Kinetics of styrene in workers from a plastics industry after controlled exposure: a comparison with subjects not previously exposed

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ABSTRACT Eight male workers from a glass reinforced plastics industry were experimentally exposed for 2 hours to 2.84 mmol/m³ (296 mg/m³) styrene during light physical exercise (50 W). About 63% of the amount supplied (4.6 mmol styrene) was taken up in the body. The arterial blood concentration of styrene reached a relatively stable level of 15 µmol/l at the end of exposure which was about 70% of the blood concentration in a group of volunteers with no previous exposure to solvents. The apparent blood clearance was significantly higher in the occupationally exposed subjects 2.01/h × kg compared with 1.51/h × kg. Contrary to the relatively stable level of styrene at the end of exposure the concentration of non-conjugated styrene glycol increased throughout the exposure and reached about 3 µmol/l in both groups. Like styrene, the non-conjugated styrene glycol seemed to be eliminated faster from the occupationally exposed workers. The blood concentration of styrene-7,8-oxide was low and seldom exceeded the detection limit of 0.02 µmol/l. The results show that long term exposure in a glass reinforced plastics industry may facilitate the metabolism of styrene.

The most extensive exposures to styrene (vinylbenzene, phenylethylene) occur in plants manufacturing glass reinforced plastics.¹ During lamination by hand the evaporation of styrene is considerable and 60–70% of the amount inspired is taken up in the body.²

The metabolism of styrene takes place in the liver but extrahepatic metabolism has not been ruled out.^{3–7} The first step in the major metabolic pathway is the formation of styrene-7,8-oxide (phenyloxirane), a reaction preferentially catalysed by microsomal cytochrome P-450.^{4,8–10} Styrene-7,8-oxide is hydrated to styrene glycol (1-phenyl-1,2-ethanediol) by microsomal epoxide hydratase and this is conjugated with β-glucuronic acid or oxidised to mandelic acid and further to phenylglyoxylic acid. In man about 90% of a styrene dose is eliminated as mandelic and phenylglyoxylic acids in the urine.⁸ The biotransformation may be stimulated by styrene itself,^{11–13} phenobarbital,^{4,14} or the chronic intake of ethanol¹⁵; it is inhibited by the coadministration of ethanol, toluene, and trichloroethylene.^{16–18}

The main purpose of the present study was to analyse styrene, styrene-7,8-oxide, and styrene glycol in

blood from workers exposed to styrene. We also wished to discover if a long term exposure at a glass reinforced plastics industry modified the elimination of styrene.

Subjects

The volunteers from a plant manufacturing glass reinforced plastics were eight men with an average age of 34 (range 25–47), an average weight of 76 (range 68–105) kg, and an average height of 178 (range 170–188) cm. The amount of body fat of the respective subjects was estimated by means of anthropometric measurements.¹⁹ The mean amount of adipose tissue in the subjects, 18 (SD 13) kg, was estimated from the total amount of body fat on the assumption that the average fat content of adipose tissue is 80%.²⁰ None of the workers was taking medication or had suffered from any disease having a detrimental effect on the function of the respiratory and circulatory organs. They had been employed for seven to 12 years. Four were smokers and three used snuff. The consumption of ethanol was considered moderate. The styrene exposure in the plant ranged from 5 to 125 mg/m³ with a mean level of 44.4 mg/m³ during a week with normal work intensity.

Unsaturated polyester resins containing about 40% styrene as a reactive diluent were used. Organic peroxides were added to regulate the exothermic hardening reaction and acetone was used for cleaning tools.

The volunteers with no previous exposure to solvents² were eight healthy men with an average age of 27 (range 23–34), an average weight of 71 (range 60–80) kg, an average height of 179 (range 174–191) cm, and a mean amount of adipose tissue of 12 (SD 7) kg. Three were smokers and the consumption of ethanol was low. None was taking any medicine.

Methods

The experimental exposure of workers took place on a Friday morning after occupational exposure during the preceding days of the week. The subjects were exposed in pairs for two hours to a styrene concentration of 2.84 (SD 0.07) mmol/m³ (296 mg/m³) (Merck, analytical grade). The Swedish short term exposure limit concentration is 2.88 mmol/m³ (300 mg/m³). The exposures were performed in an exposure chamber (volume 12 m³, air change 10 times/h, inlet air flow 115 m³/h, outlet air flow 135 m³/h) during light physical exercise (work load of 50 W) on a bicycle ergometer. Solvent was injected in the influent air stream by means of a high performance liquid chromatography pump (Gilson 302) and the concentration in the chamber was continuously monitored by an infrared spectrophotometer (Miran 1A) at 11.1 μ m, sampling air from the upper central section of the chamber. The air in the chamber was at the desired concentration when the volunteers entered. The exposure of the reference subjects took place in the same exposure chamber under identical conditions (2 h, 2.84 mmol/m³, 50 W) and has been described earlier.²

The respiratory uptake of styrene was determined in each individual using the Douglas bag technique. The exhaled air was collected during four minutes at regular intervals, and the uptake during each 30 minute period was calculated from the mean value of two sampling periods during this time. The methods for determining the styrene concentration in the inspired and expired air and the measurements of the solvent uptake were basically the same as described elsewhere.²¹ The error of the method was estimated to be $\pm 3\%$.

Arterial blood samples were withdrawn from a catheter introduced into a brachial artery. For the analysis of styrene in blood, samples of 1 ml were equilibrated with air at 37°C for 20 minutes in citrate treated headspace bottles. Headspace air was analysed for styrene by gas chromatography (3% SE-30

on Chromosorb GAW, 2.0 m, 130°C, nitrogen flow 20 ml/min, flame ionisation detector, Perkin Elmer F 45). The peak area was integrated (Varian Vista 401 chromatography data system). Individual calibration curves were obtained by adding 2 μ l of standard solutions of styrene in dimethylsulphoxide (Merck, analytical grade) to blood sampled before exposure (2 μ l of dimethylsulphoxide was added to all samples taken during and after exposure). The error of the method at concentrations below 6 μ mol/l was estimated to be $\pm 7\%$.

An apparent styrene clearance, Cl_{app} , was calculated for each subject as the dose of styrene divided by AUC (area under the blood concentration versus time curve). The total uptake was regarded as the dose as the solvent rapidly diffuses into the blood. AUC for the exposure period was calculated by the trapezoidal rule. For the elimination phase, AUC was calculated by integration of the equation, $y = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$ where y is the solvent concentration in the blood, t represents the time, A and B are the y intercepts, and α and β are the slopes of the lines.

Styrene-7,8-oxide and styrene glycol in blood were analysed after an extraction procedure (fig 1). Each blood sample (2 ml) was extracted with hexane (Merck, analytical grade) to remove styrene-7,8-oxide

Fig 1 Scheme for extraction of styrene-7,8-oxide (step 1), styrene glycol (step 2), and conjugated styrene glycol (step 3) from blood. Allylbenzene glycol (ABG) was used as an internal standard. Styrene-7,8-oxide was hydrolysed with sulphuric acid (H₂SO₄) to styrene glycol (step 4). Ethyl acetate extracts were treated with pentafluorobenzoyl chloride and analysed by gas liquid chromatography with an electron capture detector (EC). (NaOH = sodium hydroxide.)

(fig 1, step 1) and then with ethyl acetate (Merck, analytical grade) to remove styrene glycol (fig 1, step 2). Conjugated styrene glycol was cleaved with β -glucuronidase type H-1 (Sigma) in 0.07 M acetate buffer pH 5.0 at 37°C overnight (fig 1, step 3). Allylbenzene glycol (synthesised according to Duverger-van Bogaert *et al*)²² was added as the internal standard before the extraction with ethyl acetate. Acidification converted styrene-7,8-oxide to styrene glycol (fig 1, step 4). The ethyl acetate extracts were derivatised with pentafluorobenzoyl chloride (Aldrich 98%) and analysed by a gas chromatographic technique based on electron capture detection.²² In the determination of styrene-7,8-oxide and non-conjugated styrene glycol the conditions were: 3% SE-30 on Chromosorb GAW-DMCS, 2.0 m, 220°C, nitrogen flow 50 ml/min, Carlo Erba FTV 2350. Both styrene-7,8-oxide and enzymatically liberated styrene glycol were analysed on a capillary column (BP-1-0.25, 0.2 mm $\times$ 12 m, 230°C, helium flow 1.5 ml/min, Carlo Erba FTV 2350). The peak areas were integrated (Varian Vista 401 chromatography data system). Calibration curves were obtained by adding 10 μ l of standard solutions of styrene-7,8-oxide (Fluka AG, Buchs SG >97% purity, distilled) or styrene glycol (Aldrich, 97% purity) in toluene to blood before extraction. The blood concentration range was 0–1 μ mol/l for styrene-7,8-oxide, 0–10 μ mol/l for styrene glycol, and 0–1 μ mol/l for conjugated styrene glycol. The calibration curves were linear for the concentration range in question and could be applied down to a concentration of 0.02 μ mol/l for styrene-7,8-oxide, 0.08 μ mol/l for styrene glycol, and 0.02 μ mol/l for conjugated styrene glycol. No

detectable contamination with styrene glycol in the hexane extract occurs in the actual concentration range.² The error of the estimation of styrene glycol was $\pm 15\%$ at concentrations below 1 μ mol/l and $\pm 7.3\%$ at concentrations between 1.5–5.1 μ mol/l.

The calculation of the errors of the methods for a single determination was based on the differences between double determinations and expressed as the percentage of the value of the mean. The significance of differences between mean values was tested by Student's *t* test for independent observations; *p* < 0.05 was chosen as the level of significance.

Results

The total uptake of styrene in the pre-exposed volunteers was 4.6 (SD 0.5) mmol or 63 (SD 3)% of the amount supplied (table 1). The relative uptake was significantly lower than that found in the non-occupationally exposed subjects but a higher pulmonary ventilation per time unit equalised the total uptake.

At the start of the exposure the arterial blood concentration of styrene was 0.3 (SD 0.2) μ mol/l in the occupationally pre-exposed subjects (fig 2). A steady state level was almost reached after 75 minutes of exposure as seen previously in the reference group. The styrene concentration was significantly lower in the pre-exposed group both during the exposure and the following 30 minutes. At the termination of exposure the mean concentration was 14.7 (SD 2.9) μ mol/l in the pre-exposed group and 21.2 (SD 6.9) μ mol/l in the reference group (table 2). The pre-

Table 1 Values of pulmonary ventilation ($\dot{V}_E$), inhaled amount of styrene, total uptake of styrene (U_i), and the relative uptake of styrene (F) for each 30 minute period

Time period (min)	$\dot{V}_E$ BTPS* (l/min) (n = 8)		Inhaled amount (mmol) (n = 8)		Uptake (U_i)† (mmol) (n = 8)		Uptake in % of the inhaled amount (F)‡ (n = 8)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Pre-exposed subjects								
0–30	23.2	2.6	1.83	0.22	1.19	0.12	65.7	2.5
30–60	23.2	2.3	1.81	0.17	1.14	0.12	62.9	3.1
60–90	23.5	2.0	1.82	0.17	1.12	0.13	61.3	3.1
90–120	23.7	2.2	1.84	0.19	1.12	0.13	60.5	2.8
0–120	23.4	2.1	7.31	0.68	4.57	0.46	62.6	2.8
Reference subjects²								
0–30	19.8	2.6	1.56	0.20	1.10	0.14	70.9	3.9
30–60	20.6	2.4	1.64	0.20	1.10	0.12	67.3	4.2
60–90	20.6	2.2	1.65	0.18	1.11	0.14	67.3	4.6
90–120	21.5	2.9	1.71	0.25	1.13	0.17	66.1	5.0
0–120	20.6	2.2	6.56	0.73	4.44	0.52	67.9	4.3

* $\dot{V}_E$ BTPS = pulmonary ventilation per time unit, 37°C ambient pressure, saturated with water.

† $U_i = \dot{V}_E \times t \times (C_{in} - C_{ex})$; *t* = duration of exposure, C_{in} = solvent concentration in inspired air, C_{ex} = solvent concentration in expired air.

‡ $F = (C_{in} - C_{ex}) \times 100/C_{in}$.

Fig 2 Concentration of styrene in arterial blood during and after exposure to styrene for two hours during physical exercise with a work load of 50 W. (○) represents mean values and standard deviations for eight male workers from a glass reinforced plastics industry after exposure to 2.84 mmol/m³ styrene. (●) represents mean values for seven male volunteers not earlier exposed to solvents after exposure to 2.88 mmol/m³ styrene.

Table 2 Arterial blood concentrations of styrene and non-conjugated styrene glycol at the end of exposure, apparent styrene clearance (Cl_{app}) and half time of non-conjugated styrene glycol in arterial blood ($t_{1/2}SG$)

	Pre-exposed subjects (n = 8)		Reference subjects ² (n = 7)	
	Mean	SD	Mean	SD
Styrene (μmol/l)	14.7	2.9	21.2	6.9
Non-conjugated styrene glycol (μmol/l)	2.8	0.96	3.0	1.1
Cl_{app} * l/h·kg	2.0	0.4	1.5	0.3
$t_{1/2}SG$ (min)	47.0	13.3	72.1	13.3

* Cl_{app} = total uptake/AUC; AUC = area under blood concentration v time curve.

exposed group had a significantly higher apparent clearance 2.0 (SD 0.4) l/h·kg compared with 1.5 (SD 0.3) l/h·kg for the reference group (table 2).

The concentration of non-conjugated styrene glycol in the blood rose continuously during the exposure and reached about 3 μmol/l irrespective of pre-exposure (fig 3, table 2). One to two hours after the termination of exposure the concentration of non-conjugated styrene glycol was significantly lower in the occupationally pre-exposed group. The elimination of styrene glycol was considered to be mono-exponential. The mean $t_{1/2}$ was significantly lower

than that reported for the reference group (table 2). The amount of styrene glycol conjugated with β-glucuronic acid was significantly higher in the pre-exposed group compared with the reference group both during and after the exposure (table 3). When the total concentration of styrene glycol was compared, no significant difference was noted in the two groups.

A maximum concentration of styrene-7,8-oxide was determined to 0.03 μmol/l, both with the packed and the capillary columns, in the pre-exposed subjects.

Fig 3 Concentration of non-conjugated styrene glycol in arterial blood during and after exposure to styrene for two hours during physical exercise with a work load of 50 W. (○) represents mean values and standard deviations for seven male workers from a glass reinforced plastics industry after exposure to 2.84 mmol/m³ styrene. (●) represents mean values for seven male volunteers not earlier exposed to solvents after exposure to 2.88 mmol/m³ styrene.

Table 3 Percentage of styrene glycol conjugated with β-glucuronic acid

Time (min) (after onset of exposure)	Pre-exposed subjects (%) (n = 7)	Reference subjects (%) (n = 7)
60	40.8 ± 18.5	21.3 ± 5.8
120	41.9 ± 11.5	21.9 ± 5.9
180	59.6 ± 13.8	21.8 ± 7.9
240	62.8 ± 9.4	27.3 ± 8.4

Discussion

The relative uptake of styrene in the occupationally exposed subjects was similar to that reported earlier after occupational exposure²³ and lower than that found in subjects with no previous exposure. To some extent the difference in the relative uptake may be explained by the difference in pulmonary ventilation and in age. If dependent on the history of exposure it may be caused by different adsorption on and desorption from the walls of respiratory airways.²⁴

A significantly lower blood concentration over time in the pre-exposed subjects as compared with the reference group after identical external exposure and total uptake must result from an increased clearance or a higher volume of distribution of styrene in the former subjects. Ramsey *et al* have reported a half time of 13 hours for the terminal phase^{25, 26} which means that the area under the blood concentration versus time curve is underestimated and consequently Cl_{app} exceeds systemic clearance. The calculated Cl_{app}

values for styrene are of the same order as the total blood flow through the liver.²⁷ Extrahepatic metabolism³⁻⁷ and uptake by adipose tissues may also contribute to the apparent clearance. Most tissues, except adipose tissue, may be considered almost equilibrated with regard to styrene at the end of a two hour exposure at 50 W. In the reference study the concentration of styrene in adipose tissue was measured and the systemic clearance calculated to be 1.3 l/h·kg.^{2, 28} A similar clearance value was obtained from the data presented by others.^{26, 29} The systemic clearance for the pre-exposed group may be calculated to be 1.8 l/h·kg assuming a corresponding distribution of styrene to adipose tissue as in the reference group—that is, 10–15% of the total uptake.² The stated difference in amount of adipose tissue between the groups was eliminated if the most obese subject was excluded. Then the amount of adipose tissue was 14 (SD 6) kg. This indicates that the higher clearance in the pre-exposed subjects did not depend on distribution to adipose tissue. In the group as a whole a tendency towards higher clearance in lean subjects was observed. The subject in the pre-exposed group with the largest amount of adipose tissue had the lowest clearance. An increased clearance due to facilitated metabolism was also supported by the fact that the lowest clearance was seen in the oldest workers. No tendency for a higher clearance in smokers was seen.

A higher systemic clearance of styrene in the pre-exposed group may reflect a metabolic adaptation of the body. A decreased accumulation of styrene in rat

tissue has been shown after prolonged exposure and a decreased half time of mandelic acid excretion in workers exposed to high styrene concentrations ($> 600 \text{ mg/m}^3$).³⁰⁻³³ Because of the long half time of styrene in subcutaneous adipose tissue, 2.2–5.2 days,^{23,34} the workers are continuously exposed to styrene. The concentration of styrene in adipose tissue has actually been shown to increase during a working week.²³

During exposure the concentration of non-conjugated styrene glycol in the blood was similar in both the pre-exposed and the reference group but after the exposure had ceased a more rapid elimination was seen in the pre-exposed group. One route of elimination is conjugation with glucuronic acid and this glucuronide accumulated in the pre-exposed subjects may be due to an increased activity of UDP-glucuronosyltransferase. Daily intraperitoneal doses of 500 mg/kg of styrene or inhalation of 450 ppm of styrene for seven days increase the activity of UDP-glucuronosyltransferase in the rat liver.^{12,13} It is not possible to say if there was also an accumulation or a facilitated production of the oxidised products of styrene glycol as these acidic metabolites were not analysed.

The concentration of styrene-7,8-oxide was low and never exceeded $0.03 \mu\text{mol/l}$ in the blood of the occupationally exposed group. The lower limit for detection was estimated to be $0.02 \mu\text{mol/l}$ depending on some blood component with the same retention time both on the packed and the capillary column. Enzymatic studies in rats have shown an increased activity of epoxide hydratase after exposure to styrene.^{13,35} If this is applicable to man styrene-7,8-oxide levels would be expected to decrease more quickly after long term exposure to styrene.

These results show that long term exposure at a glass reinforced plastics industry may facilitate the metabolism of styrene. Both styrene and non-conjugated styrene glycol were eliminated faster from occupationally exposed workers than from volunteers with no previous exposure to solvents. Nevertheless, it cannot be excluded that some component other than styrene in the work environment—for example acetone¹¹ or other factors—may contribute to the higher clearance of the solvent.

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