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Toluene in venous blood during and after work in rotogravure printing

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Summary. Toluene exposure was studied in 62 male rotogravure printers, employed in three plants. The exposure level as measured by personal sampling during a week ranged from 8 to 1080 mg/m^3 (median 96). The concentration of toluene in venous blood sampled directly after work correlated significantly with the time-weighted average (TWA) for toluene in air during the preceding workshift ($n = 57$, Spearman's $r = 0.84$, $P < 0.00001$). The post-shift toluene level in venous blood is usable for biological monitoring of exposure. An air level of 100 mg/m^3 corresponds to an average blood toluene level of 2.9 μmol/l; an air level of 300 mg/m^3 to 8.2 μmol/l. The elimination of toluene is slow. Thus, toluene was detected in most Monday pre-shift blood samples and the levels increased statistically significantly during the work week (median 0.21 versus 0.42 μmol/l, $P < 0.0001$). The toluene level in venous blood sampled directly before work on Thursday/Friday was found to be a function of the estimated mean exposure during the work week. In a multiple linear regression analysis, the mean exposure during the week was a good predictor for the concentration of toluene in venous blood before work at the end of the week ($n = 52$, $r = 0.71$). Thus, pre-shift blood values at the end of the week can be used as a biological index for the weekly exposure, when the variation of the ambient toluene concentration is known. The slow decrease of toluene in venous blood was followed in six workers for two weeks after cessation of exposure. Two of them still had detectable amounts of toluene in blood after 13 d (detection limit = 0.01 μmol/l).

Key words: Accumulation – Biological monitoring – Elimination – Solvent exposure

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Introduction

Toluene is widely used as a solvent for paint, lacquer, varnish and glue and in synthesis of many organic chemicals. The solubility of solvents in blood and other tissues is of great importance for the total uptake via the lungs in the body (Åstrand 1975). Workload and skin absorption are, however, also important to consider when the total uptake of exposed subjects is being estimated. Considering this fact, monitoring solvent concentration in the respiratory zone is not a sufficient measure for total exposure. A biologic exposure parameter is needed as well. Knowledge of uptake, distribution and elimination of solvents in man is necessary to interpret such an index. For toluene these factors have previously been studied under experimental conditions (Veulemans and Masschelein 1978; Carlsson 1982; Wallén 1986). To choose the most adequate biologic index of occupational exposure and its best sampling time further studies on workers repeatedly exposed to toluene for several years are needed. Apostoli et al. (1982) studied 20 workers in a furniture factory exposed to mixtures of solvents. Toluene was present in all varnishes used. Environmental concentration of toluene, determined on Friday afternoon only, correlated with both the toluene level in venous blood (B-toluene) and the urine metabolite o-cresol.

The relationship between B-toluene and environmental toluene exposure during one workshift has been previously studied in different workplaces as well (Brugnone et al. 1986). They found a statistically significant correlation between toluene concentration in ambient air and B-toluene sampled immediately after the shift. The environmental concentration also correlated with next day pre-shift B-toluene. In the papers by Apostoli and Brugnone no information

about the variation of the toluene exposure is given. Such data are needed to generalize the statistically significant covariations.

In the present study a group of rotogravure printers were followed by detailed air monitoring during a work week. Blood levels of toluene were determined during work and followed two weeks after cessation of exposure.

Subjects and methods

Subjects

Toluene in ambient air and venous blood was measured in 62 subjects working in three rotogravure printing plants (A, B, C). Their ages were 22 to 62 years (median 46). The age distribution of the workers was similar in the three plants. The time of employment ranged from 2 to 43 years (median 24). The workers' health, use of drugs, smoking habits, and alcohol consumption were checked. Plants A and B had two workshifts of 8 h, while Plant C had three workshifts of 6 h.

Environmental air samples

Environmental concentration of toluene was followed with personal sampling. We followed 5 to 7 workers on each shift during a week. They wore personal samplers with which samples were continuously taken from the ambient air at 30-min intervals (The Linder Gaspirator, Instrument AB Lambda, Sweden). The samplers sucked air from the subjects' respiratory zones through a teflon capillary tube into a 30-ml all-glass syringe (Övrum 1986). The toluene content of the air was determined without delay with a portable gas chromatograph equipped with FID (AID, model 511). Standard gases were prepared by adding known amounts of toluene into glass bottles with a known volume of clean air. The error of the method calculated from 25 double determinations of air ranged from 67 to 335 mg of toluene/m^3, which was ± 1.1% of the mean value.

Venous blood samples

Blood samples were taken from 41 workers (Plants A and B) on Monday and Thursday before start of work and Thursday directly after work. For 21 printers (Plant C) blood was sampled before and after work Monday, Wednesday and Friday. For seven of them we also sampled blood directly after work on Thursday. The pre-shift blood samples were taken before the printers went into the contaminated working area, immediately upon arrival at the plants. Half a year after our investigation at Plant B the work stopped and the printers became unexposed. The elimination of B-toluene after cessation of exposure was followed in six subjects. For an additional five workers we got three blood samples during the same period. The printers stopped working on Friday afternoon. We had no opportunity to follow the rapid decrease of B-toluene during the first hours after exposure. The blood samples were analysed with headspace technique using ethylbenzene as internal standard on a gas chromatograph equipped with FID (Varian model 3700). Standards were made from venous blood, to which known amounts of toluene were added. The detection limit was 0.05 µmol/l when the study started. Further modification of the method decreased the detection limit to 0.01 µmol/l. The error of the method was ± 4%, for B-toluene levels 0.20 and 3.8 µmol/l; the SD was 0.007 and 0.13 respectively.

Statistics

Associations were investigated with multiple linear regression analysis, Spearman's rank correlation coefficient and Wilcoxon's matched pair-test. All *P*-values are two-tailed.

Results

Air levels

We obtained exposure data for seven weeks. In all we have 131 time-weighted averages (TWA) which cover more than 75% of a workshift. Ambient air levels ranged from 8 to 1080 mg/m^3 (median 96) (Table 1). Plant A is modern with good process ventilation and had a considerably lower air level: median 27 mg/m^3 (range 8 to 415 mg/m^3). For the other two plants, the median levels were 126 mg/m^3 (range 84 to 650) and 130 mg/m^3 (range 19 to 1080) respectively. As we followed the workers with consecutive 30-min

Table 1. Time-weighted averages (TWA) of toluene exposure (mg/m^3) in the respiratory zone at Plants A, B, and C. *n* is the number of shifts assessed. The Swedish exposure limit value is 300 mg/m^3 (1986)

Toluene in air			
Plant	*n*	TWA	
		Median	Range
A	42	27	8– 415
B	31	126	84– 650
C	58	130	19–1080
A + B + C	131	96	8–1080

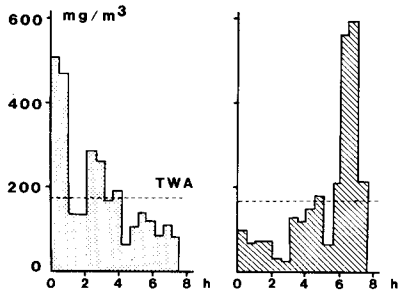

Fig. 1. Two examples of exposure variation during a shift resulting in similar time-weighted averages (TWA), 173 and 167 mg/m^3, but very different post-shift blood toluene levels of 1.9 and 8.0 µmol/l, respectively. The two subjects are marked with stars in Fig. 2

samples, we found that almost the same TWA, 173 and 167 mg/m^3 could show quite a different distribution of the toluene level for each 30-min sample (Fig. 1). The mean exposure of the week was estimated for all printers. The calculation was made by using the workers' own measured exposure levels and those found among other subjects with similar tasks.

Blood levels

In 54 out of 62 blood samples from Monday before the start of work, we could detect toluene, median 0.24 µmol/l (range < 0.05 to 3.6). The pre-shift B-toluene increased significantly from Monday to Thursday/Friday. The median value increased from 0.24 to 0.46 µmol/l (range 0.08 to 3.05, $P = 0.04$, $n = 58$). In Plant A we found three workers with very high B-toluene on Monday before work. They were asked about possible exposure over the weekend, but they could not provide any explanation. Their B-toluene decreased during the week despite their occupational exposure. In Plant B one printer went into a contaminated area before we could take the pre-shift blood sample. One of the shifts in Plant C (seven workers) had worked over the weekend. Excluding these 11 pairs of values from the comparison of pre-shift B-toluene from Monday and Thursday/Friday gives an increase of B-toluene from a median of 0.21 to 0.42 µmol/l with ranges from 0.05 to 0.75 and 0.08 to 3.05 respectively ($P < 0.00001$, $n = 47$).For 41 workers the B-toluene level increased, while it was unchanged for one of them.

Covariation between air and blood toluene levels

TWA for a workshift and B-toluene sampled directly after work correlated significantly ($r_S = 0.84$, $P < 0.00001$) (Fig. 2). Exclusion of outliers did not change the correlation coefficient ($r_S = 0.82$). The estimated exposure level for the work week also correlated significantly with B-toluene sampled directly after work on Thursday/Friday ($r_S = 0.78$, $P < 0.00001$). The exposure from a shift correlated weakly with the next day pre-shift B-toluene ($n = 53$, $r_S = 0.40$, $P = 0.003$). A multiple linear regression analysis was performed with the exposure of the previous day, the estimated mean weekly exposure and the index of Broca [= body weight (in kg) · 100/(length (in cm) − 100)] as independent variables and pre-shift B-toluene Thursday/Friday as a dependent variable. After backward selection ($F < 4$), the estimated mean weekly exposure remained as the best predictor for the pre-shift B-toluene sampled Thursday/Friday ($n = 52$, $r = 0.71$, $P < 0.0001$) (Fig. 3). The regression of B-toluene before work towards the end of the week

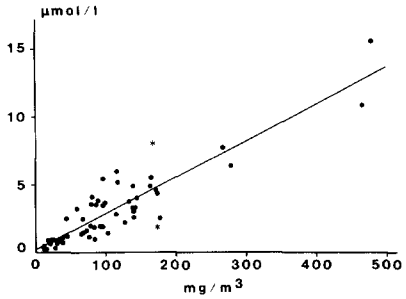

Fig. 2. Covariation between time-weighted exposure levels (mg/m^3) measured in the respiratory zone and post-shift blood toluene levels. The equation of the regression line is $y = 0.027x + 0.198$, $n = 57$, $r_S = 0.84$ and $P < 0.00001$. Stars indicate the two subjects in Fig. 1

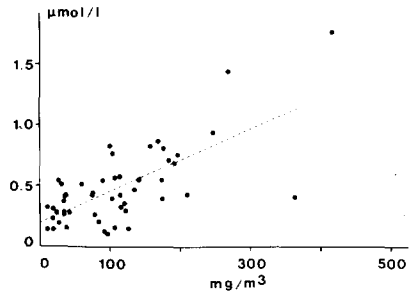

Fig. 3. Association between the estimated mean weekly exposure (mg/m^3) and the concentration of toluene in venous blood (µmol/l) before work towards the end of the week ($n = 52$, $r_S = 0.60$, $P < 0.0001$)

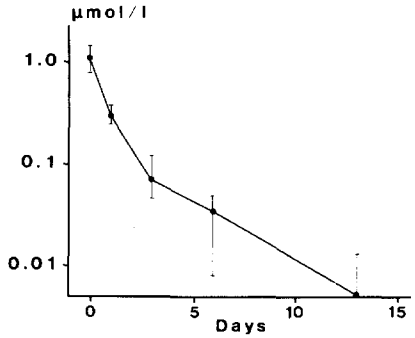

Fig. 4. Decrease of the level of toluene in venous blood (median and range, $n = 6$) after cessation of exposure

(y) on the estimated mean exposure (x) is $y = 0.003x + 0.182$. The Spearman correlation coefficient for this covariation is $r_S = 0.60$ ($n = 53$, $P < 0.0001$). In these calculations the subjects with the inexplicably high pre-shift B-toluene on Monday and the one who went into a contaminated area before sampling (see above) were excluded.

The variation of exposure levels during a shift influenced the B-toluene level directly after work. Two

workers with almost the same TWA (173 and 167 mg/m^3) could have the highest peak exposure during different periods of the shift (Fig. 1). This difference was reflected in the blood levels directly after work, 1.9 and 8.0 μmol/l respectively (Fig. 2).

Elimination

After the end of exposure at Plant B, the B-toluene decreased from a median value of 1.1 to 0.3 μmol/l at noon the following day, 22 h later. In two out of six blood samples taken 13 d after exposure, we could still detect some toluene (> 0.01 μmol/l) (Fig. 4). No subject reported any use of solvents during the investigation period. About 25% (range 21 to 33) of the toluene was left in blood after 22 h without exposure. As seen in Fig. 4 the elimination after the third day was fairly constant. From that part of the elimination curve, the half-time of the slow elimination of B-toluene can be estimated to be about 3 d. The exposure during the last workshift was calculated to 33 mg/m^3 from our regression line, using the median concentration B-toluene (Fig. 2). For seven workers in Plant C we have blood samples from Thursday after work. B-toluene varied from 2.7 to 22.9 μmol/l (median 5.4). The median B-toluene level the following day was 0.80 μmol/l (range 0.5 to 2.0). We thus found 15% (range 6 to 54) left after 18 h without exposure. The slowest elimination was found in a worker, who had consumed alcohol during the evening. He usually did not drink alcohol during the working week.

Discussion

The workers in our study were exposed almost only to toluene and almost only through inhalation. Their skin absorption was negligible, as they always used adequate protective gloves when they worked with liquid toluene. Of course, accidentally they might have been exposed through the skin.

Our results show that venous blood sampled directly after work reflects the exposure during the day. This is in accordance with previous findings with the use of venous blood (Apostoli et al. 1982; Brugnone et al. 1986) and of arterial blood (Övrum et al. 1978; Carlsson 1982). We found the regression to be $y = 0.027x + 0.198$ for the association between B-toluene in μmol/l (y) on air levels of toluene in mg/m^3 (x). The regression $y = 2.62x + 45$ was found for B-toluene (μg/l) on environmental toluene concentrations (mg/m^3) by Brugnone et al. (1986). If we transform the data in their equation to the same denominations as our data, it becomes $y = 0.028x + 0.488$. Thus, the slopes of the equations are similar. These results are also in agreement with the observations of Apostoli et al. (1982).

In our study, an exposure to 100 mg/m^3 corresponds to a post-shift B-toluene of 2.9 μmol/l. An exposure to 300 mg/m^3 (the Swedish Occupational Standard, National Board of Occupational Safety and Health, 1984) would correspond to 8.2 μmol/l. Also, they are comparable with the biologic threshold limit in the USA (ACGIH: 1 mg/l = 10.9 μmol/l at 375 mg/m^3), but differ from that in Germany (170 μg/dl = 18.5 μmol/l at 375 mg/m^3).

The elimination of toluene is slow. This is the reason for the positive intercept of B-toluene regression on air levels. It is also shown by the accumulation disclosed by the pre-shift B-toluene increase during the week. This is in accordance with findings of Konietzko et al. (1980) and Apostoli et al. (1982). Lauwerys (1983) suggested the evaluation of the possibility of using the concentration of toluene in pre-shift blood as a biological index of the exposure on the preceding day, as proposed for benzene. In fact Brugnone et al. (1986) found a statistically significant correlation between pre-shift B-toluene and the exposure during the previous day ($r_S = 0.36$, $P < 0.05$). Our results show the same weak association between pre-shift B-toluene and exposure during the previous day ($r_S = 0.40$, $P = 0.003$). However, the pre-shift B-toluene does not only reflect the exposure during the previous day. The amount of toluene accumulated in body fat is also of importance. The pre-shift B-toluene towards the end of the work week reflects both the exposure of the day before and the concentration in body fat (to be published). This is probably the reason why we obtained a better association between the estimated mean weekly exposure and pre-shift B-toluene towards the end of the work week. The pre-shift level reflects the exposure during several days preceding the sampling. The subject's amount of body fat was of less importance, and the index of Broca was first eliminated in the multiple linear regression analysis.

Due to the slow elimination, and in spite of the low exposure, the printers had detectable pre-shift B-toluene even on Monday morning after a weekend without exposure. Furthermore toluene was found in blood as long as 13 d after exposure. The slow elimination from blood suggestively reflects the elimination from adipose tissue. We found a half-time of the compartment reflecting the slow elimination of B-toluene of 3 d. Carlsson and Ljungquist (1982) observed in their study of subcutaneous adipose tissue a half-time ranging from 0.5 to 2.7 d.

B-toluene declines very rapidly during the first minutes without exposure (Åstrand 1975; Carlsson

1982). Brugnone et al. (1986) found a mean of 7.2% toluene still present in blood after 17 h without exposure, as compared with the concentration directly after work. For six printers at Plant B we found 25% toluene left in blood after 22 h, while only 14% was left after 18 h among the workers in Plant C. Variations of exposure during the day are important for such differences. In many workplaces the day ends up with cleaning work, which often causes high exposure and therefore a high B-toluene at the end of the shift. However, in the printing plants we investigated, shifts seldomly ended with cleaning work. Thus, the greater proportion of toluene left among the workers in Plant B may depend on low exposure during their last few hours at work. The blood level had probably already started to decrease when we took the first sample. Furthermore, in order not to contaminate the samples the printers walked from their workplaces to a toluene-free sampling room. Differences in this time lag may explain the variation between the plants. Such conditions may also explain the differences between various investigations.

In conclusion, toluene in venous blood is a useful exposure index to follow workers' exposure after an elaborate ambient air investigation. Post-shift level reflects the exposure during the preceding shift and pre-shift level at the end of the week is an approximate index of the accumulated weekly exposure. Moreover, toluene accumulates in the body even at low exposure levels. A slow elimination phase means that rotogravure printers are not free of toluene until at least two weeks without exposure.

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