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Biological monitoring of occupational exposure to low levels of benzene

by Kaija Pekari, PhL,[1] Sinikka Vainiotalo, MSc,[1] Pirjo Heikkilä, PhL,[1,2] Aarno Palotie, MD,[3] Marita Luotamo, PhD,[1] Vesa Riihimäki, MD[1]

PEKARI K, VAINIOTALO S, HEIKKILÄ P, PALOTIE A, LUOTAMO M, RIIHIMÄKI V. Biological monitoring of occupational exposure to low levels of benzene. *Scand J Work Environ Health* 1992;18: 317—22. To obtain reference values for the biological monitoring of benzene, the kinetics of benzene were studied in volunteers. Benzene in blood and expired air could easily be followed until the next morning after a 4-h exposure to a benzene concentration of 10 $cm^3 \cdot m^{-3}$. Even after exposure to 1.7 $cm^3 \cdot m^{-3}$ the benzene levels in the morning blood and expired air samples differed from those in unexposed subjects. One hour after exposure to 10 and 1.7 $cm^3 \cdot m^{-3}$ the mean levels of benzene were 238 and 25 $nmol \cdot l^{-1}$ in blood and 13.2 and 2.5 $\mu mol \cdot m^{-3}$ in exhaled air, respectively. It was concluded that, at high benzene levels (~ 10 $cm^3 \cdot m^{-3}$), samples collected 16 h after exposure reflect the body burden of benzene, while at low exposure (<1 $cm^3 \cdot m^{-3}$) samples collected 1 h after exposure may be used to estimate the exposure over the preceding few hours. Exposure to benzene from smoking is a potential confounder in estimating occupational exposure to low levels of benzene.

Key terms: blood, elimination, expired air, kinetics, urinary phenol.

Benzene is myelotoxic and causes leukemia in humans (1, 2). It occurs widely in the work environment and also in outdoor air, albeit mostly at low concentrations, and it is therefore important to be able to assess exposure to benzene.

It is known that total benzene uptake through the lungs may be highly variable, depending on pulmonary ventilation (3). Some absorption may occur even through the skin. Therefore the uptake in individual workers cannot be reliably estimated by ambient air measurements only.

The determination of benzene in blood is a specific way to monitor occupational exposure. Methods based on its urinary metabolites, such as phenol and the newly proposed *trans, trans*-muconic acid (4, 5), are nonspecific because these compounds are also generated from sources other than benzene. *S*-phenylmercapturic acid in urine is reported to be useful in monitoring exposures even below benzene concentrations of 1 $cm^3 \cdot m^{-3}$ (6). The analytical method is, however, too complicated for routine monitoring purposes. The determination of benzene in blood with gas chromatography, using head-space techniques and photoionization detection, is a simple and sensitive method for benzene monitoring (7). With this method exposures below 1 $cm^3 \cdot m^{-3}$ can be monitored. However, data on the relationship between exposure and levels of benzene in blood at different points in time are scant. Thus reliable reference values are not available.

The objective of this study was to develop a reliable method for the biological monitoring of benzene on the basis of blood benzene measurements. The kinetics of benzene were investigated through the exposure of human volunteers to two concentrations of benzene (10 and 1.7 $cm^3 \cdot m^{-3}$) and through the measurement of the benzene concentrations in blood and expired air, as well as urinary phenol after exposure to 10 $cm^3 \cdot m^{-3}$. Concentrations of urinary phenol (intra- and interindividual variation) in unexposed persons and possible interference due to benzene originating from cigarette smoke were also investigated.

Subjects and methods

Subjects

Three healthy nonsmoking research workers who were familiar with the health effects of benzene, between the ages of 30 and 45 years, and with lean to normal body constitutions (height 180—190 cm, weight 55—90 kg) volunteered for the study. They were clinically healthy, and no abnormal findings were observed in routine blood chemistry, hematology, or electrocardiography. The study protocol was approved by the Ethics Committee of the Institute of Occupational Health, and it was carried out with strict adherence to the principles of the Helsinki Declaration (8).

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Exposure

The exposures were conducted in a dynamic exposure chamber with a volume of 15 m^3. Ventilation was adjusted to approximately 10 air changes per hour. Benzene-containing atmosphere was generated by mixing saturated benzene vapor with laboratory room air drawn into the chamber. There was no recirculation of benzene. The content of benzene in the chamber air was monitored by an infrared spectrophotometer (Miran I A), and the benzene concentration in the air was automatically controlled with the aid of an industrial processor by varying the feed rate of saturated benzene vapor (9). The concentration of benzene in the air was adjusted to 10 $cm^3 \cdot m^{-3}$ (30 $mg \cdot m^{-3}$), high exposure, or to 1.7 $cm^3 \cdot m^{-3}$ (5.2 $mg \cdot m^{-3}$), low exposure. The exposure lasted 4 h.

Sample collection

Experimental exposure study. Venous blood specimens were drawn with an indwelling catheter. The first specimen was drawn just before the exposure, then specimens were drawn twice an hour for 3 h, and one specimen was drawn just before the end of the exposure period. After the exposure, specimens were collected every 10 min at first and later at longer intervals. In 24 h altogether 16 blood specimens were drawn from each individual. After of the low exposure only five blood specimens were collected from one of the subjects.

A volume of 5 l of mixed exhaled air was collected (in approximately 30 s) through a two-way valve (dead space approximately 70 ml) into an aluminium bag laminated with polyethyleneterephthalate. The collection intervals were the same as for the blood specimens.

Spot urine specimens were collected for phenol determinations immediately before and during the exposure and about 50 h after the high exposure.

Blood samples from smokers and nonsmokers. Another group of three male research workers, age 42—45 years, who were heavy smokers and had no known occupational exposure to benzene, gave blood specimens in the morning after they had smoked four or five cigarettes, and in the afternoon, by which time each of them had smoked about 20 cigarettes. Blood specimens were also collected from two of the smokers in the morning and afternoon of a day during which they refrained from smoking. One of the three smoked one cigarette in the morning by mistake. Blood specimens were also collected from six nonsmokers.

Urine for the determination of phenol in unexposed workers. Urine samples were collected from 121 unexposed persons mainly representing office employees and laboratory personnel without known exposure to benzene or phenol. From this group 101 persons gave one spot sample in the afternoon, and 20 gave a sample both in the morning and in the afternoon.

Analytical methods

Benzene in blood. Benzene in blood was determined gas chromatographically (Sigma 2000 and HS-100, Perkin Elmer, United States) with a photoionization detector (HNU Systems, United States) by a head-space method using fluorobenzene as the internal standard (7). A gas chromatograph with two successive columns, methylsilicone and 5% phenylmethyl silicone capillary columns [both 30 m long, 0.53 mm (inner diameter), and film thickness 2.65 μm (HP-1 and HP-5, Hewlett Packard, United States)] was used. The detection limit was usually 1 $nmol \cdot l^{-1}$ and always < 5 $nmol \cdot l^{-1}$, depending on the age of the ultraviolet lamp.

Benzene in expired air. An aliquot of 1 ml from the expired air sample was injected with a gas-tight syringe and a loop system into a gas chromatograph (Hewlett Packard 5890) equipped with a flame ionization detector (temperature 280°C). A split ratio 1:2 was used. The separation was carried out with a capillary column [HP-1, 30 m, 0.53 mm (inner diameter), film thickness 2.65 μm, Hewlett Packard]. The flow rate of the carrier gas (helium) was 8.5 $ml \cdot min^{-1}$. The oven temperature program was as follows: 2 min at 30°C followed by a gradient of 3°C per minute to 47°C and 25°C per minute to 100°C. The retention time for benzene was 5.9 min. The primary standards were prepared by the addition of an accurately measured microliter amount of benzene into sampling bags (aluminium laminated with polyethyleneterephthalate) containing 5 l of air. The calibration standards were prepared by the dilution of the primary standards with a gas-tight syringe into sampling bags. The coefficient of variation for the method was 4.6% ($N = 5$) at 4.40 $cm^3 \cdot m^{-3}$ and 5.4% ($N = 5$) at 0.44 $cm^3 \cdot m^{-3}$. The detection limit was 0.005 $cm^3 \cdot m^{-3}$.

Phenol in urine. The phenol conjugates in urine (5 ml) were hydrolyzed (1 h, 100°C) with 2 ml of concentrated sulfuric acid (10), and phenol was extracted with 2 ml of isopropyl ether. After centrifugation 1 μl of the ether layer was analyzed by gas chromatography. Separation was achieved using 25 m × 0.3 mm (inner diameter) capillary columns [CP-WAX 52 CB (film thickness 1.1 μm, Chrompack, The Netherlands) or OV 351 (film thickness 0.2 μm, Nordion Instruments Oy Ltd, Finland)]. The temperatures of the injector and detector in the two gas chromatographs with flame ionization detection (Hewlett Packard 5730 and 5880) used in the study were 250 and 300°C, respectively; the oven temperature programs were (i) from 120 to 230°C at a rate of 10°C per minute, kept for 2 min and (ii) from 80 to 150°C at a rate of 30°C per minute, then from 150 to 170°C at a rate of 10°C per minute, and kept there for 1 min and then from 170 to 235°C at a rate of 30°C per minute, where it was kept for 5 min. Phenol was eluted in 4.7 and

6.9 min, respectively. The within-run coefficient of variation calculated from duplicate determinations was 6.8—8.0% at a concentration range of 13—230 μmol · l^{-1} (2N = 66). As an internal quality control, two samples of pooled urine from exposed workers, stored frozen, were analyzed within each series. The concentrations of phenol in urine were corrected to creatinine excretion and also to a relative density of 1.024.

Determination of elimination rates

By inspection, the elimination rates of benzene in blood and expired air seemed to follow a three-phase course. The slow (gamma) phase was resolved from a linear regression line drawn through the last points of the measurements (7—20 h for the blood samples, 9—35 h for the exhaled air samples). The transition from the apparent alpha to the beta phase was after the first postexposure hour. The slopes of beta and alpha were resolved by the method of residuals (11).

Results

Experimental exposure

The amount of benzene absorbed into the body was estimated from the average difference in the concentration of inhaled and exhaled air. It was 48.0 (SD 4.3)% for the high exposure and 52.0 (SD 7.3)% for the low exposure. On the assumption that the lung ventilation was 11 l · min^{-1} (12), the estimated uptake was 518 (SD 47) μmol in the high exposure and 95 (SD 13) μmol in the low exposure. In the three studied individuals 8.5, 9.3, and 10.4% of the estimated uptake of benzene was exhaled unchanged within the high exposure, and the corresponding values for the low exposure were 12.5, 10.6, and 14.3%. The diurnal baseline excretion of phenol into the urine of each subject was determined over 30—50 h postexposure and subtracted from the observed phenol excretion over 0—30 h. (See figure 2.) Assuming that this calculation gives a crude estimate of benzene-derived phenol, we concluded that 11.5, 18.7, and 22.9% of the pulmonary uptake of benzene at the high concentration was excreted in the urine of the three individuals.

After the high exposure (10 $cm^3 \cdot m^{-3}$, 4 h) the benzene concentrations in the blood decreased within 30 h to close to the detection limit, while in the expired air the detection limit was not reached until after 45 h (figure 1). After the low exposure (1.7 $cm^3 \cdot m^{-3}$) the benzene concentration in the blood could easily be followed for 8—10 h, and that in the expired air was observable for nearly 20 h (figure 1). The calculated concentrations of benzene in the blood 16 h after the exposure, at times which would correspond to samples prior to the next shift, were 19—21 nmol · l^{-1} for the high and 5—8 nmol · l^{-1} for the low exposure. The calculated values in the expired air were 1.01—1.42 and 0.53—0.57 μmol · m^{-3} for the high and low exposure, respectively.

The elimination of benzene after the high exposure showed a good fit to a three-compartment model. The mean half-times for benzene in blood and exhaled air were 55 and 61 min for the alpha phase, 3.2 and 5.9 h for the beta phase, and 19.7 and 14 h for the gamma phase for blood and expired air, respectively. The elimination half-times for benzene after the low exposure were very similar, the alpha phase giving half-times between 20 and 60 min, and the beta phase between 3 and 6 h, for both blood and expired air.

The level of phenol in urine increased during the 4 h of exposure from the starting level of 26—74 μmol · l^{-1} to a maximum of 192—315 μmol · l^{-1}. The excretion of phenol returned to the level found before the exposure in about 14—35 h (figure 2).

Phenol in the urine of unexposed persons

The mean values for the urinary phenol concentrations corrected to a common relative density in unexposed subjects are given in figure 3. The distribution showed the best fit to a log-normal distribution with a mean value of 62 μmol · l^{-1}, 90% of the results being under 153 μmol · l^{-1} and 95% being under 180 μmol · l^{-1}. The corresponding mean value corrected for creatinine excretion was 8 mmol · mol^{-1} creatinine, 90% being under 28 mmol · mol^{-1} creatinine and 95% being under 33 mmol · mol^{-1} creatinine. The range of the phenol concentrations in the unexposed population varied from 4 to 450 μmol · l^{-1} (from 2 to 63 mmol · mol^{-1} creatinine). Among the individuals who gave specimens two times a day, there was no consistent or marked difference in the urinary phenol concentration over the day (figure 4). The average concentration was 10.9 (SD 28.4) μmol · l^{-1} (corrected to the density) lower in the afternoon than in the morning.

Benzene in the blood of the smokers and nonsmokers

Blood specimens were collected from three smokers. In the morning, after the smoking of four or five cigarettes, the concentrations of benzene in the blood were between 4 and 13 nmol · l^{-1}; in the afternoon, after the smoking of 20 cigarettes during the day, they were between 5 and 8 nmol · l^{-1}. When two of the smokers refrained from smoking, their blood benzene concentrations were <2 nmol · l^{-1}, both in the morning and in the afternoon. The third smoker inadvertently smoked one cigarette on the day he was supposed to refrain from smoking; his level of benzene in blood was 6 nmol · l^{-1}. The mean level in the blood of six nonsmokers was 0.8 (range <1—2, SD 0.8) nmol/l.

Discussion

This experimental study on benzene kinetics indicates that, although benzene is eliminated from the body rather rapidly, uptake, after an exposure to approxi-

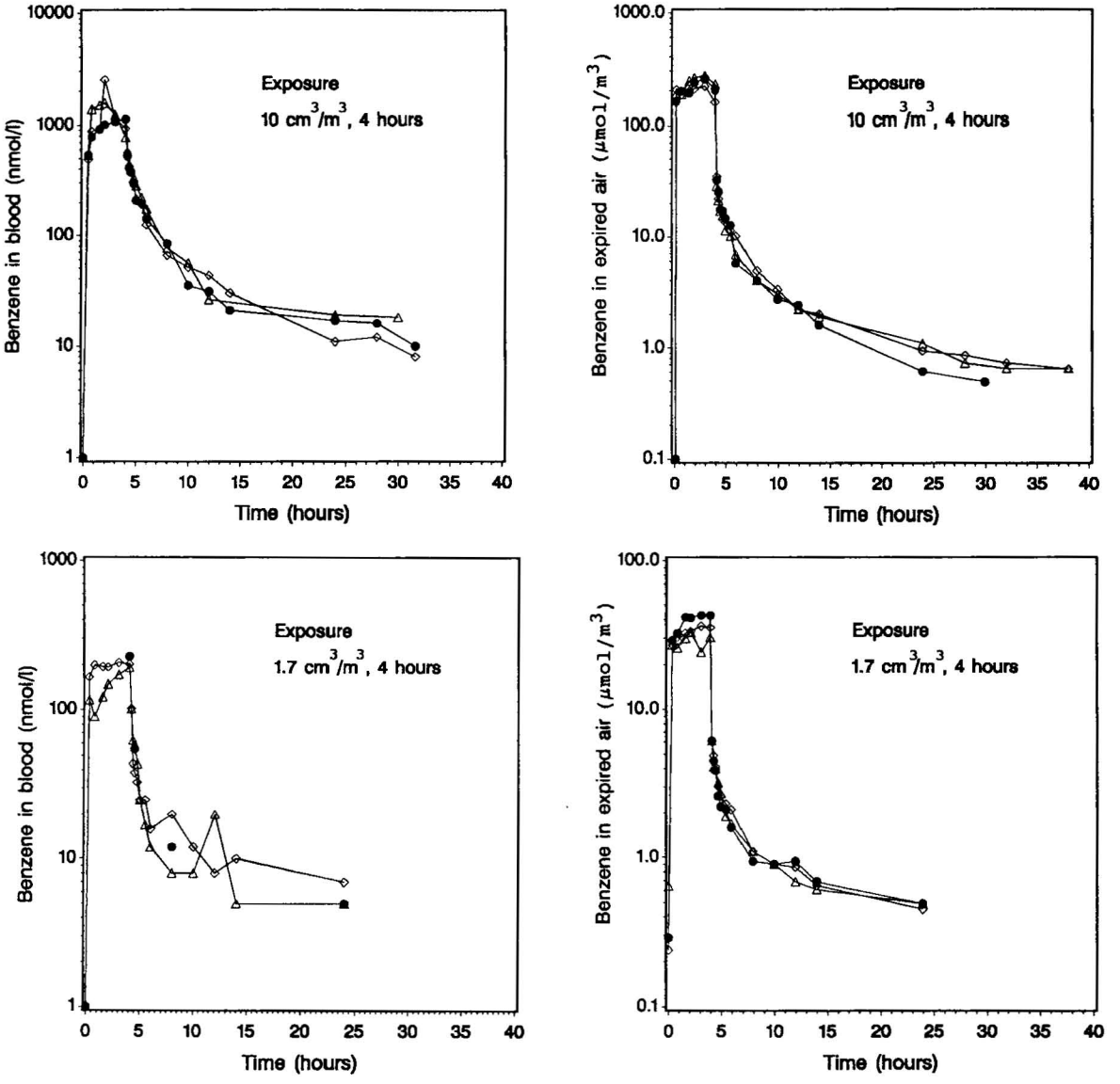

Figure 1. Benzene in the blood and expired air of the three volunteers during and after 4 h of exposure to a benzene concentration of 10 $cm^3 \cdot m^{-3}$ (30 $mg \cdot m^{-3}$) and 1.7 $cm^3 \cdot m^{-3}$ (5 $mg \cdot m^{-3}$). The results were corrected to a relative density of 1.024.

mately 10 $cm^3 \cdot m^{-3}$ for 4 h, can be followed from the levels in blood or expired air specimens without difficulty until the next morning. After a six times lower exposure (1.7 $cm^3 \cdot m^{-3}$, 4 h) the concentrations of the morning specimens still differed from the values measured for the unexposed subjects. During the high benzene exposure there was a high benzene peak in the blood of one subject, and, in the elimination phase after the low benzene exposure, another subject showed a transient elevation in blood level, while the others showed a slight passing rise in their breath concentrations. The causes of these unexpected findings are unknown.

We observed three consecutive phases of elimination for benzene in blood and exhaled breath. The slow elimination (half-time 15—20 h) indicates that benzene will, to some extent, accumulate in the body during continuous exposure, as noted by Berlin at al (13) earlier. For the purpose of routine exposure monitoring the specimen collection should therefore be performed toward the end of the week. One can use the elimination kinetics of benzene to advantage in biological monitoring by measuring the compound in blood or expired air at defined time points. If the exposure is more intense, samples collected in the morning after the day of exposure (16-h sample) are both practical and informative, as they indicate the body burden of benzene (provided that cigarette smoking in the morning has been excluded).

The difference in the phenol concentrations before

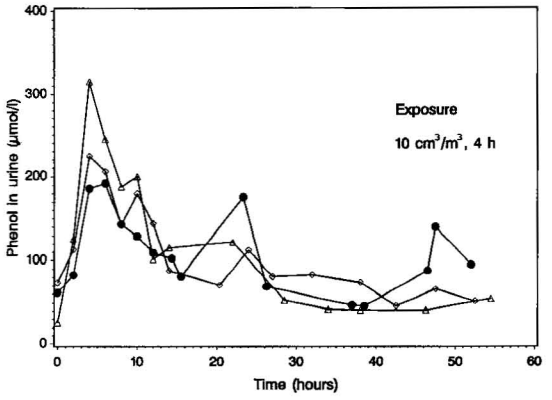

Figure 2. Urinary phenol concentrations of the three volunteers during and after the benzene exposure chamber test (10 $cm^3 \cdot m^{-3}$, 4 h).

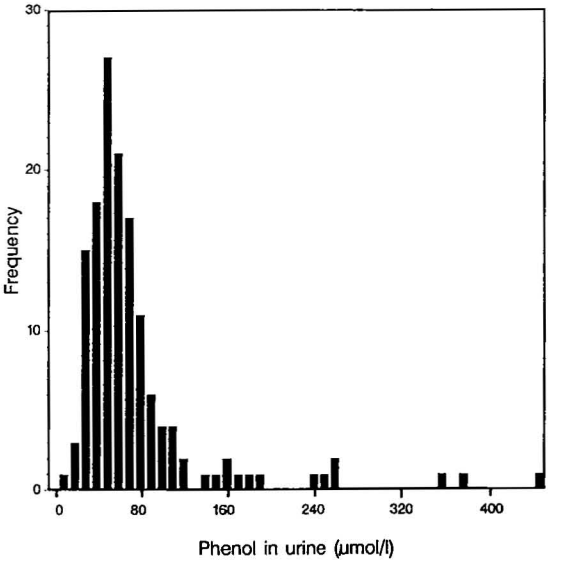

Figure 3. Frequency of the urinary phenol concentrations of the unexposed persons (N = 121). The results were corrected to the density of 1.024.

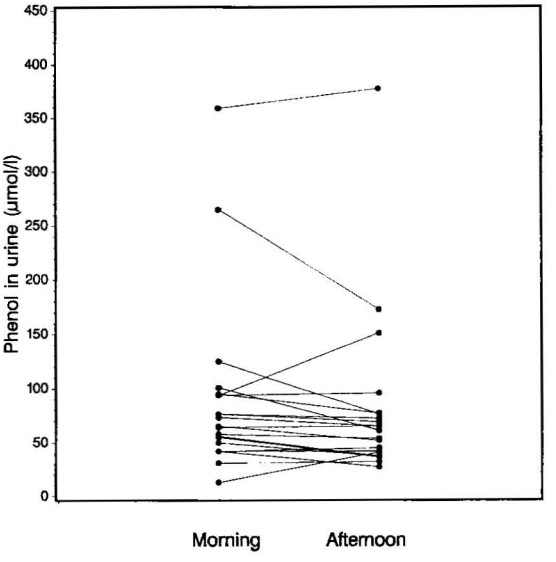

Figure 4. Daily variation in the urinary phenol concentrations of the unexposed persons.

and right after the high exposure (10 $cm^3 \cdot m^{-3}$, 4 h) were 124, 150, and 289 $\mu mol \cdot l^{-1}$ for the three exposed subjects. A corresponding dose of benzene (5 $cm^3 \cdot m^{-3}$, 8 h) over a whole workday raises the average urinary phenol level after the workhours to approximately 200 $\mu mol \cdot l^{-1}$ above that in a morning sample (14). In the unexposed population of our study the geometric mean value of phenol in urine was 62 (range 13—451) $\mu mol \cdot l^{-1}$, and 95% of the phenol concentrations were under 180 $\mu mol \cdot l^{-1}$. The difference between the urinary phenol concentration in the afternoon and in the morning was, in 95% of the cases, under 46 $\mu mol \cdot l^{-1}$ (figure 4). That value would correspond to exposure to 1—2 $cm^3 \cdot m^{-3}$ of benzene. Our results confirm that the concentrations of urinary phenol in unexposed persons are high and vary to a great extent. They therefore do not provide reliable information about the preceding exposure, even at rather high exposure levels.

The concentration of benzene in the blood of the occupationally unexposed smokers reached 13 $nmol \cdot l^{-1}$. On the day when they refrained from smoking, blood benzene varied between 1 and 2 $nmol \cdot l^{-1}$, and the values agreed with our measurements from nonsmoking persons. The maximal benzene level in the blood of unexposed nonsmokers reported in the literature is about 6 $nmol \cdot l^{-1}$, and that of unexposed smokers about 12—15 $nmol \cdot l^{-1}$ (15, 16). When nonsmoking subjects were exposed to a benzene concentration of 1.7 $cm^3 \cdot m^{-3}$ for 4 h in our study, they still had some benzene in their blood the following morning (5, 5, and 7 $nmol \cdot l^{-1}$, 20 h postexposure). Smoking as few as four cigarettes yielded that level in the blood. Yet there was no correlation between the number of cigarettes smoked and the benzene level in the blood. The confounding effect of smoking on the biological monitoring of very low occupational exposure to benzene, on the basis of blood or exhaled air specimens, can be overcome if the subjects refrain from smoking on the day of specimen collection. If the specimens are collected 1 h after a high exposure, of the order of 5 $cm^3 \cdot m^{-3}$ for 8 h or higher, smoking does not have a marked effect on the estimation of benzene exposure.

The German maximum concentrations at the workplace and the biological tolerance values for working materials [MAK values or BAT values) (17)] do not give any reference values for benzene. However, the information provided about benzene blood levels corresponding to air concentrations at the workplace at the end of a shift are very similar to what we observed towards the end of our experimental exposure. The end

of a shift is not, however, the ideal time for specimen collection because of the rapid elimination of benzene from blood during the first half-hour after exposure.

The current hygienic standard recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) (18) in the United States for benzene in the work atmosphere is 10 $cm^3 \cdot m^{-3}$. For benzene in expired air prior to the next shift the ACGIH has set a biological exposure index of 0.08 $cm^3 \cdot m^{-3}$ (mixed exhaled sample). Our results for the mixed exhaled samples are in good agreement with the reference value of the ACGIH. Exposure to 10 $cm^3 \cdot m^{-3}$ for 4 h gave 1.01—1.42 $\mu mol \cdot m^{-3}$ (0.025—0.034 $cm^3 \cdot m^{-3}$) prior to the next shift. No corresponding reference value for benzene in blood has been proposed. Benzene has now been placed on the list of intended changes by the ACGIH Board of Directors. A proposal has been made to lower the hygienic standard of benzene to 0.1 $cm^3 \cdot m^{-3}$.

The determination of benzene in expired air proved to be very simple and sensitive. However, sampling in the field and transport of the specimens may give rise to problems with repeatability and stability. New collection systems (such as breath sample collectors using head-space vials) may serve as an incentive to the wider application of exhaled air determination, a readily acceptable noninvasive sampling method. As an analytical method, the determination of benzene in blood is sensitive enough to trace exposure down to a benzene concentration of 1 $cm^3 \cdot m^{-3}$ in the air or even less. At present blood specimens, which can be taken reproducibly by health care personnel, seem to serve well for the purpose of biologically monitoring exposure to benzene.

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