Recent Advances in Measuring Exhaled Breath and Estimating Exposure and Body Burden for Volatile Organic Compounds (VOCs)

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An improved portable breath measurement method has been developed that allows 1-min sampling times. The equipment has been successfully tested in field and chamber studies. Results of these studies suggest that breath levels following known exposures are predictable and reproducible across a small number of volunteers. The residence times in the body and the distribution in body compartments of several common air toxics have been determined. A simple four-compartment linear model is capable of fitting the observed data. The main parameters of the model include the fraction of the parent compound exhaled under steady-state conditions and the residence times in the compartments. The values of these parameters for several VOCs and for the four body compartments (blood, vessel-rich tissues, vessel-poor tissues, and fat) are provided.

Key words: breath, volatile organic chemicals, VOC, pharmacokinetics, personal monitors, Tenax, residence times, half-lives

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Introduction

Measurement of volatile organic compounds (VOCs) in human breath has the promise of identifying important routes of exposure and relating exposure to body burden. Over the past decade, such measurements have been carried out for about 800 residents of eight cities and towns in the United States (1-10). Important findings from these efforts included the discovery that cigarette smoking is the single largest source of exposure to benzene and styrene. These early measurements employed a van-mounted spirometer. Breath samples were 20 to 40 liters and required 5 min to collect.

Over the past 2 years, a major improvement in breath sampling methods has allowed a rapid expansion of our understanding of how exposure to VOCs at environmental concentrations affects measured levels in exhaled breath; the time course of decay of the VOCs in breath; and the relationship of these breath concentrations to concentrations in other body tissues (total body burden).

Materials and Methods

A method for sampling exhaled breath capable of measuring sub-ppb levels was developed in 1979 (1). The method employs Tenax sorbents to collect breath samples from a Tedlar bag that has been filled by the subject exhaling through a two-way mouthpiece. The subject inhales pure humidified and charcoal-scrubbed air from a cylinder.

The entire system was mounted in a van to allow "house calls" to the participants in the U.S. EPA-sponsored Total Exposure Assessment Methodology (TEAM) studies of 1980 to 1987 (2-10). In these studies, about 800 residents of eight cities provided breath samples following a 12-hr period in which they carried personal monitors to measure their exposure to about 25 target VOCs. (Samples of drinking water were also collected to determine potential exposure through that pathway.) The TEAM studies have provided a unique database on typical personal air and drinking water exposures and breath levels for about a dozen prevalent VOCs.

One reason for collecting the breath sample was to check all important routes of exposure had been measured. In fact, an early important finding was directly due to breath measurements: the fact that smoking cigarettes is the single most important source of exposure to benzene for millions of Americans (11-13). Breath measurements revealed at once that smokers had 5 to 10 times the concentrations of benzene as nonsmokers (Table 1); the personal monitor, because it could not measure mainstream smoke, had detected only a modest increase in airborne exposure of about 50%. Similar results were noted for styrene.

A recent study (14) employed breath measurements to estimate contributions from a route of exposure (skin absorption) that is difficult to measure directly. In this study, chloroform was measured in the breath of persons immediately following a normal shower, and a shower wearing a rubber suit to prevent skin absorption. Breath levels from the normal shower were about twice those from the wet-suit shower, suggesting that skin absorption accounted for about as much chloroform uptake as inhalation.

The TEAM studies provided data on the relationship of breath levels to previous exposures. Typical breath-to-air ratios ranged from about 0.08 for xylenes and ethylbenzene up to about 0.75 for tetrachloroethylene (Table 2) (15). Awareness of these ratios allows a rough estimate to be made of previous exposure from a measured breath sample.

However, it is clear that the breath level following exposure to a given VOC is

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affected by such factors as the existing levels in breath, blood, and other body tissues, as well as the metabolic rate and other rate constants affecting the distribution and ultimate fate of the chemical. To take account of these effects, an initial linear mass-balance compartmental model was developed (16) and tested in a chamber study of four volunteers (17). The model had predicted a "deep" compartment residence time of 31 hr for tetrachloroethylene; the calculated residence time for one volunteer who had sat in a dry cleaner shop for 2 hr before entering the chamber was 31 hr.

The model was further developed and tested in a second chamber study (18). Estimates of about 1 to 2 hr for the residence time in the second compartment, and 6 to 8 hr for the residence time in the third compartment, were obtained (19).

However, the model predictions of a few minutes for the residence time in breath and blood could not be observed in this study due to the 20 min required between successive breath samples.

The model is fully derived elsewhere (20). For a constant concentration $C_{AIR}$, the alveolar breath concentration $C_{ALV}$ is given by

$$C_{ALV} = fC_{AIR} \Sigma a_i(1-\exp(-t/\tau_i))$$

where $f$ = fraction of parent compound exhaled at equilibrium; $\tau_i$ = residence time in $i$th compartment; $a_i$ = fraction of total breath concentration contributed by the $i$th compartment at equilibrium ($t = \infty$); and $\Sigma a_i = 1$.

**Recent Advances**

Because of the limitations noted in the second chamber study, the U.S. EPA sponsored an effort to produce an improved breath sampling method. One goal was to collect a breath sample in less than 2 min, and be ready to collect another in 5 min. Another goal was to measure alveolar breath as much as possible. Finally, it was desirable to have a completely portable system that could be carried by a technician to potential high-exposure microenvironments (e.g., beauty salons, hardware stores) to collect breath samples immediately following the exposure.

All these goals were met with the new system (21,22). The subject inhales through a charcoal mask to scrub the air and exhales through a meter-long flexible tube. The breath remaining in the tube following expiration is alveolar air; this is sucked into an evacuated electropolished sphere (1.8 # liters) at a constant rate through a critical orifice. The system has no moving parts or power needs and can be transported in a suitcase.

The new breath system was tested by having subjects spend several hours in six microenvironments (23). Their personal exposures were monitored, and a series of breath samples were collected over the next 2 to 4 hr for a total of 21 aliphatic, aromatic, and halogenated VOCs. Residence times in the first two compartments (blood and vessel-rich tissues) were estimated. The model predictions of a few minutes for the residence time in the blood were verified.

A third chamber study was then designed to gather information on the deeper compartments (24). Five subjects were exposed in a chamber for 10 hr to moderately elevated levels (~1 ppm) of nine VOCs. Breath samples were collected intermittently over the next 24 hr.

**Results**

A four-phase decay in breath concentrations following the 10-hr exposure was noted (Figure 1). Residence times for all four compartments were estimated: 3 to 10 min (blood); 30 to 100 min (vessel-rich tissues); 3 to 7 hr (vessel-poor tissues); and 30 to 100 hr (fat) (LA Wallace, in preparation). The coefficients ($a_i$) of the four compartments were also estimated. These coefficients represent the fraction of the total breath concentrations contributed by each compartment at equilibrium. Observed values were on the order of 30% for the blood and the fat, and 20% for the vessel-rich and vessel-poor tissues (Figure 2). These coefficients can be multiplied by the tissue/air partition coefficients to obtain the fraction of the body burden in each compartment at equilibrium.

Values of $f$ (the fraction of the parent chemical exhaled at equilibrium) were determined for nine chemicals by averaging across all results for five subjects. Xylenes and ethylbenzene had values of 0.06 to 0.08, in good agreement with the values of 0.08 to 0.10 calculated from the TEAM studies of several hundred nonsmokers (Table 2). Toluene had a value of 0.16 ± 0.02 (SD). Trichloroethylene had a value of 0.22 (± 0.05), again in good agreement with previous estimates from the TEAM studies. Dichloromethane had a value of 0.23 (± 0.03). Hexane and

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**Table 1. Benzene breath values (µg/m³).**

| Location           | Smokers |          | N   | Geometric mean |          | N   | Geometric mean |
|--------------------|---------|----------|-----|----------------|----------|-----|----------------|
| Eliz-Bay, NJ (9/81)| 160     | 19       | 170 | 5.2            |          |     |                |
| Eliz-Bay, NJ (2/83)| 27      | 18       | 22  | 4.2            |          |     |                |
| Los Angeles (2/84) | 39      | 12       | 78  | 2.0            |          |     |                |
| Los Angeles (5/84) | 17      | 15       | 25  | 1.2            |          |     |                |
| Ant-Pitts, CA (6/84)| 22      | 11       | 49  | 0.8            |          |     |                |
| Los Angeles (2/87) | 11      | 19       | 37  | 4.3            |          |     |                |
| Los Angeles (7/87) | 8       | 24       | 32  | 5.2            |          |     |                |
| Baltimore (4/87)   | 26      | 14       | 44  | 1.5            |          |     |                |

* Cities of Elizabeth and Bayonne. 1981 data may have been contaminated by exhaust fumes. * Cities of Antioch and Pittsburg. * Community of Dundalk. Sources: New Jersey data, TEAM study data base; 1984 data, (7); Los Angeles 87, TEAM study database; Baltimore 87, TEAM study database.

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**Table 2. Breath/air ratios of VOCs for 328 nonsmokers.**

| Chemical                | Ratio<sup>a</sup> | SD<sup>a</sup> |
|-------------------------|-------------------|----------------|
| Aromatics and aliphatics|                   |                |
| Benzene                 | 0.17              | 0.06           |
| Styrene                 | 0.20              | 0.11           |
| m+p-Xylene              | 0.08              | 0.04           |
| o-Xylene                | 0.08              | 0.02           |
| Ethylbenzene            | 0.10              | 0.03           |
| Octane                  | 0.15              | 0.06           |
| Chlorinated             |                   |                |
| 1,1-Trichloroethane     | 0.21              | 0.16           |
| Carbon tetrachloride    | 0.26              | 0.14           |
| Trichloroethylene       | 0.19              | 0.07           |
| Tetrachloroethylene     | 0.75              | 0.19           |
| m+p-Dichlorobenzene     | 0.44              | 0.18           |

<sup>a</sup>From TEAM studies in New Jersey (1983), Los Angeles (1984), and Antioch-Pittsburgh, CA (1984).

<sup>b</sup>Mean and standard deviation of observed median values in the three locations.

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**Figure 1. Uptake and decay of p-xylene in a female subject exposed to 11 mg/m³ in a chamber for 10 hr.** Breath levels reached a value of 400 µg/m³ and fell off to a concentration of 28 µg/m³ 24 hr postexposure. Shown is the fit of a four-compartment model to the data.
of the blood and mental state.

Figure 2. Estimated contributions of each body compartment to the average alveolar concentration of the nine VOCs. The first and fourth compartments (blood and fat, respectively) appear to account for about 30% of the total breath concentration. The second and third compartments may be identified with the vessel-rich and vessel-poor tissue groups (VRG and VPS), respectively.

decane had values of 0.35 (±0.08) and 0.10 (±0.02), respectively. Methyl chloroform (1,1,1-trichloroethane) had a value of 0.88 (±0.07). This value was in disagreement with the value of 0.21 suggested by the TEAM studies.

Discussion

Breath measurements have proved useful in identifying important sources of environmental exposure from pathways that are otherwise difficult to measure (benzene from smoking, chloroform from skin absorption). They would also be useful in identifying exposure from ingestion of VOCs in food or beverages, particularly since techniques for measuring food samples are often difficult or expensive. With the completion of a simple, inexpensive, portable device for rapid collection of breath samples, scores of interesting studies have become possible.

A research need is to compare breath and blood measurements at environmental levels. Present pharmacokinetic models rest partially on estimates of blood/air partition coefficients obtained from measurements at high levels of exposure; however, recent studies (25) suggest that the apparent partition coefficients at environmental concentrations of benzene are 2 to 4 times larger than the literature values. The recent improvement by the Centers for Disease Control (CDC) of an isotope-dilution measurement method for blood (26) has made it possible to carry out such studies without delay. Initial studies on a few subjects have been promising.

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