

Environmental and Biological Monitoring of Benzene during Self-Service Automobile Refueling

Peter P. Egeghy, Rogelio Tornero-Velez, and Stephen M. Rappaport

Department of Environmental Sciences and Engineering, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Although automobile refueling represents the major source of benzene exposure among the non-smoking public, few data are available regarding such exposures and the associated uptake of benzene. We repeatedly measured benzene exposure and uptake (via benzene in exhaled breath) among 39 self-service customers using self-administered monitoring, a technique rarely used to obtain measurements from the general public (130 sets of measurements were obtained). Benzene exposures averaged 2.9 mg/m^3 (SD = 5.8 mg/m^3 ; median duration = 3 min) with a range of $< 0.076\text{--}36 \text{ mg/m}^3$, and postexposure breath levels averaged $160 \text{ }\mu\text{g/m}^3$ (SD = $260 \text{ }\mu\text{g/m}^3$) with a range of $< 3.2\text{--}1,400 \text{ }\mu\text{g/m}^3$. Log-transformed exposures and breath levels were significantly correlated ($r = 0.77$, $p < 0.0001$). We used mixed-effects statistical models to gauge the relative influences of environmental and subject-specific factors on benzene exposure and breath levels and to investigate the importance of various covariates obtained by questionnaire. Model fitting yielded three significant predictors of benzene exposure, namely, fuel octane grade ($p = 0.0011$), duration of exposure ($p = 0.0054$), and season of the year ($p = 0.032$). Likewise, another model yielded three significant predictors of benzene concentration in breath, specifically, benzene exposure ($p = 0.0001$), pre-exposure breath concentration ($p = 0.0008$), and duration of exposure ($p = 0.038$). Variability in benzene concentrations was remarkable, with 95% of the estimated values falling within a 274-fold range, and was comprised entirely of the within-person component of variance (representing exposures of the same subject at different times of refueling). The corresponding range for benzene concentrations in breath was 41-fold and was comprised primarily of the within-person variance component (74% of the total variance). Our results indicate that environmental rather than interindividual differences are primarily responsible for benzene exposure and uptake during automobile refueling. The study also demonstrates that self-administered monitoring can be efficiently used to measure environmental exposures and biomarkers among the general public. **Key words:** benzene, biological monitoring, exhaled air, exposure, exposure variability, gasoline, mixed models, self-monitoring. *Environ Health Perspect* 108:1195–1202 (2000). [Online 15 November 2000] <http://ehpnet1.niehs.nih.gov/docs/2000/108p1195-1202egeghy/abstract.html>

Benzene is a volatile organic compound that is toxic to the hematopoietic system (1) and has caused acute myelogenous leukemia in populations with high-level occupational exposures (2,3). Although there is considerable doubt concerning the leukemogenic effect of benzene at lower concentrations (4,5), the suspicion that long-term exposure to even small amounts of benzene may be harmful (6–8), together with the widespread exposure of the general population (9–11), has caused concern.

Environmental concentrations of airborne benzene in the United States tend to range from 2 to $19 \text{ }\mu\text{g/m}^3$, with the higher levels in urban areas (10). Because approximately 85% of atmospheric benzene is derived from mobile sources, higher concentrations are often found inside motor vehicles and adjacent to major roadways (8,12,13). Among nonsmokers the greatest short-term exposures to benzene arise from inhalation of gasoline vapors during automobile refueling. Although current regulations limit the benzene content of all grades of gasoline in the United States to 1% (v/v) (10,14), concentrations as high as 5% have been reported in Europe (15,16).

Self-service gasoline customers are exposed to benzene emitted from fuel combustion as well as from underground storage tanks, spills, and displacement of vapors from the fuel tank (17). Of these, displacement of fuel vapors is thought to be responsible for most of the exposure. A number of studies have found that exposures to benzene vary greatly during self-service refueling from a few parts per billion to several parts per million (18–21). Thus, the general population is regularly exposed to a known carcinogen, sometimes at high levels, albeit for short periods.

Following inhalation, benzene vapor is rapidly absorbed into the blood and distributed throughout the body (22,23). The kinetics of benzene uptake and distribution have been investigated among human volunteers under experimental conditions (24–30) and among occupationally exposed workers (31–41). These studies have relied on unmetabolized benzene in exhaled air (breath), blood, and urine, as well as benzene metabolites in urine. Of these, unmetabolized benzene in breath is an attractive measure of uptake because it is easily obtained by non-invasive means (42,43).

A few investigators have reported benzene uptake associated with gasoline refueling (44,45) and other ambient sources (46–49). In this study we report benzene exposures during self-service gasoline refueling and evaluate the relationship between benzene in ambient air and in breath. In doing so we will apply mixed-effects statistical models to evaluate effects related to the environment and to the individual person. Because such models require rather large sample sizes, we developed a self-administered test kit to assist subjects in obtaining measurements of benzene in ambient air and breath during refueling.

Materials and Methods

Sample collection. A test kit (Figure 1) was developed to facilitate measurements of benzene in air and breath without professional assistance. The kit contains a passive monitor for measuring personal exposure, two glass bulbs of 75-mL volume for obtaining breath (end-exhaled air), and simple illustrated instructions for their use. Both types of monitors are reusable.

The passive monitors consist of aluminum tubes (90 mm \times 6.3 mm o.d. \times 5.0 mm i.d.) fabricated to the dimensions of commercial stainless steel devices designed for this purpose. Each monitor contains 0.1 g of 20/35 mesh Tenax TA (SKC Inc., Eighty Four, PA). The adsorbent is maintained in place by stainless steel screens to create an open diffusion channel of 1.5 cm \times 5.0 mm i.d. An additional screen, recessed 1 mm from the surface, serves as a turbulence barrier to maintain the stable concentration gradient

Address correspondence to S.M. Rappaport, Department of Environmental Sciences and Engineering, CB#7400, University of North Carolina School of Public Health, Chapel Hill, NC 27599-7400 USA. Telephone: (919) 966-5017. Fax: (919) 966-4711. E-mail: stephen_rappaport@unc.edu.

We thank J. Pleil, U.S. Environmental Protection Agency (U.S. EPA), for advice and assistance with measurement of CO_2 , A. Lindstrom (U.S. EPA) for advice, S. Waidyanatha (University of North Carolina) for assistance with chemical analysis methods, and L. Cabalo and C. Ghoddoussi for assistance with chemical analysis of samples.

This work was supported by the National Institute for Environmental Health Sciences through grants P42ES05948 and T32ES07018.

Received 12 May 2000; accepted 15 August 2000.

necessary for constant diffusive uptake. Air sampling is initiated by simply removing one end cap from the monitor. This type of sampler has been used effectively for monitoring volatile organic compounds under various environmental conditions (50).

The locally fabricated breath samplers consist of glass bulbs (75-mL volume, 13-cm length) that are slightly larger than those used elsewhere for this purpose (43,51). The bulbs are sealed with threaded, plastic end caps containing PTFE-lined septa (Chemglass, Vineland, NJ). The subject is instructed to remove the end caps and then to completely exhale through the bulb. Because the bulb volume is small compared to the vital capacity, only end-exhaled air is collected. The subject can obtain the sample while located in a contaminated environment because any unabsorbed benzene from the anatomical dead space should be flushed from the bulb during the initial stage of exhalation. Significant losses are prevented by capping the free end of the device while it is still in the subject's mouth and then quickly replacing the remaining cap.

Subjects and conditions of measurement.

The study was conducted between July 1998 and March 1999, with samples collected

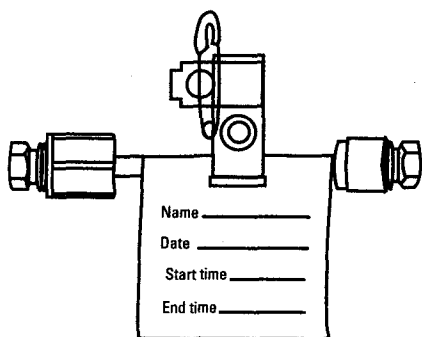


Figure 1. Components of the self-administered test kit. The thermally desorbable passive monitor measured benzene exposure and the glass bulbs captured 75 mL end-exhaled air after exposure.

during three different seasons (no measurements were taken during winter 1998/1999). Stage II vapor recovery controls were not used on gasoline pumps in the local area, but pump nozzles were outfitted with rubber splash collars. Pump nozzle latches were generally absent.

Although no qualifications were placed on participation, 27 of the 39 subjects were affiliated with the University of North Carolina. Thirty-four subjects were non-smokers, three were smokers, and two did not indicate smoking status. Each subject was provided with two test kits at the time of recruitment and encouraged to obtain at least two independent measurements of exposure and breath levels; more kits were provided to subjects as needed. A total of 130 usable sets of measurements were obtained from 39 different participants, with 70% of the samples from males. Repeated measurements were obtained from 31 of the 39 participants. Subjects were instructed to obtain a preexposure breath sample while seated in their vehicle before refueling and then to immediately begin personal sampling by uncapping the passive monitor and clipping it to clothing in the breathing zone. After refueling, the cap was reattached to the passive monitor to terminate sampling, the postexposure breath sample was collected, and all times were recorded. No instructions were provided concerning the refueling process itself; participants were encouraged to refuel their vehicles as customary.

We provided a simple data sheet to assist subjects in recording the start and stop times for the environmental sampling as well as his or her height, weight, and sex. A variety of body types was represented in the study as summarized in Table 1. The questionnaire also requested information regarding several

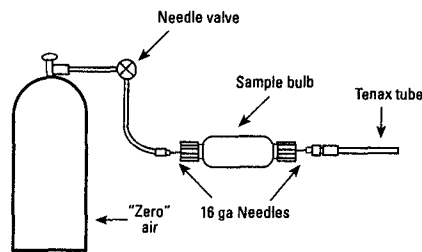


Figure 2. Apparatus for transferring breath samples to sample tubes. Each breath sample bulb was flushed with 400 mL purified air at 100 mL/min, sending the sample through a Tenax-trap to capture the volatile constituents.

covariates related to the refueling process (i.e., duration, octane grade, time lag between refueling and postexposure breath sample, and general weather conditions).

About 5% of the kits were returned with poorly sealed breath monitors, and other types of user error invalidated three samples. These observations were excluded from the statistical analysis. Additionally, the process of concentrating the breath sample onto a thermal desorption cartridge failed in a few instances, and some measurements were lost due to instrument malfunction during analysis.

Preparation of monitors. Passive monitors were initially conditioned at 250°C for 30 min with a continuous flow of ultra high purity helium gas at a rate of 45 mL/min using an automatic thermal desorption system (Model ATD 400; Perkin-Elmer Corp., Norwalk, CT). Just before use, the monitors were also conditioned for 3 min at 250°C followed by 3 min at 225°C to remove trace levels of benzene. (Preliminary experiments determined that this two-step conditioning regimen produced lower levels of residual benzene than conditioning at a single temperature.) Breath sampling bulbs were thoroughly cleaned in an industrial glassware washer and the cap liners were replaced before each use.

Analysis of monitors. Before analysis, breath samples were transferred from the bulbs to air monitors using apparatus illustrated in Figure 2. Each septum was punctured with a 16-gauge needle, and the bulb was flushed with 400 mL zero-grade air at 100 mL/min through an air monitor (of the same type used for passive sampling) to capture the volatile constituents. To minimize surface and condensation losses, the bulb was heated to 90°C before this transfer.

Passive monitors and breath samples were initially analyzed with a Hewlett Packard 5890 Series II gas chromatograph equipped with a flame ionization detector (GC/FID), which was later replaced by a Hewlett Packard 6890 Series Plus GC/FID (Hewlett Packard Corp., Palo Alto, CA). Separation was achieved with a megabore DB-1, 60-m × 0.53-mm dimethylpolysiloxane column (1.5 μm film thickness; J&W Scientific, Folsom, CA). The oven temperature was held at 30°C for 13 min, increased at 50°C/min to a final temperature of 250°C, and held for 5 min. Ultra high purity helium was used as the carrier gas at a flow of approximately 8 mL/min. Chromatograms were manually integrated using Hewlett Packard gas chromatography (GC) ChemStation software. Benzene was identified by the retention time of 10.97 min.

Samples were desorbed with a Perkin-Elmer ATD 400 automatic thermal desorption system (52,53) for 2 min at 225°C to

Table 1. Mean height, weight, and body mass index (BMI) of subjects (range in parentheses).

	No.	Height (cm)	Weight (kg)	BMI
Females	15	168 (157–175)	62.1 (54.4–83.0)	22.1 (18.8–28.7)
Males	24	179 (170–196)	63.0 (59.0–95.3)	23.9 (20.4–28.5)
Overall	39	175 (157–196)	71.2 (54.4–95.3)	23.2 (18.8–28.7)

transfer analytes onto a Tenax-packed, cryogen-free focusing cold trap maintained at -30°C . (Tenax is a registered trademark of Buchem B.V., Apeldoorn, Netherlands.) The cold trap was then rapidly heated to 225°C and held at that temperature for 0.1 min to transfer the contents to the analytical column via a fused silica transfer line, maintained at 200°C . No inlet or outlet splitting was used.

Samples were quantified against external standards prepared by drawing precisely metered volumes of benzene vapor through identical adsorption tubes at 50 mL/min. All benzene vapor standards were prepared by serial dilution as follows: 2 μL liquid benzene (99.9%, Fisher Scientific, Pittsburgh, PA) was injected with a 10- μL syringe (Hamilton Co., Reno, NV) into a 250-mL sealed glass container from which various volumes were removed with a 250- μL Gastight syringe (Hamilton Co.) and injected into a 10- or 40-L Tedlar bag (SKC Inc.), which had been filled with a precisely metered volume of zero-grade air. For example, to achieve a benzene vapor standard of 0.035 mg/m^3 (11 ppb), 200 μL of vapor from the glass container was injected into 40 L zero-grade air. These standards were analyzed in the same manner as the samples. Calibration curves, using at least five points, were determined by linear least-squares regression. The limit of quantitation (LOQ) was estimated as three times the average size of a residual benzene peak from analysis of a conditioned air sampler.

Determination of sampling rates for benzene by passive monitors. Although sampling rates for benzene by Tenax-based passive monitors have been reported for periods of hours to weeks (50), no applications have been reported for periods of a few minutes. Thus, we conducted chamber experiments to estimate the sampling rate for benzene by the passive monitors between 1 and 10 min. The chamber (Figure 3) consisted of a glass flask (1,120-mL) sealed with an aluminum foil-covered rubber stopper and a rubber septum. A Gastight syringe was used to inject 205 μL benzene vapor ($17,800\text{ mg/m}^3$ at 22°C) into the flask to produce an atmosphere of 3.2 mg/m^3 (1.0 ppm) benzene. A magnetic stir bar with blades fashioned from aluminum foil constantly mixed the air. Two passive monitors, each sealed on one end, were exposed simultaneously for each test. After exposure, monitors were analyzed by thermal desorption-GC/FID and sampling rates were calculated.

CO_2 content of breath samples. We investigated the assumption of alveolar sampling by measuring the levels of CO_2 in supplementary breath samples. Five volunteers each provided three breath samples following brief instruction. To measure the CO_2 levels we punctured the septa that sealed the bulbs

with 16 gauge needles and used ultra high purity N_2 at a flow rate of 96.5 mL/min to flush the samples through a Sable CA-1 CO_2 Analyzer (Sable Systems, Henderson, NV). The peak CO_2 readings were normalized to the average of the peak readings measured for bulbs filled with a standard clinical blood gas mixture containing 5.0% CO_2 in air (National Specialty Gases, Durham, NC).

Storage stability of breath samples. We evaluated the sample integrity during storage by measuring the benzene content of standard breath samples over a 4-week period. Thirteen sampling bulbs were filled with benzene in zero-grade air at a concentration of $105\text{ }\mu\text{g/m}^3$ and then stored in the dark at room temperature. Groups of at least 4 bulbs were analyzed after 0, 14, and 28 days had elapsed.

Statistical analysis. We used mixed-effects models to investigate levels of benzene in ambient air and breath using the MIXED procedure available with SAS Statistical Software (SAS Institute, Cary, NC). Histograms and the Shapiro-Wilks test for normality indicated that the distributions of exposure and breath concentration were positively skewed and approximately lognormal. These variables were log-transformed (base e) before analysis to provide nearly Gaussian distributions and to stabilize the variances. Two separate models were used: the first with the log-transformed benzene exposure as the response variable (Model 1), and the second with the log-transformed breath concentration as the response variable (Model 2).

The general mixed model equation is

$$Y_i = X_i A + Z_i B_i + e_i$$

where Y_i is a vector of observations of the response variable at different times for the i -th individual; X_i is a matrix of observed values of fixed-effect predictor variables for the i -th individual; A is a vector of fixed regression coefficients describing the association between Y and X ; Z_i is a matrix of observed values of random-effect predictor variables for the i -th individual; B_i is a vector of individual regression coefficients for these random effects; and e_i is a vector of within-person random errors (54).

Model 1 is presented in nonmatrix form as follows:

$$Y_{ij} = \ln(X_{ij}) = \alpha_0 + \sum_{m=1}^p \alpha_m V_m + \beta_i + \varepsilon_{ij}$$

for $m = 1, 2, \dots, p$ covariates,

for $i = 1, 2, \dots, k$ individuals,

for $j = 1, 2, \dots, n_i$ measurements of the i -th individual,

where X_{ij} represents the exposure level on the j -th day for the i -th individual, and Y_{ij} is the natural logarithm of the individual measurement X_{ij} . The logged variate Y_{ij} represents

the sum of the effects consisting of α_0 representing the intercept, α_m representing the fixed effect for the m -th variable, β_i representing the random effect for the i -th individual, and ε_{ij} representing the random error for the j -th observation on the i -th individual. Additionally, categorical variables were represented by $g-1$ indicator variables for the g levels of each variable. It is assumed that β_i s and ε_{ij} s are normally distributed with means of zero and variances of σ_{β}^2 and σ_{ε}^2 , respectively (representing the between- and within-person components of variance). Model 2 differs from Model 1 only in its response and explanatory variables.

For Model 1 the Y_i were estimated as $\ln(\text{Exposure})$ and the X_i consisted of the observed values for the following variables: duration of exposure (minutes), height of subject (centimeters), sex, octane grade of gasoline (87, 89, 93, or diesel), season (fall, spring, summer), subject's reporting of high humidity conditions (yes or no), subject's reporting of hot ambient temperature (yes or no), and subject's reporting of a noticeable breeze (yes or no). (The final three variables were gleaned from subjects' responses to "notable weather conditions" in the questionnaire.) Of these, all variables were categorical except for duration of exposure and the subject's height. For Model 2 the Y_i were estimated as $\ln(\text{Breath})$ and the X_i consisted of the observed values for the following variables: benzene concentration in breath before refueling [$\ln(\text{Preexposure breath, parts per billion})$], exposure [$\ln(\text{Benzene exposure, parts per million})$], duration of exposure (minutes), time lag between the end of refueling and collection of postrefueling breath sample (minutes), height (centimeters), weight (kilograms), body mass index (BMI; kilograms per meter squared),

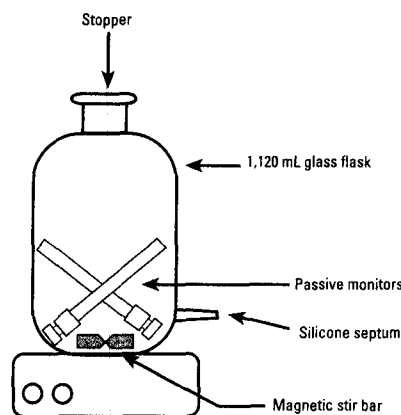


Figure 3. Apparatus for determining sampling rates of benzene by passive monitors. Passive monitors were exposed in duplicate to a well-mixed atmosphere with a benzene concentration of 3.2 mg/m^3 (1.0 ppm) for short periods. Sampling rates (ng/ppm/min) were calculated from the mass of benzene absorbed (as determined by GC analysis) and the duration of the test.

and sex. All predictor variables except sex were continuous.

In the 130 sets of measurements, 97 pre-exposure breath samples (75%), 128 post-exposure breath samples (98%), and 114 external exposure samples (88%) were above the LOQ. Measurements below the LOQ were assigned a value of two-thirds of the limit before statistical analysis. Restricted maximum likelihood (REML) estimation was chosen because of its strong finite sampling properties and its advantage in treating unbalanced data (55).

We used manual backward stepwise regression procedures to build models for each of the two response variables from the available covariates and their plausible two-way interactions. The least significant variable was eliminated at each step, and the models were refitted until only those variables with a significance level of $p < 0.05$ remained. Regression diagnostics were limited to the investigation of collinearity among the potential variables using a simple Pearson correlation matrix (neither eigenvalues nor condition indices were calculated), and to graphical analysis of the observed residuals. To avoid computational inaccuracies due to potential scaling problems, measurement units of the variables were chosen to be similar in ranges. Extreme values identified using the UNIVARIATE procedure available with SAS Statistical Software were investigated for data-input errors, but no data were excluded from the analysis.

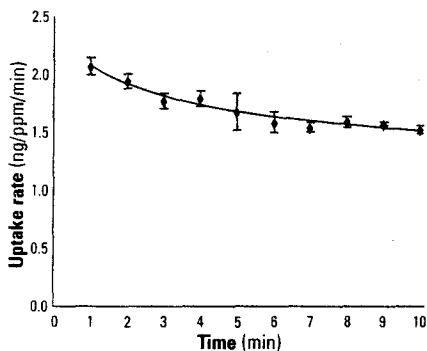


Figure 4. Short-term sampling rates of benzene by passive monitors. Each point represents the estimated mean \pm SD from duplicate measurements. The sampling rate decreased markedly as length of exposure increased.

Table 2. CO₂ levels (%) in breath monitors.

Subject	Sample 1	Sample 2	Sample 3
A	4.7	4.7	5.1
B	5.0	NA	4.9
C	4.1	4.4	4.2
D	4.5	4.8	NA
E	5.1	3.4	3.6

NA, not available (lost during analysis). The weighted mean for all subjects is 4.56%.

Results

Sampling rate of benzene by passive monitors. We estimated the rate of diffusive sampling of benzene from pairs of monitors exposed in a chamber to a concentration of 3.2 mg/m³ (1 ppm) for periods of 1–10 min. As shown in Figure 4, the sampling rate decreased from 2.1 ng/ppm/min (corresponding to 0.66 cm³/min) for a 1-min exposure to 1.5 ng/ppm/min (0.47 cm³/min) for a 10-min exposure.

CO₂ content of breath samples. The CO₂ content of the replicate breath samples obtained from five volunteers is shown in Table 2. Analysis of variance found no significant differences among subjects ($p = 0.28$). The weighted mean benzene concentration was 4.56%, which compares favorably with published measurements of 4.6–4.7% CO₂ using another accepted measure of alveolar air sampling (56). Because alveolar air is considered to be 4–5% CO₂ (57), the results indicate that the breath monitors are effective in capturing alveolar air.

Storage stability of breath samples. Measurements of the benzene content of standard breath samples stored for up to 4 weeks are shown in Table 3. The results indicate that benzene can be stored in the glass breath samplers for at least 2 weeks before analysis with losses of < 5% and a coefficient of variation of < 2%.

Exposure and breath concentrations. Measurements of benzene exposure and benzene in breath are summarized in Table 4. Prerrefueling breath concentrations of benzene averaged 8.6 μ g/m³ (SD = 11.2 μ g/m³) with a range of < 3.2–70 μ g/m³, and postexposure

Table 3. Recovery (%) of benzene from breath monitors stored for various periods of time.

Storage period	Mean recovery (%)	No.	SD	CV
No storage	100	4	1.3	1.3
2 Weeks	96	4	1.5	1.6
4 Weeks	92	5	6.0	6.5

CV, coefficient of variation.

Table 4. Summary of levels of benzene in environmental air and breath during automobile refueling.^a

	No.	Mean \pm SD (mg/m ³)	Minimum (mg/m ³)	Maximum (mg/m ³)
Exposure	130	2.9 \pm 5.8	< 0.076	36
Breath, preexposure	130	0.0086 \pm 0.011	< 0.0032	0.070
Breath, postexposure	130	0.16 \pm 0.26	< 0.0032	1.4

^aDuration 1–10 min (median = 3 min).

Table 5. REML estimates of covariance parameters based on mixed-effects models including important covariates.

Measure	Variance component	Estimate	Percent of total	$\hat{R}_{0.95}^a$
ln(Exposure) (mg/m ³)	Between-person	0.00	0%	274
	Within-person	2.05	100%	
ln(Concentration in breath) (μ g/m ³)	Between-person	0.23	26%	41
	Within-person	0.67	74%	

^aFold range containing 95% of the lognormal distribution of levels.

breath levels averaged 160 μ g/m³ (SD = 260 μ g/m³) with a range of < 3.2–1,400 μ g/m³. Benzene exposure averaged 2.9 mg/m³ (SD = 5.8 mg/m³) with a range of < 0.076–36 mg/m³. The median refueling time was 3 min with a range of 1–10 min.

Within- and between-person variance components. We used mixed-effects regression analysis to obtain REML estimates of between-person and within-person variance components, as summarized in Table 5 (58). The estimated within-person variance component contributed most of the variation in both exposure and breath measurements, indicating that variability among individuals was small relative to that occurring within an individual fueling his or her vehicle at different times. The intraclass correlation coefficient (ratio of the between-subject variance component to the total variance) was zero for exposure measurements and 0.26 for breath measurements. An intuitive measure of the variability of log-normally distributed variates is $\hat{R}_{0.95}$, defined as the estimated fold range containing 95% of the observations (59). As shown in Table 5, the values of $\hat{R}_{0.95}$ for these datasets were 274 for exposure and 41 for benzene in breath.

Benzene in breath versus benzene exposure. The relationship between benzene in breath and benzene exposure is illustrated with the scatter plot shown in Figure 5. Because of the small intraclass correlation of exposure and breath measurements noted in Table 5, repeated measurements from the same individual can be treated as independent observations. Overall, we observed significant linear correlation between the 130 pairs of log-transformed exposures and breath levels ($r = 0.77$, $p < 0.0001$).

Mixed-effects models. Results of fitting Model 1 to the exposure data are summarized in Table 6. The final model contained three significant predictors of benzene exposure, namely, fuel octane grade ($p = 0.0011$), duration of exposure ($p = 0.0054$), and season ($p = 0.032$). Among the types of fuels, mid-grade unleaded gasoline was associated with the

highest benzene exposures and diesel fuel with the lowest; among seasons, fall was associated with the highest exposures and spring with the lowest. The magnitude of benzene exposure decreased with increasing duration. Figure 6 summarizes the effects of octane and season upon benzene exposure with duration held constant at the median value of 3 min. Neither the subject's height nor any of the weather-related variables were found to significantly affect benzene exposure.

Fitting of Model 2 to the data yielded three significant predictors of benzene levels in breath, namely, benzene exposure ($p = 0.0001$), preexposure breath concentration ($p = 0.0008$), and duration of exposure ($p = 0.038$). Table 7 presents the parameter estimates for the model and the tests of fixed effects. The parameter estimate for duration of exposure was positive, in contrast to Model 1, where it was negative. None of the following variables were found to have a significant effect: time lag, sex, BMI, weight, or height.

Discussion

We observed remarkable variability of benzene exposures during automobile refueling, with 95% of the concentrations covering a 274-fold range (Table 5). Faced with such great variability in air levels, large numbers of

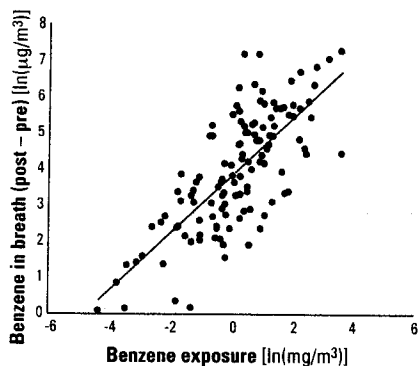


Figure 5. Correlation between benzene exposure and concentration in breath, post - pre, postexposure - preexposure. Repeated measurements from the same individual were treated as independent observations, and a significant linear correlation was observed between the log-transformed exposures and breath levels ($n = 130$, $r = 0.77$, $p < 0.0001$).

Table 6. Fixed effects for benzene exposure.

Effect	Estimate	SE	p -Value
Intercept	-0.25	0.39	-
Duration (min)	-0.24	0.084	0.0054
Octane	-	-	0.0011
Diesel	-2.22	0.88	0.0131
87 Grade	-0.04	0.30	0.8935
89 Grade	1.21	0.45	0.0081
93 Grade	0	-	-
Season	-	-	0.0322
Fall	0.27	0.35	0.4400
Spring	-0.53	0.30	0.0844
Summer	0	-	-

observations are required to adequately characterize exposures. To obtain sufficient data for this purpose, it is necessary to apply methods that allow more measurements to be made at a given cost (59,60). Our approach to increasing sample size was to use passive monitors suitable for use by the subjects themselves and to package the devices in simple test kits that can be transported via the mail. Although several recent studies have used self-monitoring to obtain exposure data from workers (61-63), we are unaware of any other application of self-monitoring to obtain exposure data from the general public.

Despite the simplicity of our study design and methods, the benzene exposures we measured were not markedly different from those reported in recent conventional studies of automobile refueling, as summarized in Table 8. We estimated a mean benzene exposure of 2.9 mg/m^3 ($n = 130$) compared to mean values of 1.3 mg/m^3 ($n = 120$ measurements pooled from 1,013 self-service customers in the United States) (18), 0.9 mg/m^3 ($n = 8$ measurements pooled from 167 self-service customers in Finland, where benzene is also limited to 1% by volume) (21), and a median value of 1.3 mg/m^3 ($n =$

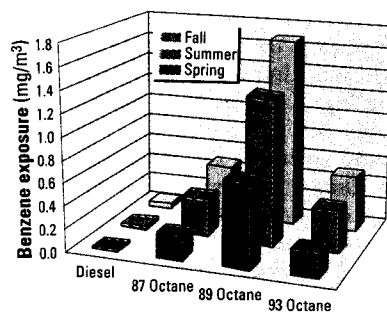


Figure 6. Estimated exposures for a typical refueling time of 3 min. Mixed-effects analysis found octane grade, season, and refueling duration to be significant determinants of benzene exposure. Here duration is held constant to illustrate the effects of octane grade and season.

Table 7. Fixed effects for benzene in breath after refueling.

Effect	Estimate	SE	p -Value
Intercept	3.05	0.217	-
ln(Exposure)	0.70	0.051	0.0001
ln(Preexposure)	0.32	0.091	0.0008
Duration (min)	0.11	0.055	0.0384

Table 8. Recent short-term measurements of benzene concentration during gasoline refueling.

Year	Reference	Country	Avg duration (minutes)	No.	Mean (mg/m^3)	Maximum (mg/m^3)	% Benzene in fuel
1993	Clayton (18)	United States	1.72	120 ^a	1.3	8.4	1.6 ^b
1997	Backer et al. (44)	United States	NR	30 ^c	1.3 ^d	2.7	0.87
1999	Vainiotalo et al. (21)	Finland	1.13	8 ^a	0.9	NR	0.64

Abbreviations: Avg, average; NR, not reported.

^aEach sample was comprised of 8-10 (18) or 20-21 (21) different refuelings. ^bRange: 0.35-4.1. ^cRegular (non-ethanol) unleaded gasoline group only. ^dMedian.

30 self-service customers in Alaska at temperatures of -3°C and below) (44).

Because we obtained repeated exposure measurements from the subjects, it was possible to estimate the within- and between-person variance components. Such partitioning of exposure variability allows inferences to be made regarding the relative influences upon exposure of both environmental factors, indicated by within-person variation, and subject-specific factors, indicated by between-person variation (64). That is, if exposure were governed largely by random factors related to the mix of locations, atmospheric conditions, content of benzene in fuel, duration of refueling, movements patterns, etc., experienced by a typical subject on different days, the within-person variance component would represent most of the variability. In contrast, if factors specific to the individual, such as body size, behavior (e.g., always facing away from the nozzle during refueling), or type of vehicle, were important, the between-person variance component would represent a sizable proportion of the total variation. Because the estimated within-person variance component (Table 5) accounted for all of the variation in benzene exposures estimated in our study, we conclude that environmental rather than subject-specific factors were primarily responsible for benzene exposures during automobile refueling. In a study of benzene exposures among gasoline-station attendants, Lagorio et al. (65) similarly reported a large within-person component of variance, comprising about 83% of the total variance.

Our analysis yielded three significant predictors of benzene exposure, namely, fuel octane grade ($p = 0.0011$), season ($p = 0.0322$), and duration of refueling (0.0054). Regarding octane grade, benzene exposures were lowest when diesel fuel was dispensed and highest when mid-grade (89-octane) gasoline was dispensed. The finding that diesel fuel led to smaller exposures was expected because diesel fuel is known to have a very low benzene content, generally below 0.02% (66). However, the elevated exposures associated with mid-grade gasoline are more difficult to interpret. Octane grade does not refer to the hydrocarbon content but rather to the knock resistance of gasoline that can be achieved through a variety of

hydrocarbon blends (67), and no apparent association between octane grade and benzene exposure has been established. Only two recent studies provide data regarding the benzene content of different grades of gasoline. In the first of these, regular unleaded gasoline (87-octane) was reported to have the highest benzene content at four of six locations (18), whereas in the second, octane grade was reported to be inversely related to benzene content in two of three cities (68).

Regarding the seasonal effect on benzene exposure during refueling ($p = 0.032$), properties of the fuel (e.g., vapor pressure and benzene content) could be involved as well as meteorologic differences (17,19,37,65,69–73). Gasoline is often designated as either “winter blend” or “summer blend” because its volatility reaches a maximum during winter and a minimum during summer to ensure good “driveability” and to comply with regulations restricting evaporative hydrocarbon emissions (16,74). Previous studies have reported higher exposures in winter than in summer (20,75) and also have identified body orientation as an important contributor (in cold weather people tend to lean over the pump nozzle thereby placing their heads directly into the rising vapor stream) (20). Our finding that benzene exposures were higher in summer than in spring cannot readily be explained by known seasonal volatility differences in gasoline. Furthermore, our study included no winter measurements and thus did not permit the full range of seasonal factors to be investigated.

Duration of refueling was inversely related to benzene exposure in our investigation ($p = 0.0054$). Because Lagorio et al. (65) and Backer et al. (44) reported that the volume of fuel dispensed was an important predictor of benzene exposure among service-station attendants and self-service customers, respectively, our finding of lower exposures at longer durations of refueling might appear contradictory. However, given generally rapid gasoline dispensing rates (30–40 L/min) and the rather long refueling times in our study (ranging up to 10 min, with a median of 3 min), it seems unlikely that longer durations corresponded to larger dispensed volumes. Rather, we suspect that longer durations of refueling reflected ancillary tasks associated with payment, checking oil levels, cleaning windshields, etc., where benzene concentrations would be very low. Because individuals continued to wear the personal monitors during such periods of very low exposure, the time-weighted average air concentration recorded with a long duration (many ancillary tasks) would therefore be smaller than one with short duration (few ancillary tasks).

The mean concentration of benzene in breath before refueling was $8.6 \mu\text{g}/\text{m}^3$ (Table

4). Because benzene concentrations have been found to be 3–8 times higher inside a passenger vehicle than in ambient air (10,13,46), this level is probably higher than the background value in the ambient area. Background levels of benzene in the breath of nonsmokers have been reported to be between 0.8 and $5.3 \mu\text{g}/\text{m}^3$ in the United States (76) and to average $6.2 \mu\text{g}/\text{m}^3$ in an urban population in Sweden (77).

Immediately after refueling, benzene levels in the breath of our subjects ranged from < 0.0032 to $36 \text{ mg}/\text{m}^3$, with a mean value of $0.16 \text{ mg}/\text{m}^3$. This range is consistent with a pair of measurements by Lindstrom and Pleil (45), who reported a benzene concentration of $0.025 \text{ mg}/\text{m}^3$ for a single subject immediately after dispensing fuel and $0.007 \text{ mg}/\text{m}^3$ for an observer. In a study of self-service gasoline refueling in Alaska, Backer et al. (44) reported benzene levels between 0.13 and 4.20 ppb in venous blood among 60 subjects. Assuming a blood/breath partition coefficient of 7.4 (38), these blood concentrations correspond to a range of benzene concentrations in alveolar air between 0.019 and $0.60 \text{ mg}/\text{m}^3$, which also seems reasonable in light of our findings.

The range containing 95% of the postexposure breath concentrations was 41-fold compared to the 274-fold range for the corresponding distribution of exposures during refueling (Table 5). This reduction in variability of a biomarker (i.e., benzene in breath) relative to the corresponding exposure distribution arises from accumulation of the contaminant in the body and has been observed over both long and short time scales [reviewed by Rappaport (59)]. Such physiologic damping of exposure variability provides an impetus for using benzene in breath as a biomarker of exposure in future studies of automobile refueling.

Because three-fourths of the variability of benzene measurements in breath was associated with the within-subject variance component (Table 5), we conclude that breath levels were affected primarily by environmental factors operating at different times of refueling rather than by interindividual differences among the subjects. This conclusion is consistent with results shown in Table 7, which indicate that although benzene in breath (after refueling) was highly associated with both benzene exposure [$\ln(\text{Exposure})$: estimated coefficient = 0.70, $p = 0.0001$] and the preexposure breath concentration [$\ln(\text{Preexposure})$: estimated coefficient = 0.32, $p = 0.0008$], subject-specific differences in sex, height, weight, and BMI were not significantly associated with breath levels. The duration of exposure was also positively associated with benzene in breath (estimated coefficient = 0.11, $p = 0.038$) suggesting that

over the few minutes our subjects were exposed, the benzene concentrations in blood and breath increased as the contaminant was distributed to the highly perfused tissues (43,78).

The ratio of the alveolar benzene concentration to inspired benzene concentration has typically been in the range of 0.4–0.6 at steady state [$111\text{--}223 \mu\text{g}/\text{m}^3$ for 0.5–2 hr, Yu and Weisel (79); $80\text{--}100 \mu\text{g}/\text{m}^3$ for 3–4 hr, Hunter and Blair (25)], whereas a median value of 0.17 has been reported for mixed exhaled air among subjects exposed to benzene in residential settings (76). These ratios represent the fractions of the inhaled benzene dose that are exhaled unchanged at steady state (80). The median ratio of alveolar air to inspired air among our subjects was considerably lower at 0.06, again reflecting non-steady-state conditions associated with the short duration of exposure (43,78,81,82) and also reflecting the rapid elimination of benzene following exposure (82,83). Likewise, we suspect that this brief duration of exposure reduced any potential effects of BMI and sex upon benzene in breath, which might have been anticipated due to variation in body fat among subjects (23,25). For example, previous chamber studies [80 mg/m^3 for 2 hr, Sato et al. (29)] showed that women, who have more body fat than men, had decreased respiratory excretion of benzene compared to men, and physiologically based pharmacokinetic (PBPK) modeling [simulation of $32 \text{ mg}/\text{m}^3$ for 8 hr, Brown et al., (84)] predicted that women would have greater metabolism of benzene than men.

Conclusions

This study documents exposure to benzene during self-service refueling. Using mixed-effects regression models and repeated measurements, we showed that the within-person component of variability was quite large for both exposures during refueling and the resulting concentrations in breath. This suggests that environmental rather than individual factors were primarily responsible for the magnitude of benzene exposure during refueling. Of the possible environmental factors affecting benzene exposure, we found significant effects due to fuel-octane grade (mid-grade gasoline produced the highest exposures), season (exposures were greatest in the fall), and duration of refueling (longer times led to lower air concentrations). We also found that levels of benzene in breath were greatly affected by the exposure concentration and the preexposure breath level of benzene, and that the duration of refueling increased breath levels slightly. Finally, this study demonstrated the utility of self-collection of samples of both environmental air and breath among subjects from the general

population. Although not yet in common practice, self-administered monitoring offers an efficient alternative to traditional methods for collecting the large numbers of measurements necessary to accurately characterize exposures and the relationships between exposure and biomarker levels.

REFERENCES AND NOTES

- IARC. Some industrial chemicals and dyestuffs. IARC Monogr Eval Carcinog Risks Hum 29:95–148 (1982).
- Infante PF, Rinsky RA, Wagoner JK, Young RJ. Leukaemia in benzene workers. *Lancet* 2(8028):76–78 (1977).
- Wong O. Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene. *Occup Environ Med* 52:380–384 (1995).
- Austin H, Delzell E, Cole P. Benzene and leukemia: a review of the literature and a risk assessment. *Am J Epidemiol* 127(3):419–439 (1988).
- Hotz P, Lauwerys RR. Hematopoietic and lymphatic malignancies in vehicle mechanics. *Crit Rev Toxicol* 27(5):443–494 (1997).
- Baak YM, Ahn BY, Chang HS, Kim JH, Kim KA, Lim Y. Aplastic anemia in a petrochemical factory worker. *Environ Health Perspect* 107:851–853 (1999).
- Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ. Benzene and leukemia: an epidemiologic risk assessment. *N Engl J Med* 316:1044–1050 (1987).
- Wolff SP. Correlation between car ownership and leukaemia: is non-occupational exposure to benzene from petrol and motor vehicle exhaust a causative factor in leukaemia and lymphoma? *Experientia* 48:301–304 (1992).
- Akland GG. Exposure of the general population to gasoline. *Environ Health Perspect* 101(suppl 6):27–32 (1993).
- Wallace L. Environmental exposure to benzene: an update. *Environ Health Perspect* 104(suppl 6):1129–1136 (1996).
- Wixtrom RN, Brown SL. Individual and population exposures to gasoline. *J Expo Anal Environ Epidemiol* 2(1):23–78 (1992).
- Wallace L. Major sources of exposure to benzene and other volatile organic chemicals. *Risk Anal* 10(1):59–64 (1990).
- Weisel CP, Lawryk NJ, Lioy PJ. Exposure to emissions from gasoline within automobile cabins. *J Expo Anal Environ Epidemiol* 2(1):79–96 (1992).
- Menkes DB, Fawcett JP. Too easily lead? Health effects of gasoline additives. *Environ Health Perspect* 105:270–273 (1997).
- Brief RS, Lynch J, Bernath T, Scala RA. Benzene in the workplace. *Am Ind Hyg Assoc J* 41:616–623 (1980).
- Owen K, Coley T. *Automotive Fuels Reference Book*. 2nd ed. Warrendale, PA: Society of Automotive Engineers, 1995.
- Guldborg PH. Gasoline and vapor exposures in service station and leaking underground storage tank scenarios. *J Expo Anal Environ Epidemiol* 2(1):97–107 (1992).
- Clayton Environmental Consultants. *Gasoline Vapor Exposure Assessment at Service Stations*. API Publication no. 4553. Washington, DC: American Petroleum Institute, 1993.
- Lynge E, Andersen A, Nilsson R, Barlow L, Pukkala E, Nordlinder R, Boffetta P, Grandjean P, Heikkilä, Hörte L, et al. Risk of cancer and exposure to gasoline vapors. *Am J Epidemiol* 145(5):449–458 (1997).
- Tironi G, Nebel GJ, Williams RL. Measurement of vapor exposure during gasoline refueling. SAE Technical Paper Series no. 860087. Warrendale, PA: Society of Automotive Engineers, 1986.
- Vainiotalo S, Peltonen Y, Ruonakangas A, Pfäffli P. Customer exposure to MTBE, TAME, C₈ alkyl methyl ethers, and benzene during gasoline refueling. *Environ Health Perspect* 107:133–140 (1999).
- Hunter CG. Aromatic solvents. *Ann Occup Hyg* 9:191–198 (1966).
- Travis CC, Quillen JL, Arms AD. Pharmacokinetics of benzene. *Toxicol Appl Pharmacol* 102:400–420 (1990).
- Berlin M, Gage J, Gullberg B, Holm S, Knutsson P, Tunek A. Breath concentration as an index of the health risk from benzene: studies on the accumulation and clearance of inhaled benzene. *Scand J Work Environ Health* 6:104–111 (1980).
- Hunter CG, Blair D. Benzene: pharmacokinetic studies in man. *Ann Occup Hyg* 15:193–199 (1972).
- Nomiyama K, Nomiyama H. Respiratory retention, uptake and excretion of organic solvents in man. *Int Arch Arbeitsmed* 32:75–83 (1974).
- Nomiyama K, Nomiyama H. Respiratory elimination of organic solvents in man. *Int Arch Arbeitsmed* 32:85–91 (1974).
- 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* 18:317–322 (1992).
- Sato A, Nakajima T, Fujiwara Y, Hirotsawa K. Pharmacokinetics of benzene and toluene. *Int Arch Arbeitsmed* 33:169–184 (1974).
- Srbová J, Teisenger J, Skramovsky S. Absorption and elimination of inhaled benzene in man. *Arch Ind Hyg Occup Med* 2(1):1–8 (1950).
- Brugnone F, Perbellini L, Romeo L, Bianchin M, Tonello A, Pianalto G, Zambon D, Zanon G. Benzene in environmental air and human blood. *Int Arch Occup Environ Health* 71:554–559 (1998).
- Drummond L, Luck R, Afacan AS, Wilson HK. Biological monitoring of workers exposed to benzene in the coke oven industry. *Br J Ind Med* 45:256–261 (1988).
- Ghittori S, Maestri L, Fiorentino ML, Imbriani M. Evaluation of occupational exposure to benzene by urinalysis. *Int Arch Occup Environ Health* 67:195–200 (1995).
- Hotz P, Carbonnelle P, Hautroid V, Tschopp A, Buchet JP, Lauwerys R. Biological monitoring of vehicle mechanics and other workers exposed to low concentrations of benzene. *Int Arch Occup Environ Health* 70:29–40 (1997).
- Money CD, Gray CN. Exhaled breath analysis as a measure of workplace exposure to benzene ppm. *Ann Occup Hyg* 33(2):257–262 (1989).
- Ong CN, Kok PW, Ong HY, Shi CY, Lee BL, Phoon WH, Tan KT. Biomarkers of exposure to low concentrations of benzene: a field assessment. *Occup Environ Med* 53:328–333 (1996).
- Parkinson GS. Benzene in motor gasoline—an investigation into possible health hazards in and around filling stations and in normal transport operations. *Ann Occup Hyg* 14:145–153 (1971).
- Perbellini L, Faccini GB, Pasini F, Cazzoli F, Pistoia S, Rosellini R, Valsecchi M, Brugnone F. Environmental and occupational exposure to benzene by analysis of breath and blood. *Br J Ind Med* 45:345–352 (1988).
- Popp W, Rauscher D, Müller G, Angerer J, Norpeth K. Concentrations of benzene in blood and s-phenylmercapturic and t,t-muconic acid in urine in car mechanics. *Int Arch Occup Environ Health* 66:1–6 (1994).
- Sherwood RJ. Evaluation of exposure to benzene vapour during the loading of petrol. *Br J Ind Med* 29:65–69 (1972).
- Sherwood RJ, Carter FWG. The measurement of occupational exposure to benzene vapour. *Ann Occup Hyg* 13:125–146 (1970).
- Medeiros AM, Bird MG, Witz G. Potential biomarkers of benzene exposure. *J Toxicol Environ Health* 51:519–539 (1997).
- Wilson HK. Breath analysis: physiological basis and sampling techniques. *Scand J Work Environ Health* 12:174–192 (1986).
- Backer LC, Egeland GM, Ashley DL, Lawryk NJ, Weisel CP, White MC, Bundy T, Shortt E, Middaugh JP. Exposure to regular gasoline and ethanol oxyfuel during refueling in Alaska. *Environ Health Perspect* 105:850–855 (1997).
- Lindstrom AB, Pleil JD. Alveolar breath sampling and analysis to assess exposures to methyl tertiary butyl ether (MTBE) during motor vehicle refueling. *J Air Waste Manag Assoc* 46:676–682 (1996).
- Björkqvist S, Spetz A, Ramnäs O, Petersson G. Isoprene from expired air inside a private car. *Sci Total Environ* 207:63–67 (1997).
- Fustinoni S, Buratti M, Giampiccolo R, Colombi A. Biological and environmental monitoring of exposure to airborne benzene and other aromatic hydrocarbons in Milan traffic wardens. *Toxicol Lett* 77:387–392 (1995).
- Romieu I, Ramirez M, Meneses F, Ashley D, Lemire S, Colome S, Fung K, Hernandez-Avila M. Environmental exposure to volatile organic compounds among workers in Mexico City as assessed by personal monitors and blood concentrations. *Environ Health Perspect* 107:511–515 (1999).
- Wallace LA, Pellizzari E, Hartwell T, Rosenzweig M, Erickson M, Sparacino C, Zelon H. Personal exposure to volatile organic compounds I. Direct measurements in breathing-zone air, drinking water, food, and exhaled breath. *Environ Res* 35:293–319 (1984).
- Brown RH. Environmental use of diffusive samplers: evaluation of reliable diffusive uptake rates for benzene, toluene and xylene. *J Environ Monit* 1:115–116 (1999).
- Stewart RD, Dodd HC. Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride, and 1,1,1-trichloroethane through the human skin. *Am Ind Hyg Assoc J* 23:439–446 (1964).
- Periago JF, Prado C, Ibarra I. Application of thermal desorption to the biological monitoring of organic compounds in exhaled breath. *J Chromatogr A* 657:147–153 (1993).
- Verma DK, des Tombe K. Measurement of benzene in the workplace and its evolution process, part II: present methods and future trends. *Am Ind Hyg Assoc J* 60:48–56 (1999).
- Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. *J Pediatr* 131:809–814 (1997).
- Lemasters GK, Shukla R, Li YD, Lockey JE. Balancing cost and precision in exposure assessment studies. *J Occup Environ Med* 38(1):39–45 (1996).
- Pleil JD, Lindstrom AB. Collection of a single alveolar exhaled breath for volatile organic compounds analysis. *Am J Ind Med* 28:109–121 (1995).
- Wallace L, Buckley T, Pellizzari E, Gordon S. Breath measurements as volatile organic compound biomarkers. *Environ Health Perspect* 104(suppl 5):861–869 (1996).
- Rappaport SM, Weaver M, Taylor D, Kupper L, Susi P. Application of mixed models to assess exposures monitored by construction workers during hot processes. *Ann Occup Hyg* 43(7):457–469 (1999).
- Rappaport SM. Assessment of long-term exposures to toxic substances in air. *Ann Occup Hyg* 35(1):61–121 (1991).
- Bartolucci GB, Perbellini L, Gori GP, Brugnone F, Corona PC, De Rosa E. Occupational exposure to solvents: field comparison of active and passive samplers and biological monitoring of exposed workers. *Ann Occup Hyg* 30(3):295–306 (1986).
- Liljelind IE, Strömbock AE, Järholm BG, Levin JO, Brangert BL, Sunesson AK. Self-assessment of exposure—a pilot study of assessment of exposure to benzene in tank truck drivers. *Appl Occup Environ Hyg* 15(2):195–202 (2000).
- Loomis DP, Kromhout H, Peipins LA. Sampling design and field methods of a large, randomized, multisite survey of occupational magnetic field exposure. *Appl Occup Environ Hyg* 9(1):49–52 (1994).
- Saariainen L, Hakkola M, Pekari K, Lappalainen K, Aitio A. Exposure to gasoline road-tanker drivers to methyl tert-butyl ether and methyl tert-amyl ether. *Int Arch Occup Environ Health* 71:143–147 (1998).
- Krumhout H, Symanski E, Rappaport SM. A comprehensive evaluation of within- and between-worker components of occupational exposure to chemical agents. *Ann Occup Hyg* 37:253–270 (1993).
- Lagorio S, Iavarone I, Iacovella N, Proietto AR, Fuselli S, Baldassarri LT, Carere A. Variability of benzene exposure among filling station attendants. *Occup Hyg* 4:15–30 (1997).
- IARC. Occupational exposures in petroleum refining; crude oil and major petroleum fuels. IARC Monogr Eval Carcinog Risks Hum 45:219–237 (1989).
- King RW. Automotive gasoline: its composition and manufacture - past, present, and future. *J Expo Anal Environ Epidemiol* 2(1):9–22 (1992).
- Hartle R. Exposure to methyl tert-butyl ether and benzene among service station attendants and operators. *Environ Health Perspect* 101(suppl 6):23–26 (1993).
- Halder CA, Van Gorp GS, Hatoun NS, Warne TM. Gasoline vapor exposures; part I: Characterization of workplace exposures. *Am Ind Hyg Assoc J* 47(3):164–172 (1986).
- Jakobsson R, Ahlbom A, Bellander T, Lundberg I. Acute myeloid leukemia among petrol station attendants. *Arch Environ Health* 48(4):255–259 (1993).
- McDermott HJ, Vos GA. Service station attendants' exposure to benzene and gasoline vapors. *Am Ind Hyg Assoc J* 40:315–321 (1979).
- Nordlinder R, Ramnäs O. Exposure to benzene at different workplaces in Sweden. *Ann Occup Hyg* 31(3):345–355 (1987).
- Periago JF, Zambudio A, Prado C. Evaluation of environmental levels of aromatic hydrocarbons in gasoline service

- stations by gas chromatography. *J Chromatogr A* 778:263-268 (1997).
74. Chevron Product Services Home Page. Gasoline and Driving Performance. Available: <http://www.chevron.com/prodserv/bulletin/motorgas> [cited 3 September 1999].
 75. Cheng WK, Bebee G, Groats JFK, Rezek. A Study of Exposure to Motor Gasoline Hydrocarbon Vapors at Service Stations. CPPI Report No. 90-8. Ottawa, Ontario, Canada: Canadian Petroleum Products Institute, 1990.
 76. Wallace LA, Pellizzari E, Hartwell TD, Perritt R, Ziegenfuss R. Exposures to benzene and other volatile compounds from active and passive smoking. *Arch Environ Health* 42(5):272-279 (1987).
 77. Ljungkvist GM, Nordlinder RG. A field method for sampling benzene in end-exhaled air. *Am Ind Hyg Assoc J* 56:693-697 (1995).
 78. Opdam JGG. Respiratory input in inhalation experiments. *Br J Ind Med* 46:145-156 (1989).
 79. Yu R, Weisel CP. Measurement of benzene in human breath associated with an environmental exposure. *J Expo Anal Environ Epidemiol* 6(3):261-277 (1996).
 80. Gordon SM, Wallace LA, Pellizzari ED, O'Neill HJ. Human breath measurements in a clean-air chamber to determine half-lives for volatile organic compounds. *Atmos Environ* 22(10):2165-2170 (1988).
 81. Petreas MX, Woodlee J, Becker CE, Rappaport SM. Retention of styrene following controlled exposure to constant and fluctuating air concentrations. *Int Arch Occup Environ Health* 67:27-34 (1995).
 82. Thomas KW, Pellizzari ED, Raymer JH, Cooper SD, Smith DJ. Kinetics of low-level volatile organic compounds in breath I: experimental design and data quality. *J Expo Anal Environ Epidemiol* 2(suppl 2):45-66 (1992).
 83. Fiserova-Bergerova V, Vlach J. Timing of sample collection for biological monitoring of occupational exposure. *Ann Occup Hyg* 41(3):345-353 (1997).
 84. Brown EA, Shelley ML, Fisher JW. A pharmacokinetic study of occupational and environmental benzene exposure with regard to gender. *Risk Anal* 18(2):205-213 (1998).

Upcoming 2001-2002 Monographs

- Reviews in Environmental Health
- Toxicology of Fumonisin
- Assessment of Climate Variability and Change
- Nutrition-Toxicology: Evolutionary Aspects
- Lead Model Development: Probabilistic Risk Assessment
- Volatile Irritants and Allergens

For subscription information, see Subscription Insert.

For advertising information, call 919-541-5257 or e-mail dowd@niehs.nih.gov