metabolites (MA, PGA, and MA+PGA)

Table 3 shows the concentrations of airborne styrene and styrene metabolites (MA and PGA) in urine. The geometric mean concentration was 9.6 ppm with the range of 0.45–56.1 ppm. The geometric mean concentration of urinary MA was 267.7 mg/g creatinine in the exposure group (n = 36) and 8.6 mg/g creatinine in the nonexposure group (n = 20), with a statistically significant difference between the two groups (p < 0.001). The geometric mean concentration of urinary PGA was 143.3 mg/g creatinine in the exposure group and 14.4 mg/g creatinine in the nonexposure group (p < 0.001). The geometric mean concentration of urinary MA + PGA was 416.8 mg/g creatinine in the exposure group and 38.1 mg/g creatinine in the nonexposure group (p < 0.001).

3.3. Correlation analysis between styrene exposure and biological indicators

Fig. 1 compares the correlation of airborne styrene concentration and biological indicators. The correlation coefficients (r) between the concentration of airborne styrene and concentrations of urinary MA, PGA, and MA + PGA were 0.714, 0.604, and 0.769, respectively. The correlation was statistically significant (n = 56, p < 0.001). The correlation of MA + PGA was higher than that of MA or PGA.

3.4. Prediction of biological exposure index for 20 ppm of styrene

Simple regression analysis was used in this study to predict the concentration of urinary MA + PGA at 20 ppm, which is the concentration for current BEI for airborne styrene in Republic of Korea. The analysis predicted that the concentration of urinary MA + PGA would be 603.4 mg/g creatinine when the concentration of styrene in air is 20 ppm (Fig. 2).

3.5. Analysis of factors influencing styrene metabolites in urine

Multiple regression analysis was performed to assess the effects of smoking, drinking, and BMI on the concentrations of urinary MA and PGA. The effects of smoking, drinking, and BMI were analyzed after the adjustment of airborne styrene, which could have the largest effect on the concentrations of styrene metabolites in urine (MA and PGA). Concentrations of urinary MA, PGA, and MA + PGA decreased as smoking increased, but the difference was not statistically significant. Concentrations of urinary MA, PGA, and MA + PGA increased as drinking and BMI increased, but the changes were not statistically significant (Table 4).

4. Discussion

The purpose of this study was to provide logical backgrounds for establishing the BEI of Republic of Korea corresponding to the exposure of 20 ppm of styrene. Correlation analysis to test the effectiveness of biological determinants of airborne styrene showed that the correlation coefficients for airborne styrene and urinary MA, PGA, and MA + PGA were 0.714, 0.604, and 0.769, respectively (n = 56, p < 0.001), with MA + PGA showing the highest correlation. Previous study results also indicated that the correlation with airborne styrene was higher when urinary MA + PGA was evaluated than when urinary MA and PGA were evaluated individually [24–28,19].

The sum of urinary MA and PGA is suggested as an indicator of exposure to styrene in Germany and Japan. The ACCIH recommends monitoring urinary MA + PGA as an indicator of styrene, and Republic of Korea has also recommended it since 2016. If urinary MA or PGA levels were used for evaluation according to the

| Parameters | Exposed group (n = 36) | Nonexposed group (n = 20) | p* |
|------------|-----------------------|--------------------------|----|
|            | GM (GSD)              | AM ± SD                  | Range | GM (GSD)              | AM ± SD                  | Median | Range | p*     |
| Urinary MA (mg/g creatinine) | 267.7 (2.5) | 403.3 ± 414.1 | 258.2 | 46.4–1,611.0 | 8.6 (6.6) | 21.58 ± 22.78 | 15.3 | 0.1–82.6 | <0.001 |
| Urinary PGA (mg/g creatinine) | 143.3 (2.7) | 205.0 ± 151.3 | 206.9 | 12.5–579.1 | 14.4 (5.7) | 27.65 ± 30.19 | 21.3 | 0.03–139.6 | <0.001 |
| Urinary MA + PGA (mg/g creatinine) | 416.8 (2.5) | 608.3 ± 558.0 | 425.9 | 58.9–2,174 | 38.1 (2.0) | 49.23 ± 45.44 | 39.0 | 8.3–222.1 | <0.001 |

* Mann–Whitney U test.

AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation; MA, mandelic acid; PGA, phenylglyoxylic acid; SD, standard deviation.
previous BEI in Republic of Korea, the results may vary depending on the biological determinants applied. In other words, if only one of the two determinants exceeds the standard, confusion may arise as to which determinant represents the true situation. This is not specifically addressed even in the Worker’s Health Examination Practice Guidelines (2013), which makes it challenging to present the result [29]. About 85% and 10% of the total amount of absorbed styrene are excreted as MA and PGA, respectively, and the styrene glycol is oxidized to MA and then to PGA in the metabolism of styrene [17]. Hence, using MA + PGA, which is closer to the total amount of metabolites excreted instead of using either MA or PGA, is likely to be more accurate for evaluation.

Fig. 1. Coefficients for the correlation between airborne styrene and mandelic acid (MA), phenylglyoxylic acid (PGA), and mandelic acid plus phenylglyoxylic acid in urine.

Fig. 2. Sum of mandelic acid and phenylglyoxylic acid concentrations in urine at the end of a shift in humans exposed to 20 ppm of styrene (n = 56).
Table 4

| Variables | Urinary MA | Urinary PGA | Urinary MA + PGA |
|-----------|------------|-------------|-----------------|
|           | B         | β          | B              | β            |
| Constant  | 1.688     | 2.555      | 3.601           |
| Styrene   | 1.023     | 0.698***   | 0.768           | 0.603***     |
|           | -0.013    | -0.061***  | -0.049**       | -0.271**     |
| Alcohol   | 0.325     | 0.071      | 0.893           | 0.224        |
| BMI       | 0.055     | 0.085      | 0.022           | 0.039        |
| R²        | 0.517     | 0.421      | 0.587           |
| F         | 12.035    | 18.800     | 16.002          |
| p-value   | <0.001    | <0.001     | <0.001          |

***, p < 0.001.

BMI, body mass index; MA, mandelic acid; PGA, phenylglyoxylic acid.

We used regression analysis for MA + PGA, which was shown to have the highest correlation among the biological determinants of styrene exposure, and predicted the concentration of total metabolites (MA + PGA) at 20 ppm, which is the BEI for airborne styrene in Republic of Korea. The result showed that the concentration of MA + PGA was 603.4 mg/g creatinine, which was different from the indices of the ACCIH (400 mg/g creatinine) and Japan (430 mg/g creatinine), but was similar to that of Germany (600 mg/g creatinine). In the ACCIH, the value of BEI was similarly reduced to 40% of the previous BEIs of 800 mg MA/g of creatinine and 240 mg PGA/g of creatinine because the TLV-TWA of styrene was reduced by 40% from 50 ppm to 20 ppm. Therefore, 400 mg MA + PGA/g of creatinine was established as the biological tolerance value for occupational exposure to styrene in Germany [30]. Urinary concentration of MA + PGA from other studies with 20 ppm airborne styrene was 400–445 mg/g creatinine, which was lower than in our study result [31–33,19].

At an airborne styrene concentration of 8.6–17.4 ppm, the concentration of urinary MA was predicted to be 418.5–422.4 mg/g creatinine as the BEI for airborne styrene in Republic of Korea (20 ppm) [1,26]. On the other hand, for a concentration of 10.4–18.2 ppm, which is similar to that in Republic of Korea, the predicted concentration of urinary MA was 303–307 mg/g creatinine at 20 ppm in some countries such as Singapore [19] and Belgium [33], showing a tendency of lower urinary MA than in Republic of Korea despite similar exposure. Some reports suggested that smoking, drinking, and BMI could affect the concentration of styrene metabolites [34,127], but the aforementioned three variables showed no significant effects in our results, and Lee et al. (2002) also showed no significant difference between the exposure group and nonexposure group in terms of weight, height, BMI, drinking, and smoking [35]. Other factors that can affect the concentration of styrene metabolites include simultaneous organic solvent exposure (acetone, toluene, etc.), intensity of work, level of exposure, climate, genetic factors, and ethnicity, which may contribute to the difference in concentrations between Republic of Korea and other countries [36,37,28]. In particular, the metabolism of MA and PGA is largely affected by the level of exposure, sampling time, and ethnic differences between Asians and Caucasians, and the differences in physiological parameters concerning the metabolic rate may cause variations in concentrations which can be predicted based on the concentration of airborne styrene [17].

However, our study has a limitation. The participants of this study were not exposed to styrene exclusively and were simultaneously exposed to other chemicals, such as methyl ethyl ketone (0.33 ± 0.23 ppm), methyl isobutyl ketone (2.59 ± 2.89 ppm), and acetone (6.09 ± 5.33 ppm). When workers are directly or indirectly exposed to other chemical substances that have structures similar to those of ethyl benzene, styrene glycol, styrene oxide, methyl phenyl ketone, α-phenylaminocetic acid, phenacetinic acid, phenylglyoxylic acid, and phenylglycol, they are excreted as MA and PGA in the urine, thereby increasing the concentration of urinary metabolites, but conflicting solvents such as toluene, xylene, and trichloroethylene can affect and decrease the concentration of urinary metabolites [17]. Besides, the simultaneous exposure to acetone slows down styrene excretion [38]. However, the exposed chemicals and their concentrations were different depending on the participants, and the concentrations were very low. The MA + PGA in urine is recommended as a biological indicator of exposure to ethyl benzene as well as styrene. Because we controlled ethyl benzene, which has the same urinary metabolites as styrene, we believe that a more accurate result was obtained. The range of concentrations that can be explained by regression in this study is 0–56.1 ppm, a wide exposure range from low to high concentrations. Therefore, it is considered favorable to estimate the concentration that corresponds to 20 ppm, which is the accepted Korean occupational exposure limit.

Considering the results from other studies as well as those of our study, the metabolic processing of styrene, and BEI in other countries, it was more suitable to evaluate the biological monitoring of styrene using urinary MA + PGA than using MA or PGA individually for the evaluation. In addition, based on the effects of numerous variables and the results of our study, we suggested the MA + PGA of 600 mg/g creatinine for the BEI of styrene in Republic of Korea.

5. Conclusion

To evaluate the suitability of BEI for styrene, air samples and urine samples of workers were collected and analyzed according to the standardized methods of the KOSHA guidelines and the National Institute for Occupational Safety and Health. The concentration of airborne styrene showed a wide distribution from 0 to 56.1 ppm, and based on this, the concentration of urinary MA + PGA at 20 ppm styrene could be predicted more accurately using regression.

In the correlation between airborne styrene and urinary metabolites, urinary MA + PGA showed a higher correlation than MA or PGA alone, and previous reports also showed a higher correlation when the sum was used for evaluation. The urinary MA + PGA has already been recommended as a biological determinant of styrene in other countries, and the previous BEI for styrene in Republic of Korea may cause confusion when evaluating biological exposures because of the styrene glycol being oxidized to MA and then to PGA in the metabolism of styrene; therefore, based on the effects of numerous variables and the results of our study, it was considered appropriate to amend the concentration of urinary MA + PGA levels to 600 mg/g creatinine as a BEI, which corresponds to an airborne styrene concentration of 20 ppm in Republic of Korea.

Conflict of interest

The authors declare that they have no conflict of interest.

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