

Human Exposure to Methyl *tert*-Butyl Ether (MTBE) While Bathing with Contaminated Water

by

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Foreword

The mission of the National Exposure Research Laboratory (NERL) is to provide scientific understanding, information, and assessment tools that will quantify and reduce the uncertainty in EPA's exposure and risk assessments for environmental stressors. These stressors include chemicals, biologicals, radiation, and changes in climate, land use, and water use. The Laboratory's primary function is to measure, characterize, and predict human and ecological exposure to pollutants. Exposure assessments are integral elements in the risk assessment process used to identify populations and ecological resources at risk. The EPA relies increasingly on the results of quantitative risk assessments to support regulations, particularly of chemicals in the environment. In addition, decisions on research priorities are influenced increasingly by comparative risk assessment analysis. The utility of the risk-based approach, however, depends on accurate exposure information. Thus, the mission of NERL is to enhance the Agency's capability for evaluating exposure of both humans and ecosystems from a holistic perspective.

The National Exposure Research Laboratory focuses on four major research areas: predictive exposure modeling, exposure assessment, monitoring methods, and environmental characterization. Underlying the entire research and technical support program of the NERL is its continuing development of state-of-the-art modeling, monitoring, and quality assurance methods to assure the conduct of defensible exposure assessments with known certainty. The research program supports its traditional clients – Regional Offices, Regulatory Program Offices, ORD Offices, and Research Committees – and ORD's Core Research Program in the areas of health risk assessment, ecological risk assessment, and risk reduction.

Monitoring techniques for volatile organic compounds (VOCs) in air or exhaled breath are constantly evolving as the needs of the exposure assessment and health effects communities change. The continuous real-time breath analyzer provides a unique means of collecting abundant data with which to track the uptake, distribution in the body, and decay of numerous compounds of interest to NERL. The purpose of the present study was to better understand the uptake and disposition of methyl *t*-butyl ether (MTBE) and dibromochloromethane (DBCM) within the human body during bathing or showering following realistic dermal exposures through the use of contaminated tap water.

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Director
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Abstract

The oxygenate methyl tert-butyl ether (MTBE) has been added to gasoline to meet national ambient air quality standards in those parts of the U.S. that are non-compliant for carbon monoxide. Although MTBE has provided important health benefits in terms of reduced hazardous air pollutants, the increasing occurrence and detection of MTBE in drinking water sources in California, New Jersey, and elsewhere has raised concerns about potential exposures from water usage and resulting health effects. In addition to MTBE, disinfection byproducts can be present in the water people use for showering, bathing, or drinking, as a result of the reaction of disinfection agents with organic material already present in water. Chlorine, a widely used disinfection agent, reacts with humic acids to form the trihalomethanes, which are the most common and abundant byproducts in chlorinated water. Besides chloroform, which has been extensively studied, the byproduct dibromochloromethane (DBCM) occurs as a result of the chlorination process in those areas that naturally have bromide in their ground water.

Because the breath analyzer showed almost no discernible change in MTBE and DBCM breath concentrations in the shower experiments that were conducted, we abandoned all further shower exposure efforts in favor of the bath water experiments.

Three male and two female volunteers participated in the bath water study, in which each was exposed to 40 $\mu\text{g/L}$ of DBCM and 150 $\mu\text{g/L}$ of MTBE- d_{12} in water for 30 minutes. We were unable to derive meaningful results from the real-time breath analyzer data generated for DBCM, largely because of what appeared to be an interfering contaminant with mass spectral fragment ions that occurred at the same mass as the mass used to monitor for DBCM.

All of the breath concentration/time profiles obtained for the five participants, as a result of dermal exposure to MTBE- d_{12} and MTBE in water, showed similar small increases in breath concentrations, from pre-exposure levels of 2 – 9 $\mu\text{g/m}^3$ to peak levels of 7 – 15 $\mu\text{g/m}^3$. After exposure ended, breath levels slowly decreased and tended toward the pre-exposure levels during the 30-minute elimination monitoring period. In all cases, except for one subject, the measured levels throughout the monitoring periods were above the limits of detection obtained with the real-time breath analyzer. The pre-exposure levels were roughly equal to the detection limits for MTBE- d_{12} , which ranged from 2.3 to 10.6 $\mu\text{g/m}^3$. This concentration range is similar to that reported for background levels of MTBE in previous studies that relied on batch collection and gas chromatographic/mass spectrometric (GC/MS) analysis for breath sample measurement.

Uptake and elimination residence times were estimated using a one-compartment linear model. The mean residence times for the decay phase were roughly twice as long as the mean

residence times for the uptake phase, viz., $\tau_{uptake} = 21.2 \pm 13.1$ min and $\tau_{decay} = 41.5 \pm 26.3$ min [mean \pm standard deviation]. The reasonably good agreement obtained for the residence times among the five participants suggests that our estimates of the model parameters may be fairly robust. These estimated values are much greater than the residence times obtained in our earlier study of the dermal absorption of chloroform from bath water, for which the mean uptake residence time was 8.2 ± 3.1 min and the mean decay residence time was 7.7 ± 1.0 min. This may be due to the greater solubility of MTBE in water, which is reflected by their respective Henry's Law coefficients, namely, 1.6 mole/atm for MTBE vs. 0.26 mole/atm for chloroform. These residence times also are significantly larger than the uptake and decay residence times for MTBE determined in our companion inhalation study.

The total amount of MTBE-d₁₂ exhaled during the exposure and post-exposure periods was estimated by integrating the area under the breath uptake and elimination curve. The mean amount of MTBE-d₁₂ exhaled at an average temperature of 39.5°C was 3.0 ± 1.1 (SD) μg (range: 1.7 – 4.6 μg). The mean exhaled amount obtained in our earlier bath water study of chloroform absorption at roughly the same temperature was 7.0 ± 2.0 μg . This indicates that the dermal uptake of MTBE from bath water is significantly smaller than that of chloroform under similar exposure conditions.

It is interesting to note that, although dermal absorption of MTBE from water has been measured directly in the blood of human subjects in at least one earlier study, our measurements appear to be the first of the dermal uptake of MTBE using continuous breath analysis. Finally, the model parameters determined in this study may be useful to risk assessors in EPA State and Regional offices for estimating dermal exposure to this contaminant while bathing.

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Chapter 1 Introduction

Methyl *tert*-butyl ether (MTBE) was first introduced in the U.S. as a synthetic gasoline additive in the 1970s. The federal Clean Air Act requirements for oxygenates in wintertime gasoline made MTBE, which has oxygen-containing properties, a popular choice of refineries manufacturing reformulated gasoline. Added to gasoline at levels of up to 15% by volume, MTBE reduces automotive emissions of carbon monoxide.

A survey of ground water throughout the United States by the US Geological Survey has indicated that MTBE is one of the most frequently detected compounds in ground water.¹ MTBE is highly water-soluble and appears to be resistant to chemical and microbial degradation in water.² When MTBE, which has a very unpleasant taste and odor,³ began appearing in groundwater and some public drinking water systems throughout the U.S., environmental agencies, state governments, regulatory groups, and researchers became concerned.^{2,3,4,5,6,7} Issues of toxicology and exposure during automobile refueling also pointed to the need for information on the exposure levels and distribution of MTBE in the human body.

Besides MTBE, the trihalomethanes (chloroform, bromodichloromethane, dibromochloromethane, bromoform) can be present in the water people use for showering, bathing, or drinking, if the water supply was disinfected with chlorine and contaminated with MTBE. The most common method of disinfecting water in the U.S. is by adding chlorine directly to the water. Disinfection byproducts (DBPs) result from the reaction of disinfection agents with organic material already present in water. Chlorine reacts with humic acids to form the trihalomethanes, the haloacetic acids, and many other halogenated compounds. Of the many classes of disinfection byproducts that occur, trihalomethanes are the most common and abundant in chlorinated water. The DBP, dibromochloromethane (DBCM) occurs in the chlorination process in those areas that naturally have bromide in their ground water. Dibromochloromethane has been reported to occur at about 40 µg/L at the 90th percentile in Los Angeles, CA⁸.

Exposure to MTBE can occur by inhalation, dermal contact, or ingestion.^{4,5,6,7,9} Vehicle refueling activities lead to the highest potential exposures by inhalation, with breathing zone levels ranging from 0.1 to 4 ppm for 1 – 2 min durations and peaks occasionally exceeding 10 ppm.^{10,11,12} The health effects of exposures to gasoline or water containing MTBE are not well-established,¹³ although acute effects such as headaches, nausea or vomiting, nasal and ocular irritation, and sensations of disorientation, have been associated with exposure to gasoline containing MTBE.^{14,15} In those areas of the U.S. that use MTBE as a gasoline oxygenate, doses from non-occupational exposure are between 0.4 and 6 µg/kg-day, and roughly 1.4 µg/kg-day as a result of exposure via contaminated water.¹⁶

Several studies, including some based on the analysis of exhaled breath, have demonstrated significant dermal absorption of chloroform and trichloroethylene while showering or bathing, and the dose is roughly comparable to that resulting from inhalation.^{17,18,19,20,21,22,23,24} The uptake of MTBE by inhalation has been measured in exhaled breath under controlled conditions using integrated sampling techniques,^{11,25,26,27,28,29} but reports on the measurement of the potential uptake of MTBE through the skin are sparse.⁹

We recently developed and applied real-time breath analysis technology to measure dermal absorption of chloroform while bathing.²¹ Subjects bathed in contaminated water while breathing pure air through a full face mask; the chloroform in their exhaled breath was analyzed continuously in real time. Not only were we able to measure chloroform in the breath at levels up to about 12 ppb, but we also found that water temperature has a powerful effect on dermal absorption. An increase from 30°C to 40°C in bath water temperature produced about a 30-fold increase in absorbed chloroform. The real-time breath measurement method^{21,30} provides abundant data compared to previous discrete time-integrated breath sampling methods.^{31,32} It measures inhalation exposure directly, allowing us to trace the uptake, distribution in the body, and decay of various compounds of interest. Because the face mask eliminates exposure to contaminated air, it is particularly well suited to measuring dermal exposure only.

The purpose of the present study was to use the real-time breath measurement technology to determine potentially significant human exposure to MTBE and DBCM by the dermal route. A major objective was to measure directly the uptake of MTBE by dermal absorption while showering or bathing with contaminated water and the presence of tertiary-butyl alcohol (TBA) in the exhaled breath. TBA is a metabolite of MTBE, so its occurrence in the breath would provide a measure of metabolic activity. A second objective was to estimate the relative contributions of dermal and inhalation exposure to MTBE while bathing and to incorporate the breath measurements into an existing multicompartment chamber model to assess the relative significance of MTBE exposure while bathing with contaminated water.

Chapter 2 Conclusions

The real-time breath analyzer was used in an effort to better understand the uptake, distribution, and elimination of dermally absorbed MTBE and DBCM within the human body during bathing and showering as a result of realistic dermal exposures.

Two male subjects volunteered to participate in the shower experiments, which were conducted in a bathroom at the Environmental and Occupational Health Sciences Institute (EOHSI), Rutgers University, in Piscataway, NJ. However, the breath analyzer, which was used in these experiments to measure the uptake of MTBE-d₁₂ (water concentration 150 µg/L) and DBCM (water concentration 40 µg/L), showed almost no discernible change in breath concentration from pre-exposure levels throughout each 30-minute exposure period, even at the highest temperature used, i.e., 40°C. Because these experiments exhibited no measurable effects, we abandoned all further shower exposure runs in favor of the bath water experiments.

Although some bath water experiments were run at EOHSI, the temperature fluctuations and other problems encountered in the bathroom where the experiments were conducted prevented us from obtaining reliable data. As a result, we report here only on the 5 data sets that were subsequently generated from the volunteers (3 males, 2 females) who participated in the study in our laboratory at Battelle in Columbus, OH. Even so, the detection limits of the real-time breath analyzer for exposure to 40 µg/L of DBCM in water for 30 minutes were much higher than for MTBE-d₁₂ and we observed relatively high initial exhaled breath levels for DBCM. This, together with the lack of agreement that was observed between the breath analyzer and canister-gas chromatography/mass spectrometry (GC/MS) data provided a strong indication that the measured breath analyzer signal was probably due to an unknown contaminant with mass spectral fragment ions at the same mass. As a result, no meaningful results were derived from the data obtained for DBCM.

For all five participants, the breath concentration/time profiles obtained for MTBE-d₁₂ and MTBE for dermal exposure to a nominal concentration of 150 µg/L for 30 minutes showed similar relatively slow and small increases in breath concentrations, from pre-exposure levels of 2 – 9 µg/m³ to peak levels of 7 – 15 µg/m³. After exposure ended, breath levels slowly decreased and tended toward the pre-exposure levels during the 30-minute elimination monitoring period. In all cases, except for one subject, the measured levels throughout the monitoring periods were above the limits of detection obtained with the real-time breath analyzer. The pre-exposure levels were roughly equal to the detection limits for MTBE-d₁₂, which ranged from 2.3 to 10.6 µg/m³. This concentration range is similar to that reported for

background levels of MTBE in previous studies that relied on batch collection and GC/MS analysis for breath sample measurement.

Uptake and elimination residence times were estimated using a one-compartment linear model. The mean residence times for the decay phase were roughly twice as long as the mean residence times for the uptake phase, viz., $\tau_{uptake} = 21.2 \pm 13.1$ min and $\tau_{decay} = 41.5 \pm 26.3$ min [mean \pm standard deviation]. The reasonably good agreement obtained for the residence times among the five participants suggests that our estimates of the model parameters may be fairly robust. These values are much greater than the residence times obtained in our earlier study of the dermal absorption of chloroform from bath water, for which the mean uptake residence time was 8.2 ± 3.1 min and the mean decay residence time was 7.7 ± 1.0 min. This may be due to the greater solubility of MTBE in water, which is reflected by their respective Henry's Law coefficients, namely, 1.6 mole/atm for MTBE vs. 0.26 mole/atm for chloroform. These values also are significantly larger than the uptake and decay residence times for MTBE determined in our companion inhalation study.

The total amount of MTBE-d₁₂ exhaled during the exposure and post-exposure periods was estimated by integrating the area under the breath uptake and elimination curve. The mean amount of MTBE-d₁₂ exhaled at an average temperature of 39.5°C was 3.0 ± 1.1 (SD) μg (range: 1.7 – 4.6 μg). The mean exhaled amount obtained in our earlier bath water study of chloroform absorption at roughly the same temperature was 7.0 ± 2.0 μg . This indicates that the dermal uptake of MTBE from bath water is significantly smaller than that of chloroform under similar exposure conditions.

It is worth noting that, although dermal absorption of MTBE from water has been measured directly in the blood of human subjects in at least one earlier study, our measurements appear to be the first of the dermal uptake of MTBE using continuous breath analysis. Furthermore, the model parameters determined in this study may be useful to risk assessors in EPA State and Regional offices for estimating dermal exposure to this contaminant while bathing.

Chapter 3

Recommendations

The real-time breath analyzer is a promising technique for the continuous monitoring of trace-level VOCs in breath. It was used along with a specially designed face mask to isolate and examine dermal exposure to MTBE and DBCM, resulting from bathing in contaminated tap water.

Sensitivity limitations with the real-time breath analyzer prevented us from obtaining usable exhaled breath data for either MTBE or DBCM from subjects while showering, or for DBCM from subjects while bathing. Also, analysis problems experienced in the laboratory at EOHSI and a subsequent lack of funds prevented us from measuring the actual water concentrations of the target compounds. Because these data are important in developing a more complete picture of the uptake and disposition of these chemicals in the human body as a result of dermal exposures, we recommend that careful attention be paid in future studies to first maximizing the sensitivity of the breath analyzer and to ensuring that the analytical techniques for the characterization of target analytes in water are reliable and can be applied without difficulty before embarking on similar studies.

Chapter 4

Experimental Procedures

In this exposure scenario, subjects showered or bathed in water contaminated with MTBE and DBCM while wearing a full face mask connected to a supply of pure air to eliminate inhalation exposure. Exhaled breath was monitored continuously using the real-time breath analyzer. Shower and bathtub experiments were conducted in a bathroom at the Environmental and Occupational Health Sciences Institute (EOHSI), Rutgers University, in Piscataway, NJ; additional bathtub experiments were carried out in our laboratories at Battelle, in Columbus, OH.

Experimental Procedures

Subject Selection and Recruitment

Volunteers for the first part of this study were sought from amongst the student population at Rutgers University, in Piscataway, NJ by means of notices placed in buildings around the University campus and local newspaper advertisements. For the additional experiments conducted at Battelle, volunteers were recruited by word-of-mouth from amongst a group of temporary technicians who were available on site at the time. Respondents with any of the following medical conditions were excluded: neurologic disease or brain injury, significant exposure to other neurotoxicants, chronic fatigue syndrome or multiple chemical sensitivity, stroke or cardiovascular disease, serious pulmonary disease, liver or kidney disease, serious gastrointestinal disorders (e.g. colitis), claustrophobia, and major psychiatric conditions including psychoses, manic depression, alcoholism, or drug abuse. No pregnant or lactating women were included.

The subjects were healthy, young nonsmoker adults of average weight and height. Information on the subjects is provided in Table 4-1 along with a summary of the exposure conditions. Information was collected from each subject on his/her age, height, weight, respiration rate (using a dry gas meter), and percent body fat (from body circumferences and height). The study protocol was reviewed and approved by both the Battelle Human Subjects Committee and the EOHSI Institutional Review Board (IRB) before it was submitted to and approved by the EPA Human Subjects Committee. Informed written consent was obtained from each subject before participation. Each subject received financial compensation on completion of the exposure experiments.

Table 4-1. Characteristics of Subjects who Participated in Dermal Exposure Study at EOHSI and Battelle, and Associated Exposure Conditions.

Subject	Sex ^a	Height (cm)	Weight (kg)	Age (yr)	Shower (S) or Tub (T) Exposure ^b	EOHSI or BCO ^a	Expt. Date	MTBE-d ₁₂ /DBCM Conc. in Water (µg/L)	Water Temp (°C)	Shower Flow Rate (L/min)	RTBA Sample/ Calibration File ID
SM01	M	170	77.1	20	S (RTBA)	EOHSI	02/12/01	150 / 40	41.0	10.2	SM01a/Cal0212
SM03	M	185	90.7	36	S (RTBA)	EOHSI	02/13/01	150 / 40	40.5	?	SM03/cal0213
TM05	M	175	83.9	54	T (RTBA)	EOHSI	02/14/01	150 / 40	39.7	—	TM05/cal0214a —/cal0214b —/cal0214c
TF02	F	162	58.1	21	T (RTBA)	EOHSI	02/14/01	150 / 40	40.0	—	TF02/cal0214a —/cal0214b —/cal0214c
TM04	M	173	61.2	21	T (RTBA)	EOHSI	02/14/01	150 / 40	38.5	—	TM04/cal0214a TM04a/cal0214b —/cal0214c
TF06	F	163	54.4	19	T (C)	EOHSI	02/15/01	150 / 40	40.0	—	— ^c
TM07	M	?	?	?	T (C)	EOHSI	02/16/01	150 / 40	40.2	—	— ^c
BCOM1T	M	170	60.8	21	T (RTBA/C)	BCO	06/21/01	150 / 40	39.7	—	BCOM1T/cal0621a
BCOF1T	F	163	57.2	25	T (RTBA/C)	BCO	06/22/01	150 / 40	39.0	—	BCOF1T/cal0622a
BCOM2T	M	185	90.7	23	T (RTBA/C)	BCO	06/22/01	150 / 40	38.8	—	BCOM2T/cal0622b
BCOF2T	F	157	61.2	29	T (RTBA/C)	BCO	06/29/01	150 / 40	39.8	—	BCOF2T/cal0629a
BCOM3T	M	166	65.8	21	T (RTBA/C)	BCO	06/29/01	150 / 40	40.4	—	BCOM3T/cal0629b

^a Abbreviations: M, male; F, female; EOHSI = Environmental and Occupational Health Sciences Institute (EOHSI), Piscataway, NJ; BCO = Battelle Columbus Operations, Columbus, OH.

^b Breath Measurements Made: RTBA = continuous real-time breath analyzer; C = discrete evacuated stainless steel canister samples.

^c No breath analyzer or calibration file generated since only discrete canister samples were collected.

Exposure Conditions

Shower Facility

Shower experiments were conducted in a bathroom at EOHSI that contained a separate shower stall. The real-time breath analyzer and associated equipment were set up in the bathroom, next to the shower stall. Water for the shower was purified by flowing it through a charcoal filter to remove disinfection by-products as well as any MTBE that may have been present. A syringe-drive unit was connected by means of a T-piece to the inlet piping, just before it entered the shower head, and was used to inject the MTBE-d₁₂ (>99.8 atom %D; Lot No. F65P1; C/D/N/ Isotopes; CAS No. 29366-08-3) and DBCM mix into the shower stream to obtain the desired concentrations. Initial plans called for experiments at three concentrations of MTBE (50, 100, and 150 µg/L) and a single concentration of DBCM (40 µg/L). These concentrations have been found in tap or ground water in various areas of the United States. The water temperatures of interest were 35°C and 40°C, to examine the effect of temperature on dermal absorption.

The shower facility was modified by using two standard shower heads mounted opposite each other, to allow the subject, wearing a face mask with supply tubes attached, to stand facing in one direction. Thus, the subject did not have to turn around every few minutes in order to ensure uniform exposure front and back. The two showers used were commercially-available portable outdoor shower units. Each unit, which was adjustable up to a height of 1.87 m (73½ in), included a shower-head mounted on a plastic rod in a metal tripod, an adjustable on/off valve, and a length of garden hose.

At the start of an experiment, the subject was fitted with a full face mask, which was attached to a pure air supply to ensure that the only route of exposure to MTBE and DBCM was by dermal absorption. The fit of the mask was checked for leak tightness before the experiment by exposing the subject to isoamyl acetate (“banana oil”) or acetic acid vapors and determining whether the odor was detectable by the subject.

After putting on the face mask and immediately before entering the shower stall, the outlet tube from the face mask was attached to the real-time breath analyzer and the subject provided a pre-exposure breath sample (3-4 min duration). The subject then stepped into the shower stall and positioned him/herself in the water spray. Exposure continued for 30 minutes, during which time breath measurements were taken continuously to map the uptake curves for MTBE-d₁₂ and DBCM. At the end of the exposure period, the subject exited the shower stall and quickly towed him/herself down while continuing to breathe purified air and provide exhaled breath samples. Figure 4-1 is a schematic of a subject in the test shower facility, showing the subject wearing the face mask, attached to the pure air supply, and exhaling into the breath analyzer. Post-exposure breath measurements were taken continuously for a further 30 min.

The subjects were requested to drink only bottled water from the evening before the experiment, refrain from drinking any carbonated beverages, avoid bathing or showering the morning of the experiment, and refrain from the use of perfumes or toiletries.

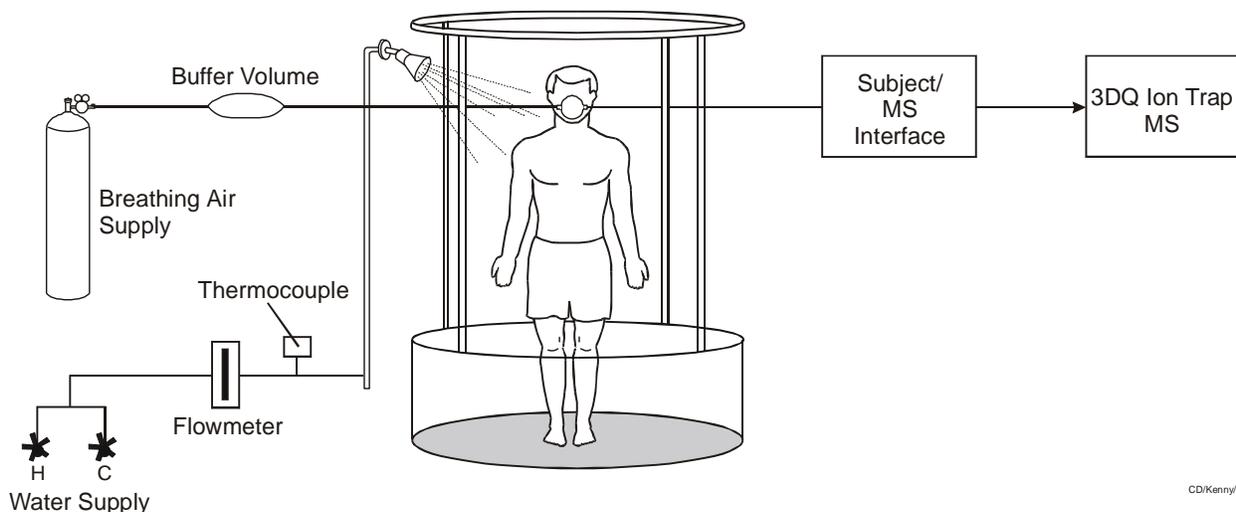


Figure 4-1. System for sampling exhaled breath samples in real time from subject exposed by dermal absorption to MTBE and DBCM in shower water. (Schematic shows only one shower unit for clarity.)

Bathtub Facility

The bathing experiments were carried out in a 380 L stainless steel hydrotherapy tub (109 cm long x 53 cm wide x 71 cm high). The tub was connected to the building hot and cold water supply and, immediately before the start of an experiment, the water inflow was adjusted to give the desired temperature, as indicated by an analog thermometer. After putting on the face mask, the subject provided a pre-exposure breath sample. Then, the subject stepped into the tub and immersed him/herself in the water up to neck height. MTBE-d₁₂, DBCM, and TBA breath measurements were made every 12 s with the real-time breath analyzer while the subject continued to breathe purified air, and readings of the water temperature were taken manually at regular intervals throughout the exposure period. Figure 4-2 is a schematic of a subject in the filled hydrotherapy tub, wearing the face mask while attached to the pure air supply and exhaling into the breath analyzer.

The subject remained in the tub for 30 min, then stepped out of the tub and quickly dried him/herself while continuing to breathe purified air and exhale into the analyzer. Post-exposure breath measurements were taken for up to 30 min before the subject was allowed to remove the face mask. This post-exposure period was sufficient to allow the breath levels of the target compounds to approach the original pre-exposure levels. Water samples were collected immediately before the subject entered the tub, midway through the exposure period, and immediately before he/she stepped out of the tub.

To confirm the results obtained with the real-time breath analyzer, we collected simultaneous whole-breath samples from the outlet of the breath analyzer system using

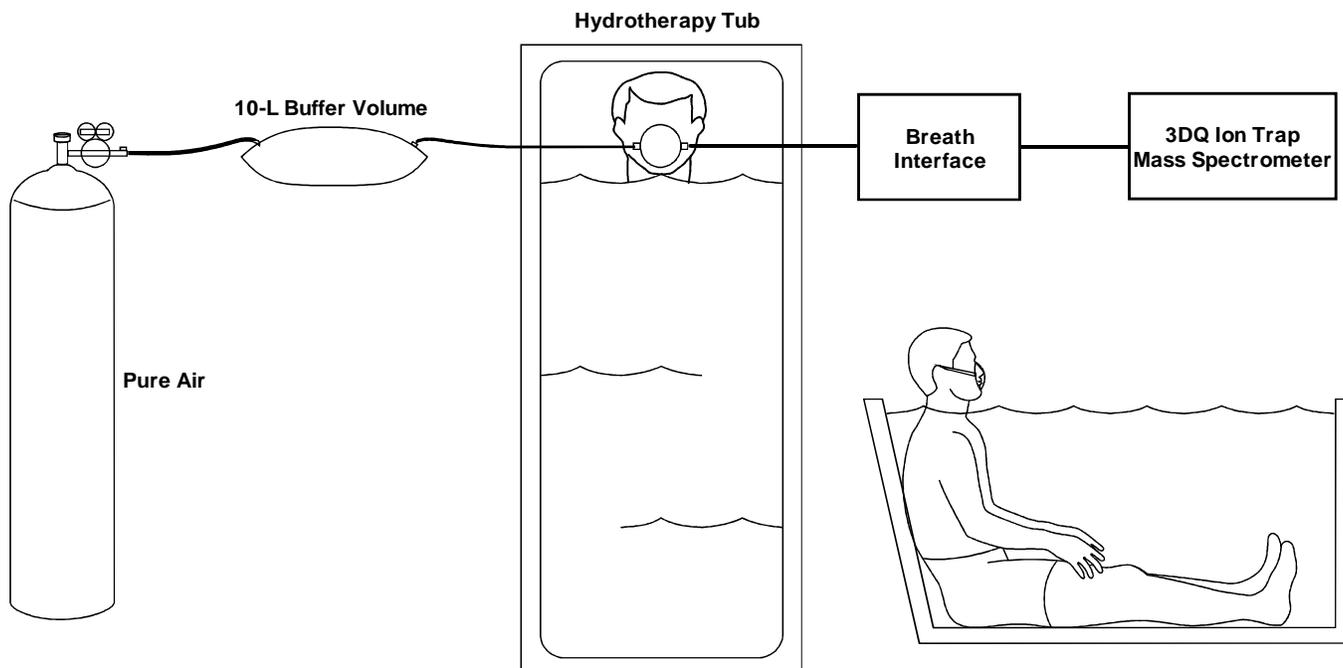


Figure 4-2. System for sampling exhaled breath samples in real time from subject exposed by dermal absorption to MTBE and DBCM in bathtub water.

evacuated stainless steel (Summa) canisters, which were analyzed independently by gas chromatography/mass spectrometry (GC/MS) for MTBE-d₁₂, DBCM, and TBA-d₁₀ using a procedure based on a standard method (EPA Method TO-15). These co-collected samples were taken during the final two bathtub runs completed at EOHSI and in all of the additional tub experiments that were subsequently conducted at Battelle. In one of these two experiments at EOHSI, breath samples were also collected using actively-pumped Tenax sorbent tubes, and these samples were subsequently analyzed at EOHSI by thermal desorption GC/MS.

Sampling and Measurement Procedures

Breath Samples

Real-Time Breath Analyzer

Exhaled breath was monitored for MTBE-d₁₂, DBCM, and TBA using the real-time breath analyzer and, in several cases, evacuated stainless steel canisters along with GC/MS.

The real-time breath analyzer, shown schematically in Figure 4-3, consists of a specially-designed breath inlet unit, a direct breath sampling interface, and an ion trap mass spectrometer (ITMS).^{21,30,33,34} For the breath measurements, a face mask (Model 8932, Hans Rudolph, Inc., Kansas City, MO) equipped with a two-way non-rebreathing valve set was attached to the breath

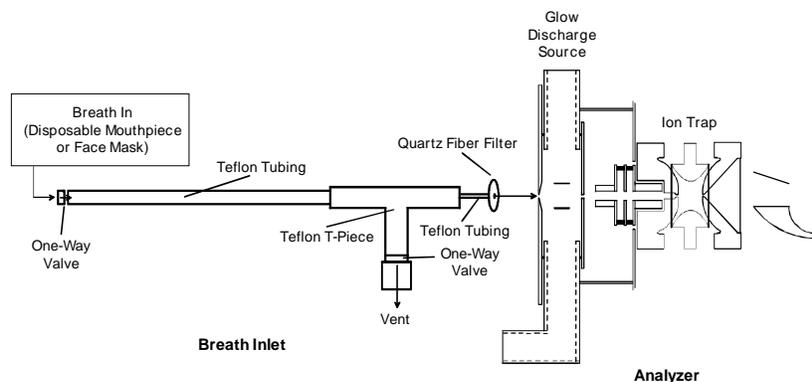


Figure 4-3. Continuous real-time breath analyzer (RTBA), consisting of breath inlet (breath holding volume) attached to direct breath sampling interface (glow discharge ionization source) and ion trap mass spectrometer (GD/ITMS).

inlet to isolate the subject from any MTBE or DBCM in the bathroom air. The inlet valve of the face mask was connected to a cylinder containing hospital-grade breathing air. The exhaust valve of the face mask was connected to the breath inlet. The breath sample is vacuum-extracted at a constant rate from the breath interface volume by the vacuum in the direct breath sampling interface and flows into the ion trap without any attention from the subject.

The volume of the breath inlet (Figure 4-3) is normally less than 100 mL, or roughly one-fifth the mean value of the adult tidal volume. Thus, each breath exhalation effectively displaces the previous breath sample while a steady gas flow is maintained into the analyzer. This ensures that unit resolution is achieved between individual breath exhalations while at the same time producing a constant and undiluted sample for analysis. A dry gas meter (Model DTM-115, American Meter Co.), attached to the vent of the breath inlet system via wide-bore flexible tubing, was used to record the respiration rate and total exhaled volume from each subject.

The direct breath sampling interface is a glow discharge ionization source, which is attached to the ITMS. The operation of this system has been described in detail elsewhere.^{35,36,37} For the work described here, we used a Teledyne Electronic Technologies (Mountain View, CA) 3DQ™ Discovery ion trap MS as the analyzer.³⁸ The 3DQ is a compact, field-deployable instrument with high sensitivity and specificity. The breath analyzer was set up to measure the MTBE-d₁₂, DBCM, and TBA-d₁₀ target analytes in both the single MS as well as the MS/MS modes. The ions selected for this purpose are listed in Table 4-2. Calibration measurements conducted in our laboratory showed that MTBE can be determined in humidified air with high sensitivity and specificity. Although the measurement of the MTBE metabolite tertiary butyl alcohol (TBA) requires the selection of the same parent ion as for MTBE, it dissociates to form two different daughter ions, thus allowing us to distinguish between the two compounds. However, tests have indicated that the sensitivity of the measurement is not as high as for MTBE. Dibromochloromethane was monitored in the single MS mode since its dissociation efficiency in the ITMS was found to be very small.

Table 4-2. Mass spectral parent and product ions used to monitor MTBE, MTBE-d₁₂, DBCM, and TBA with the real-time breath analyzer.

Compound	MW	Parent Ion	Product Ion
MTBE	88	73	43, 55
MTBE-d ₁₂	100	82	46, 50
DBCM	208	129	—
TBA-d ₁₀	84	82	62

To calibrate the real-time breath analyzer in the laboratory, gas standards containing MTBE-d₁₂ and DBCM were prepared in high-pressure aluminum gas cylinders. To confirm the concentrations of the standards, samples were taken from the cylinders in evacuated 6-L stainless steel canisters, which were analyzed by a modified U.S. EPA Method TO-15.³⁹ The gas chromatograph/flame ionization detector/quadrupole mass spectrometer (GC/FID/MS) system, in turn, was calibrated by analyzing aliquots taken from a gravimetrically-prepared standard. Calibration of the breath analyzer itself was accomplished by connecting a gas cylinder containing the standards to the glow discharge source inlet and measuring the resultant ion signals of the target ions at the known concentrations. The instrument was calibrated each day before experiments began.

During the exposure experiment, the carbon dioxide levels in the exhaled breath of each subject were monitored using an Ohmeda 5200 CO₂ monitor (Datex–Ohmeda, Tewksbury, MA). This unit provides continuous breath-by-breath measurements of CO₂ production. It is equipped with an RS-232 communications interface, which provides a convenient means of assembling and reducing the CO₂ data alongside that for breath MTBE-d₁₂, DBCM, and TBA-d₁₀ in a spreadsheet. The breath samples were introduced to the CO₂ monitor via a tube connected to the vent port of the breath inlet device.

Breath Canister Samples

During several of the exposure experiments, breath samples were collected along with the breath analyzer measurements using evacuated SilcoSteel[®] passivated 1-L stainless steel canisters. Each sample was collected first in a 20-L Teflon bag that was attached to the outlet of the dry gas meter. Once filled, the bag was removed from the system, attached via a short length of Teflon tubing to an evacuated canister, and the sample was vacuum-extracted into the canister. A label was attached to each canister recording subject identification, site location, date, start and stop times, and miscellaneous information.

A Fisons MD 800 GC, equipped with a flame ionization detector (FID) and mass spectrometer (MS) in parallel, was used for the analysis of the target compounds present in the canister samples. The GC is connected to a Nutech 3500 pre-concentrator that contains a cryogenic pre-concentration trap. The trap is a 0.32 cm by 20 cm coiled stainless steel tube packed with 60/80 mesh glass beads. The trap is cooled to –185°C for sample collection and

heated to 120°C during sample desorption. A six-port valve is used to control sample collection and injection. The Nutech 3500 is also equipped with an autosampler so that up to 16 canister samples can be analyzed in an automated fashion. Analytes are chromatographically resolved on a Restek RTX-1, 60 m by 0.5 mm i.d. fused silica capillary column (1 µm film thickness). Optimal analytical results are achieved by temperature programming the GC oven from –50°C to 220°C at 8°/min. The column exit flow is split to direct one-third of the flow to the MS and the remaining flow passes through the FID. The mass spectrometer is operated in the full scan mode so that all masses are scanned between 30 and 300 amu at a rate of 1 scan per 0.4 seconds.

Identification of VOCs is performed by matching the mass spectra acquired from the sample to the mass spectral library from the National Institute of Standards and Technology (NIST). The sample volume is 90 mL. With this sample volume, the MS detection limit is 0.05 ppb (full scan mode). Quantification of all identified peaks is based upon instrument response to known concentrations from a dilute calibration gas containing the target compounds (traceable to NIST calibration cylinders whenever possible).

Instrument calibrations were checked by first dynamically diluting a standard 6-component cylinder (LL17298), which contains the target chemicals MTBE, MTBE-d₁₂, and DBCM, as well as chloroform, benzene, and 2-methyl-2-propanol. From the known concentrations of these compounds in the cylinder (8-13 ppbv), we were able to generate average response factors. The cylinders that were taken to the field for the exposure study were similarly diluted, and the concentrations determined by GC/MS, based on the measured concentrations of the components in standard cylinder LL17298. These values were checked, in turn, by applying the generated response factor for MTBE to the measurement of the concentration of MTBE in a Scott Specialty Gas MTBE Certified Standard. Our measured values of 54.25 ppbv and 52.67 ppbv divided by the dilution factor of 0.0495 gave an estimated cylinder concentration of 1,080 ppbv versus a certified value of 1,030 ppbv. This agreement is regarded as satisfactory and allowed us to use the generated response factors to determine concentrations of the target compounds in the exposure experiments.

Water Samples

During each dermal exposure experiment, three samples each of the shower or bathtub water were collected, using glass vials sealed with aluminum caps and fitted with Teflon-faced septa. The samples were taken at the start of the sequence, midway through the exposure period, and at the end of the exposure period. Twenty mL of the water sample were transferred to a 40 mL gas bubbling vessel using a disposable 20 mL pipette. The water sample was purged with helium gas at 150 mL/min for 10 minutes at room temperature. One drop of antifoaming solution (Dow Corning Antifoam 1510-US, Midland, MI) was added to the 200 mL urine sample to prevent foaming during purging. The samples were analyzed by GC/MS.⁴⁰

GC/MS Analysis

Target compounds were analyzed and quantified using a gas chromatograph (Hewlett Packard 5890) coupled to a quadrupole mass spectrometer (Hewlett Packard 5971A Mass

Selective Detector). Analytes were stripped from the Tenax trap and transferred to the GC/MS system by thermal desorption (Perkin-Elmer, Inc, Model ATD-400). A 60 m, 5% diphenyl-95% dimethyl polysiloxane capillary column (DB-5, 0.25 mm ID, 1 μ m film thickness; J & W Scientific, Folsom, CA) was used.

The GC temperature conditions were: injector 250° C; oven held at 35°C for 8 min, then ramped at 10°/min to 170°C, ramped at 50°/min to 220°C, and held for 5 min. The target ions for deuterated MTBE and TBA were $m/e = 82$ and 68 , respectively, and their retention times were 9.5 and 7.9 minutes, respectively. Ion intensity-area data were used to determine relative response factors (RRF) for the compounds on each day the instrument was operated. This was accomplished by injecting bromofluorobenzene (BFB) and ^{13}C -benzene, using amounts similar to those obtained from the purged samples.

The detection limit (DL) for each compound in the blood and urine samples was determined by estimating the standard deviation of the blank (σ_B) and the level of the analytical noise (y_B). The standard error of the regression line was used as an estimated standard deviation of the blank, and the intercept of the regression line was used as an estimate of the analytical noise. The method detection limit (MDL) were calculated from

$$y_{DL} - y_B = 3\sigma_B$$

where σ_B = standard error of the regression line; y_B = intercept of the regression line; and y_{DL} = signal level. When $y = y_{DL}$, DL has the value of x .

Skin Blood Flow Measurements

Our earlier work on the dermal absorption of chloroform suggested that water temperature had a powerful effect on dermal absorption, with about a 30-fold increase in absorbed chloroform resulting from a 10°C increase in bathwater temperature.²¹ This finding was attributed to increased blood flow to the skin at the higher temperatures.

To further examine this effect, we used a Lisca PIMII Laser Doppler Perfusion Imager to make blood flow measurements and determine the relative change in skin perfusion near the skin surface as a function of bathwater temperature. In this device, a low power solid state laser beam successively scans the tissue of interest, recording several thousand measurement points. In the tissue, the laser beam is scattered by reflective components within the tissue. A portion of the light is reflected back onto a photodetector inside the device. Generally, this received light will have been reflected many times by stationary structures within the tissue as well as by moving particles (mainly red blood cells) within the tissue. This is the moving Doppler effect. The received signal spectrum is processed in the monitor using algorithms applicable to this type of reflective environment to calculate volume flow of tissue (in mL/min/gm tissue sampled).

To maximize the potential change with temperature, Lisca recommended that measurements be confined to areas of the body with many blood vessels near the surface of the skin, such as the upper shoulder area or the upper portions of the index and middle fingers on the

hand. Because of the crowded conditions in which the tub experiments were conducted at EOHHSI, we chose the finger option. In setting up the data collection with the Laser Doppler Imager, we found that the technique displays a great deal of inherent variability, even at the same temperature. Consequently, in an effort to obtain reasonably reproducible baseline data, measurements were limited to only one hand of a single subject.

Measurements were made using a regular bucket filled with water. The sensor (laser) head was kept at a uniform distance from the fingers (15 cm) for each run. The entire hand was submerged the same distance beneath the surface of the water (~2 cm), with the hand resting on top of a submerged bottle near the top of the bucket, thus allowing the bulk of the water in the bucket to act as a temperature reservoir. A dark cloth was placed beneath the hand to prevent laser light reflections back into the detector, which would have given false high perfusion readings. It was found that, to obtain the most reliable perfusion measurements, it was necessary to allow a warming or cooling period for the hand, which typically took several minutes. Multiple measurements were made over the range from 0°C to about 50°C.

Questionnaire

A brief questionnaire (shown in Appendix A) was administered to each participant to assess the participant's potential exposure to MTBE and DBCM during the previous 24 hours.

Data Analysis

The shapes of the uptake and decay curves for MTBE-d₁₂ and DBCM from dermal absorption while bathing are similar to those observed in our earlier work on the dermal absorption of chloroform while bathing.²¹ We, therefore, carried out the same analysis on the data from this study as we did previously on the chloroform data.

Briefly, to estimate the total exhaled dose and obtain kinetics information, we used the linear compartment model, developed by Wallace et al.,⁴¹ with an extension to the case of dermal exposure.²¹ The one-compartment model treats the body as a single compartment, which is exposed to a constant concentration of the contaminant in water. A very simple way to view the stratum corneum is to regard it as a membrane of infinitesimal thickness, whose only function is to impede the entry of the contaminant into the blood for a certain lag time T .

Total Exhaled Dose

The total exhaled dose is obtained by multiplying the sum of the areas under the exhaled breath uptake and decay curves by the alveolar ventilation rate.

For the situation in which an exposure occurs to a constant concentration of the contaminant in water, C_{water} , as depicted in Figure 4-4, the uptake in the case of a single compartment is given by²¹

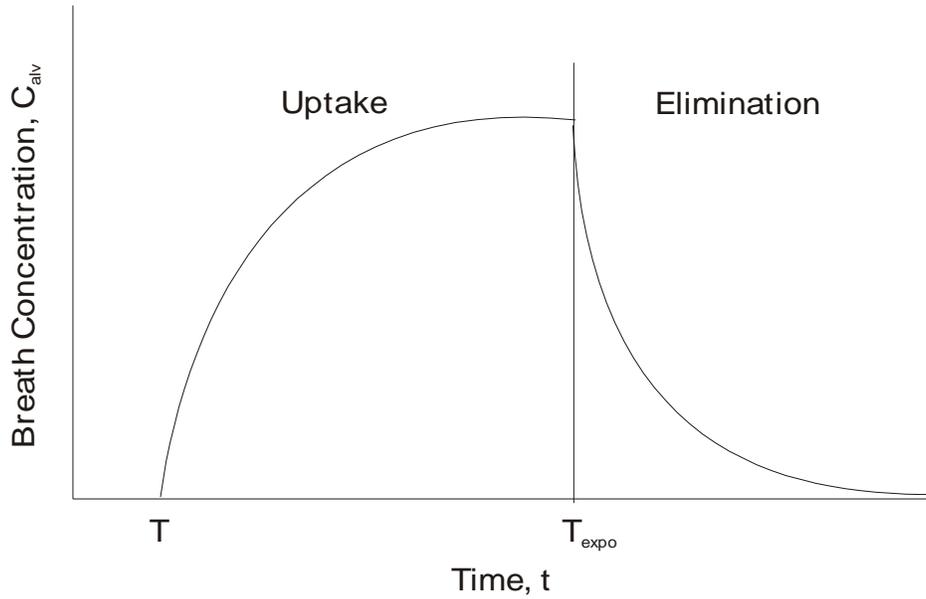


Figure 4-4. Plot showing rapid increase in alveolar breath concentration C_{alv} as a result of step function exposure to a constant water concentration C_{water} , followed by a rapid decrease in breath concentration as a result of exposure to clean air. T is the lag time, i.e., the time to the first measurable increase in the breath concentration; T_{expo} is the time at the end of exposure.

$$C_{alv} = 0 \quad (0 < t < T) \quad (4-1)$$

$$C_{alv} = f' \cdot C_{water} \left(1 - e^{-(t-T)/\tau_{uptake}}\right) \quad (t > T) \quad (4-2)$$

where C_{alv} = exhaled alveolar breath concentration of the component; C_{water} is the contaminant concentration in the water; f' is a constant relating the final equilibrium concentration in the breath to the concentration in the water; τ_{uptake} is the effective (uptake) residence time of the chemical in the body; T is the lag time; and t is the time from the start of the exposure. The residence time τ_{uptake} is expected to be affected somewhat by the fact that, in reality, the blood is not experiencing a constant exposure but rather a rapidly increasing exposure for a short period immediately after the first measurable increase. Thus, τ_{uptake} will probably be somewhat larger than the true residence time τ . The uptake model has three parameters to be determined from the data: f' , T , and τ_{uptake} .

During the decay phase, the breath concentration declines exponentially:

$$C_{alv} = f' \cdot C_{water} + Ae^{-t/\tau_{decay}} \quad (4-3)$$

where t is the time measured from when exposure ends; A is the breath concentration when exposure ends; and τ_{decay} is the effective residence time in the body during decay. τ_{decay} is again expected to be affected somewhat (i.e., increased over the true residence time τ) by the fact that the exposure experienced by the blood does not drop immediately to zero but falls off at a certain rate determined by the characteristics of the stratum corneum. If exposure has lasted long enough to reach equilibrium, then the value of A should be given by $f' \cdot C_{water}$.

The two-compartment model assumes a single metabolizing compartment and a second compartment, generally considered to be the organs or blood vessel-rich tissues.⁴¹ Again, the solution to continued exposure at a constant concentration is given by an initial period of zero breath concentration followed by a period of increasing concentration toward an asymptote:

$$C_{alv} = 0 \quad (0 < t < T) \quad (4-4)$$

$$C_{alv} = f' \cdot C_{water} + A_1 e^{-(t-T)/\tau_{1uptake}} + A_2 e^{-(t-T)/\tau_{2uptake}} \quad (t > T) \quad (4-5)$$

where A_1, A_2 are lumped combinations of physiological parameters associated with the first and second body compartments; and $\tau_{1uptake}, \tau_{2uptake}$ are the effective (uptake) residence times of the chemical in the first and second body compartments. This model has six parameters: $f', T, A_1, A_2, \tau_{1uptake}$, and $\tau_{2uptake}$.

The decay phase for the two-compartment model is given by:

$$C_{alv} = A_1 e^{-t/\tau_{1decay}} + A_2 e^{-t/\tau_{2decay}} \quad (4-6)$$

Again, if near-equilibrium has been reached, then $A_1 + A_2 = f' \cdot C_{water}$.

For the one-compartment case, the area under the uptake curve, AUC_{uptake} , is given by:

$$\begin{aligned} AUC_{uptake} &= \int_0^T C_{alv} dt \\ &= A_1 \int_T^{T_{expo}} \left(1 - e^{-(t-T)/\tau_{uptake}}\right) dt \\ &= A_1 \left[t - \left(-\tau_{uptake} e^{-(t-T)/\tau_{uptake}}\right) \right]_T^{T_{expo}} \\ &= A_1 \left[T_{expo} + \tau_{uptake} e^{-(T_{expo}-T)/\tau_{uptake}} - T - \tau_{uptake} \right] \\ &= A_1 (T_{expo} - T) - A_1 \tau_{uptake} \left(1 - e^{-(T_{expo}-T)/\tau_{uptake}}\right) \end{aligned} \quad (4-7)$$

If, now, we set $T = 0$, it follows that

$$AUC_{uptake} = A_1(T_{expo}) - A_1\tau_{uptake} \left(1 - e^{-(T_{expo})/\tau_{uptake}}\right) \quad (4-8)$$

In practice, AUC_{uptake} is estimated by integrating under the exponentially increasing curve used to model the data, i.e., $y = a(1 - e^{-bx})$, using the trapezoidal rule in SigmaPlot (Version 8.0, SPSS, Chicago, IL).

For the post-exposure decay period, the fraction $f' \cdot C_{water}$ of the inhaled air concentration of the chemical that is exhaled, is zero during elimination. If we assume that time $t = 0$ refers to the start of the post-exposure phase and the upper time limit $t = \infty$, it follows then from Equation (4-3) that the area under the decay curve is given by:⁴²

$$\begin{aligned} AUC_{decay} &= \int_0^{\infty} C_{alv} dt \\ &= \int_0^{\infty} A e^{-t/\tau_{decay}} \\ &= -A \tau_{decay} \left[e^{-t/\tau_{decay}} \right]_0^{\infty} \\ &= -A \tau_{decay} (0 - 1) \\ &= A \tau_{decay} \end{aligned} \quad (4-9)$$

Thus, AUC_{decay} may be estimated in practice from the best-fit parameters obtained from the exponentially decreasing multi-compartment curve used to model the decay data, i.e., $y = \sum a_i e^{-bx}$.

For the one-compartment case, the total area under the uptake and decay curves, AUC_{total} , is given by:

$$AUC_{total} = AUC_{uptake} + AUC_{decay} \quad (4-10)$$

and the total exhaled dose, or “unmetabolized mass”,^{42,43,44} (i.e., total amount (μg) exhaled during uptake and decay) is given by:

$$\text{Total Exhaled Dose ("Unmetabolized Mass")} = AUC_{total} \cdot AVR \quad (4-11)$$

where AVR = alveolar ventilation concentration (L/min).

Empirical Modeling of Uptake and Decay Breath Concentrations

The linear multicompartment model has the following solution for the uptake phase:⁴¹

$$C_{alv} = f' \cdot C_{water} \sum a_i \left(1 - e^{-t/\tau_{i,uptake}}\right) \quad (4-12)$$

where: C_{alv} = exhaled breath concentration of the component; a_i = capacity of the i^{th} compartment at equilibrium ($\sum a_i = 1$); t = time from the onset of exposure; and $\tau_{i\ uptake}$ = uptake residence time of the chemical in the i^{th} compartment.

The fraction f' of the compound exhaled unchanged at equilibrium, i.e., when $t = \infty$, follows from Equation (4-12) as:

$$f' = \frac{C_{t=\infty}}{C_{water} \sum a_i} \quad (4-13)$$

During the post-exposure decay phase, the concentration declines exponentially:

$$C_{alv} = f' \cdot C_{water} + \sum a_i e^{-t/\tau_{i\ decay}} \quad (4-14)$$

where, now, t is measured from the time exposure ends. In the experiment conducted here, the water concentration C_{water} was zero at the end of the exposure period, i.e., $f' \cdot C_{water} = 0$. In Equation (4-14), the first exponential term (compartment) is generally associated with blood, the second with “highly perfused tissues,” the third with “moderately perfused tissues,” and the fourth with “poorly perfused tissues.” For a broad range of VOCs, it has been found that the residence times for these compartments are roughly similar, namely, 3-11 min for the first compartment, 0.4-1.6 h for the second, 3-8 h for the third, and several days for the fourth compartment.⁴⁵ For the exposure times used in the present study, we apply a two-compartment decay model to evaluate the contributions to the breath levels during the decay period.

The residence time is defined as the time it takes for the compound to decay to $1/e$ of its initial concentration in the compartment, assuming all other compartments are at zero concentration. The biological half-life $t_{1/2}$ of the compound in the body is related to the residence time τ through the relation:

$$\tau = t_{1/2} / \ln 2 \quad (4-15)$$

All of the parameters in Equations (4-12) and (4-14) are determined empirically by fitting the background-corrected breath data using a nonlinear regression technique (SigmaPlot Version 8.0, SPSS Inc., Chicago, IL).

Quality Control

Two types of samples were collected in this study: exhaled breath (continuous real-time and discrete) and water. Continuous breath samples were collected and analyzed simultaneously using the real-time breath analyzer; discrete whole-breath samples were collected in stainless steel canisters and analyzed by cryogenic preconcentration followed by GC/MS, using a modified U.S. EPA Method TO-14.³⁹ For these analyses, calibration curves were first prepared from at least four standards. The curves are checked on a daily basis, using a standard prepared

separately from the calibration standard. The tune settings on the analytical mass spectrometer were verified daily. Holding times for the air samples were less than one week. Laboratory blanks were analyzed on a regular basis. Reproducibility was estimated from duplicate analyses. The instrument minimum detection limits were determined from multipoint calibrations.

Exhaled Breath

The 3DQ ion trap mass calibration was established and checked each day, using routine operating procedures and internal 3DQ software designed for that purpose. Specific 3DQ operating parameters and diagnostic checks were also evaluated daily.

Calibration of response of the real-time breath analyzer to the target breath components was performed, as described earlier (cf. Chapter 4, Breath Measurements), using gas standards prepared in cylinders. Samples of the cylinder contents were collected in canisters and analyzed using GC/MS. The concentrations of the MTBE, MTBE-d₁₂, DBCM, *tert*-butyl alcohol (TBA), and benzene in the canister samples were determined using a dynamic dilution of a gravimetrically-prepared in-house standard (Battelle standard LL-17298). This calibration mixture contains MTBE, MTBE-d₁₂, DBCM, trichloromethane, TBA, and benzene prepared at ppbv levels in nitrogen. Table 4-3 lists the target compounds and their concentrations in the standard. These concentrations were derived from a knowledge of the original amount injected and the pressure of the cylinder. The MTBE concentration was validated by analyzing a certified reference gas (Scott Specialty Gas), which was also dynamically diluted under the same conditions as the calibration standards.

Table 4-3. Battelle standard containing the target compounds, trichloromethane, and benzene in nitrogen.

Compound	Concentration (ppbv)
MTBE	9.31
MTBE-d ₁₂	8.17
DBCM	12.9
Trichloromethane, CHCl ₃	14.0
TBA	11.6
Benzene, C ₆ H ₆	12.5

The accuracy of the Battelle standard LL-17298 was assessed, in turn, by analyzing standard LL-17305 and the MTBE certified reference gas. Using the automated GC/MS system described earlier, the resulting peak areas were used to quantify the target compounds in the MTBE reference gas and Battelle standard. Then, the concentrations of MTBE, trichloromethane, and benzene in the standards were calculated from the peak areas using the average

Table 4-4. Comparison of measured and certified concentrations of MTBE in certified reference standard, and chloroform and benzene in NIST SRM 1804a.

Compound	Certified Concentration (ppbv)	Measured Concentration* (ppbv)	% Difference
MTBE	51.0 ^a	53.5 ± 1.1	4.9
Chloroform	16.9 ^b	16.6 ± 0.6	1.8
Benzene	14.8 ^b	15.6 ± 0.8	5.4

^a Certified reference gas (Scott Specialty Gas).

^b With respect to Battelle LL-17298 standard.

response factor (concentration/average peak area) obtained from Battelle standard LL-17298. Table 4-4 compares the certified and measured concentrations for the Battelle in-house and certified standards. These results indicate that the values obtained for the concentrations of MTBE, chloroform, and benzene in Battelle standard LL-17298 are reliable.

The calibration standard for the real-time breath analyzer was prepared in-house by static dilution in a 15.7 L cylinder. To prepare the standard, an intermediate standard consisting of 360 µL of pure DBCM (Aldrich, 98% purity) was diluted to a final 2.0 mL volume with methanol. To prepare the 3DQ calibration standard, 1.2 µL of the intermediate standard and 0.6 µL of pure MTBE-d₁₂ (C/D/N Isotopes, >99.8% atom % D) were injected into a 15.7 L cylinder through a heated syringe injection port attached to the cylinder. The cylinder then was pressurized to 1,000 psig using medical grade breathing air (Praxair). A canister sample was collected and analyzed in duplicate using the modified EPA TO-14 method and the automated GC/MSD/FID system described earlier. The measured FID peak areas were used to quantify the MTBE-d₁₂ and DBCM in the sample. Then, as before, the concentrations of MTBE-d₁₂ and DBCM in the canister were calculated from the FID peak area using the average response factor (concentration/average peak area) obtained from Battelle standard LL-17298. The concentration of MTBE-d₁₂ estimated in this way was 119.7 ppbv compared with the concentration injected, viz., 100.0 ppbv, which represents a 19.7 percent difference. The concentration of DBCM estimated in this way was 53.9 ppbv compared with the concentration injected, viz., 57.3 ppbv, which represents a 5.9 percent difference. The good agreement obtained between the measured and injected concentrations validates the accuracy of the spiking method, which has been used extensively in our laboratory.³⁴ The concentrations of MTBE-d₁₂ and DBCM injected into the cylinder (100.0 and 57.3 ppbv, respectively) and the average MTBE-d₁₂ and DBCM peak areas obtained for the canister sample were used to quantify the concentrations of MTBE-d₁₂ and DBCM in the breath sample data acquired continuously with the real-time breath analyzer. We were unable to calibrate the breath analyzer for the target compound TBA because of its apparent adsorption onto the inner surfaces of the ion trap. Consequently, the cylinders were only used to calibrate the instrument for MTBE-d₁₂ and DBCM.

Water

Quality control measures undertaken for the collection and analysis of the water samples included the following:

- All glassware used was first cleaned with 10% HCl and rinsed with de-ionized water, then baked at 300°C for 12 h before use.
- Soon after collection, all water samples were stored in a cold room at 4°C until analysis.
- Before purging a sample, helium gas was sparged through the entire system for 5 minutes to remove any MTBE contamination. In addition, to avoid DBCM contamination, the Tygon tubing connecting the purge vessel to the trap was replaced between samples.
- The operation and performance status of the GC/MS system was checked daily by analyzing 50 ng of BFB (bromofluorobenzene) and 31.6 ng of ¹³C-benzene standards.
- Blank traps were checked for contamination by GC/MS before use in the purge-and-trap analysis. These blank traps were analyzed with each set of samples to ensure that neither the traps nor the analytical system were contaminated.
- External QC standards were prepared on Tenax traps by directly injecting the BFB/-benzene standard into a flash evaporator and flushing the vapors onto the trap with zero-grade nitrogen. The QC standards were analyzed after every sixth sample to verify the stability of the GC/MS response.

Chapter 5 Results

Experiments at EOHSI

Shower Exposures

A number of unforeseen problems were encountered while attempting to conduct the shower experiments at EOHSI. Initially, difficulties were experienced with the temperature of the hot water flow into the shower unit; the highest water temperature attainable was ~36°C, about 4°C less than desired. After this problem was resolved and we were able to maintain a water temperature of 40°C, the syringe-drive unit used to inject the MTBE-d₁₂ and DBCM mixture into the shower stream malfunctioned. This unit was replaced with a second syringe-drive unit, which also proved to be unsatisfactory. The problems were compounded by the fact that the bathroom in which the experiments were conducted was unventilated and had no temperature control. Heat emitted by the real-time breath analyzer and associated equipment during the day, along with the natural heat from the operators and subjects in the room, caused the mass scale of the ITMS to drift in an unpredictable fashion, necessitating frequent recalibrations.

The shower experiments that were conducted (see Table 4-1) with the breath analyzer to measure uptake of MTBE-d₁₂ and DBCM showed almost no change in breath concentration from pre-exposure levels throughout the 30-minute exposure period, even at the highest temperature used, i.e., 40°C. Because these experiments showed no measurable effects, we decided to curtail further shower exposure runs and concentrate instead on the bathtub exposures.

Bathtub Exposures at EOHSI

To confirm that this minimal amount of dermal absorption observed in the shower experiments was real, we switched activities from the shower facility to the bathtub unit. This was based on the results of our earlier shower and bathtub experiments conducted with chloroform,^{21,46} which indicated that exposure to compounds in tub water at 40°C would be more likely to register measurable changes in breath concentration than in shower water. To avoid the earlier problems experienced with the syringe-drive units, the MTBE-d₁₂/DBCM mixture was spiked directly into the water in the tub and mixed gently by hand. In all, five experiments were run at 40°C with nominal concentrations of 150 µg/L MTBE-d₁₂ and 40 µg/L DBCM in the tub water. Of these, three (Subjects TF02, TM04, and TM05) were run using only the breath analyzer to monitor exhaled breath levels and two (Subjects TF06 and TF07) were run using the breath analyzer along with evacuated canisters to collect whole-breath samples from the outlet to

the dry gas meter, as described above. The canister samples were returned to Battelle for analysis. In one of these cases (TF06), actively-pumped Tenax sorbent tube samples were also collected for comparison with the results from the canister samples. The Tenax samples were subsequently analyzed at EOHSL.

Figure 5-1 compares the exhaled breath concentrations for MTBE-d₁₂ and DBCM for Subject TF06, obtained using evacuated canisters and Tenax sorbent tubes for sample collection,

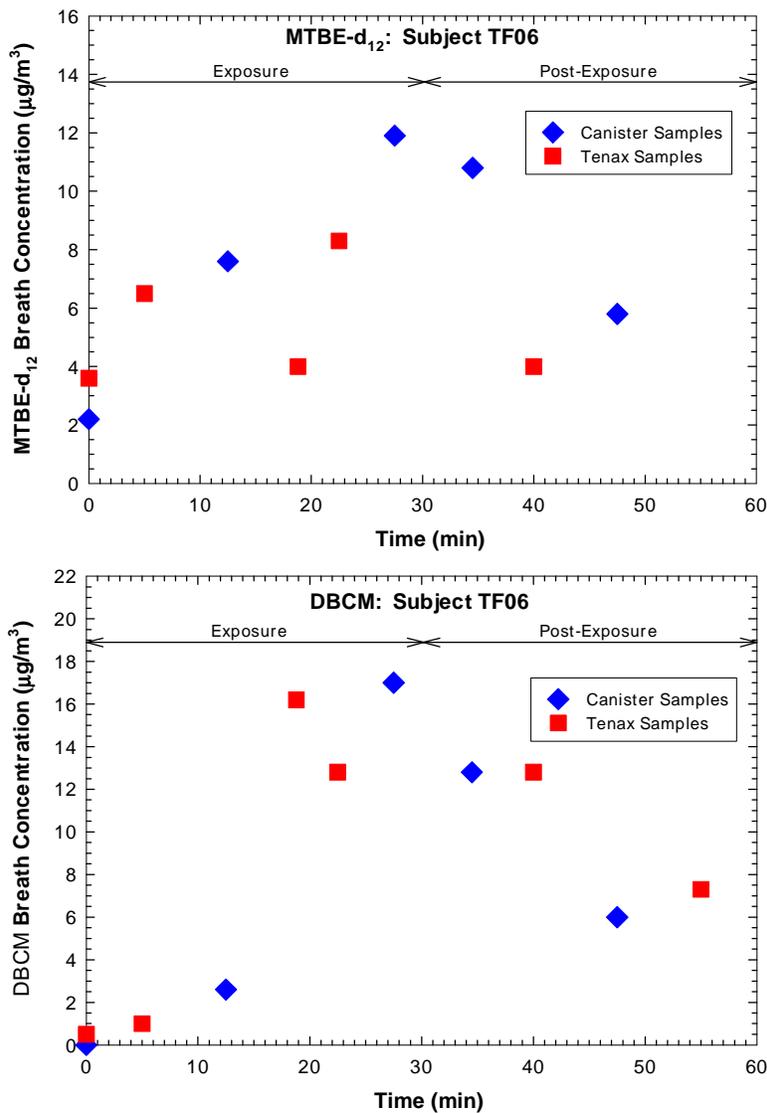


Figure 5-1. Exhaled breath concentrations of MTBE-d₁₂ and DBCM as a function of time for Subject TF06 during and following dermal exposure while bathing. Upper plot: MTBE-d₁₂ data from canister and Tenax sorbent samples collected from real-time breath analyzer system; lower plot: DBCM data from canister and Tenax sorbent samples collected from real-time breath analyzer system. All samples analyzed by GC/MS. Nominal water concentration was 150 $\mu\text{g}/\text{L}$ for MTBE-d₁₂ and 40 $\mu\text{g}/\text{L}$ for DBCM; water temperature was 40°C.

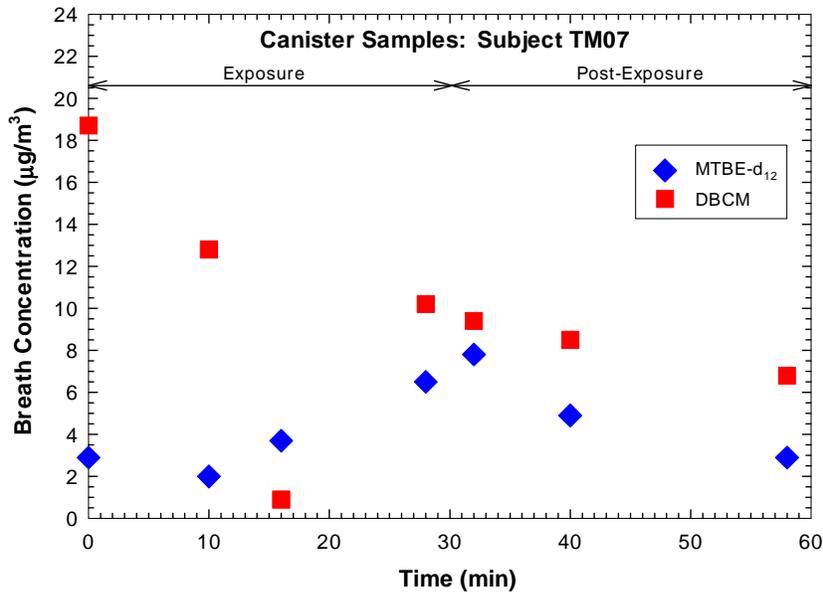


Figure 5-2. Exhaled breath concentrations of MTBE-d₁₂ and DBCM as a function of time for Subject TM07 during and following dermal exposure while bathing. Data obtained from canister samples collected from real-time breath analyzer system. All samples analyzed by GC/MS. Nominal water concentration was 150 µg/L for MTBE-d₁₂ and 40 µg/L for DBCM; water temperature was 40°C.

followed by GC/MS analysis. Overall, the agreement between the data obtained with the canisters and the Tenax sorbent tubes is good, considering the very low concentrations involved in the measurements. The data indicate that the breath MTBE-d₁₂ and DBCM concentrations increase with exposure duration, reaching maximum levels of 11 — 12 µg/m³ in the case of MTBE-d₁₂, and 16 — 17 µg/m³ in the case of DBCM, after ~30 minutes exposure by dermal absorption. Under the conditions which prevailed in the room in which the experiments were conducted, these low levels were below the limit of detection of the real-time breath analyzer, viz., ~19 µg/m³ for MTBE, ~21 µg/m³ for MTBE-d₁₂, and ~82 µg/m³ for DBCM. These levels are also much lower than the 55 — 70 µg/m³ maximum values that we observed for dermal uptake of chloroform in our earlier bathtub study.²¹ Although the samples were examined for the tertiary butyl alcohol (TBA-d₁₀) metabolite of MTBE-d₁₂, it was not observed in any of these samples.

Figure 5-2 presents the breath concentrations for MTBE-d₁₂ and DBCM for Subject TM07 obtained using evacuated canisters. Here again, we see that the breath MTBE-d₁₂ levels increase with exposure, reaching a maximum of about 7 µg/m³ before decreasing once the subject stepped out of the bathtub and exposure ended. The data for DBCM do not show the same trend, largely because of the high levels measured at the beginning of the exposure sequence, at t = 0 min and after 10 min exposure. These high values may be due to the presence of a contaminant with the same positive ion mass as that used to monitor DBCM, or it may be

the result of inadvertent exposure to DBCM from a drinking water source prior to arriving at the laboratory.

Skin Blood Flow Measurements at EOHSI

A large number of skin blood flow measurements were made at EOHSI with the Lisca PIMII Laser Doppler Perfusion Imager, using the upper portions of the first two fingers on the hand of a subject. This is an area of the body known to have a large number of blood vessels near the surface of the skin. About 70 measurements were taken from the one hand of the subject over a temperature range from 0°C to about 47°C. For comparison, several measurements were made on the first two fingers on the hand of a second subject. Both sets of results are presented in Figure 5-3.

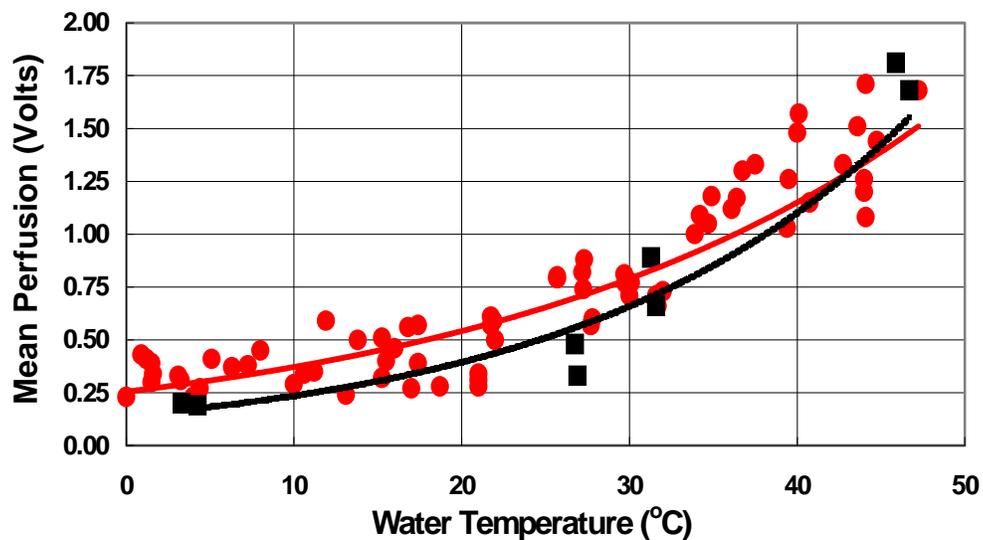


Figure 5-3. Mean perfusion of surface of first two fingers on hands of two male subjects as a function of temperature.

The plots in Figure 5-3 suggest that perfusion, under these experimental conditions, is a relatively simple exponential function of temperature and increases by about a factor of 7 as the temperature increases from 0°C to ~47°C.

Experiments at Battelle

Because of the difficulties experienced in conducting the dermal exposure measurements at EOHSI, arrangements were made to carry out a few more experiments in our laboratory at Battelle. These experiments were limited to measurements in real time of exhaled breath levels

of MTBE-d₁₂ and DBCM along with the simultaneous collection in each case, except one, of a total of six whole-breath canister samples for independent analysis by GC/MS.

The breath concentration/time profiles obtained in this way for the BCO subjects (at Battelle) listed in Table 4-1 are presented in Figures 5-4 through 5-7 for MTBE-d₁₂ and DBCM, and in Figure 5-8 for MTBE and DBCM. Under the controlled conditions that prevailed in the laboratory while these experiments were being conducted, the detection limits with the real-time breath analyzer were ~4 µg/m³ for MTBE-d₁₂ and ~13 µg/m³ for DBCM; with the canisters, the detection limits were ~0.4 µg/m³ for MTBE-d₁₂ and ~2 µg/m³ for DBCM.

Total Exhaled Dose

The total exhaled dose of MTBE-d₁₂ (or MTBE) to each subject was estimated, as indicated earlier, by multiplying the sum of the areas under the exhaled breath uptake and decay curves by the alveolar ventilation rate. Results are summarized for the five subjects in Table 5-1.

The total amount of MTBE exhaled varied from 1.94 to 5.16 µg, averaging 3.22 ± 1.23 µg at $39.5 \pm 0.6^\circ\text{C}$ [mean \pm standard deviation (SD)]. This mean value is approximately half of the total exhaled dose we obtained in our earlier study of dermal exposure to chloroform,²¹ despite the fact that the current investigation was conducted at a higher concentration (150 µg/L MTBE nominal vs. 85.8 µg/L chloroform measured) and exposure occurred for a longer period (32.5 min MTBE vs. 27.4 min chloroform). Furthermore, the average maximum observed breath concentration in the chloroform study²¹ was significantly higher than the corresponding MTBE concentration in the present study (44.9 ± 15.3 µg/m³ chloroform vs. 13 ± 4 µg/m³ MTBE). The results suggest that the uptake of MTBE by dermal absorption from bath water is much lower than that of chloroform, under similar conditions.

Because of the lack of agreement observed in Figure 5-4 through 5-8 between the canister and breath analyzer data for DBCM, together with the large scatter in the data for DBCM, no attempt was made to determine the total exhaled dose for this chemical from these results.

Empirical Modeling of Uptake and Decay Breath Concentrations

The linear compartment model developed by Wallace et al.⁴¹ was used to model the MTBE uptake and decay concentrations in the breath of the participants. The one-compartment model, from Equations 4-12 and 4-14, for the uptake and decay phases, respectively, was fitted to the observed uptake and decay data for all five subjects. Curve fitting to estimate the coefficients in the equations was accomplished using SigmaPlot. The resulting curves for MTBE-d₁₂ and MTBE are shown in Figures 5-9 to 5-16, and 5-17 to 5-18, respectively. Values obtained for f' , τ_{uptake} , and τ_{decay} are presented in Table 5-2. Application of a two-compartment model to the decay data resulted in all cases in parameters strongly dependent on one another,

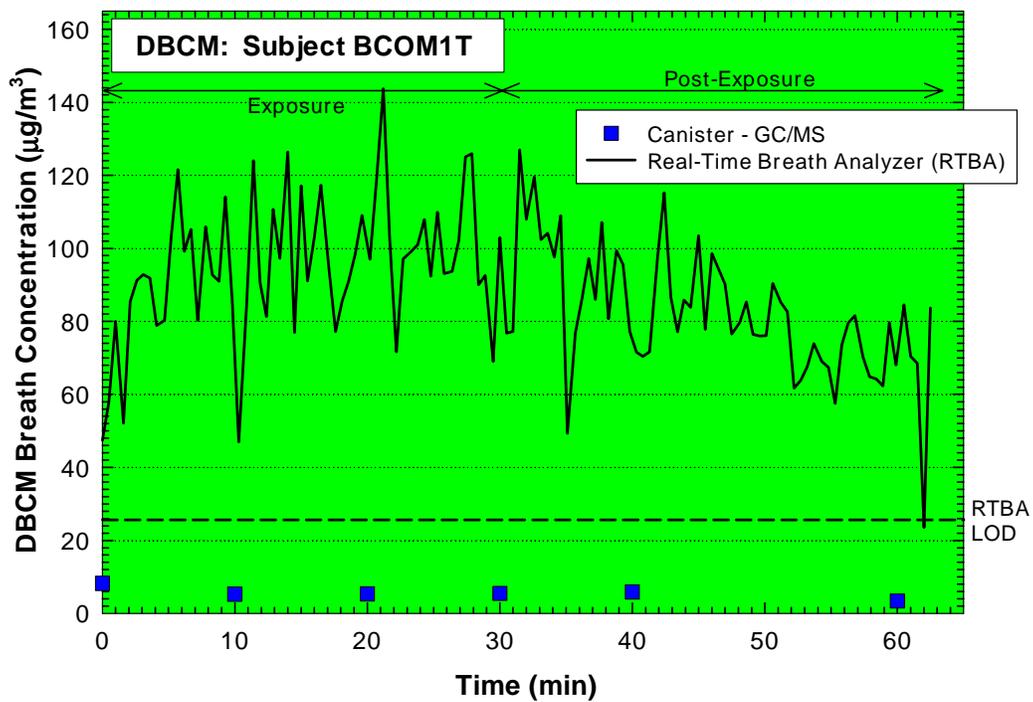
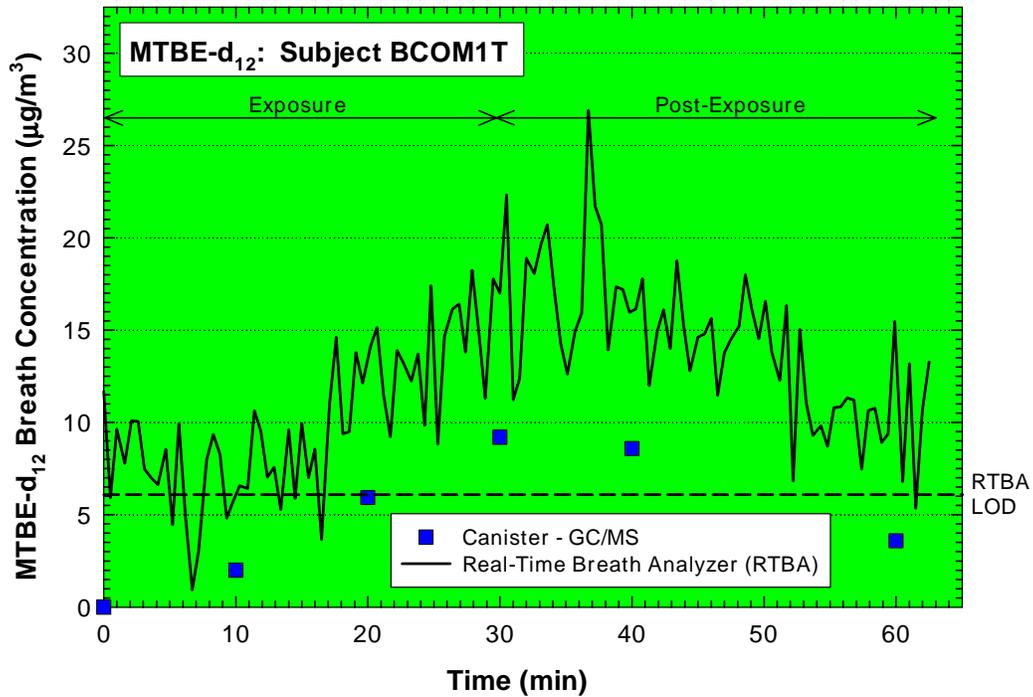


Figure 5-4. Continuous exhaled breath concentrations for MTBE-d₁₂ (upper plot) and DBCM (lower plot) as a function of time for Subject BCOM1T during and following dermal exposure while bathing. Exposure duration was 34.1 min; post-exposure monitoring continued for another 31.0 min. Water temperature was 39.7°C. Nominal concentrations were 150 µg/L for MTBE-d₁₂ and 40 µg/L for DBCM. RTBA LOD designates detection limit with real-time breath analyzer.

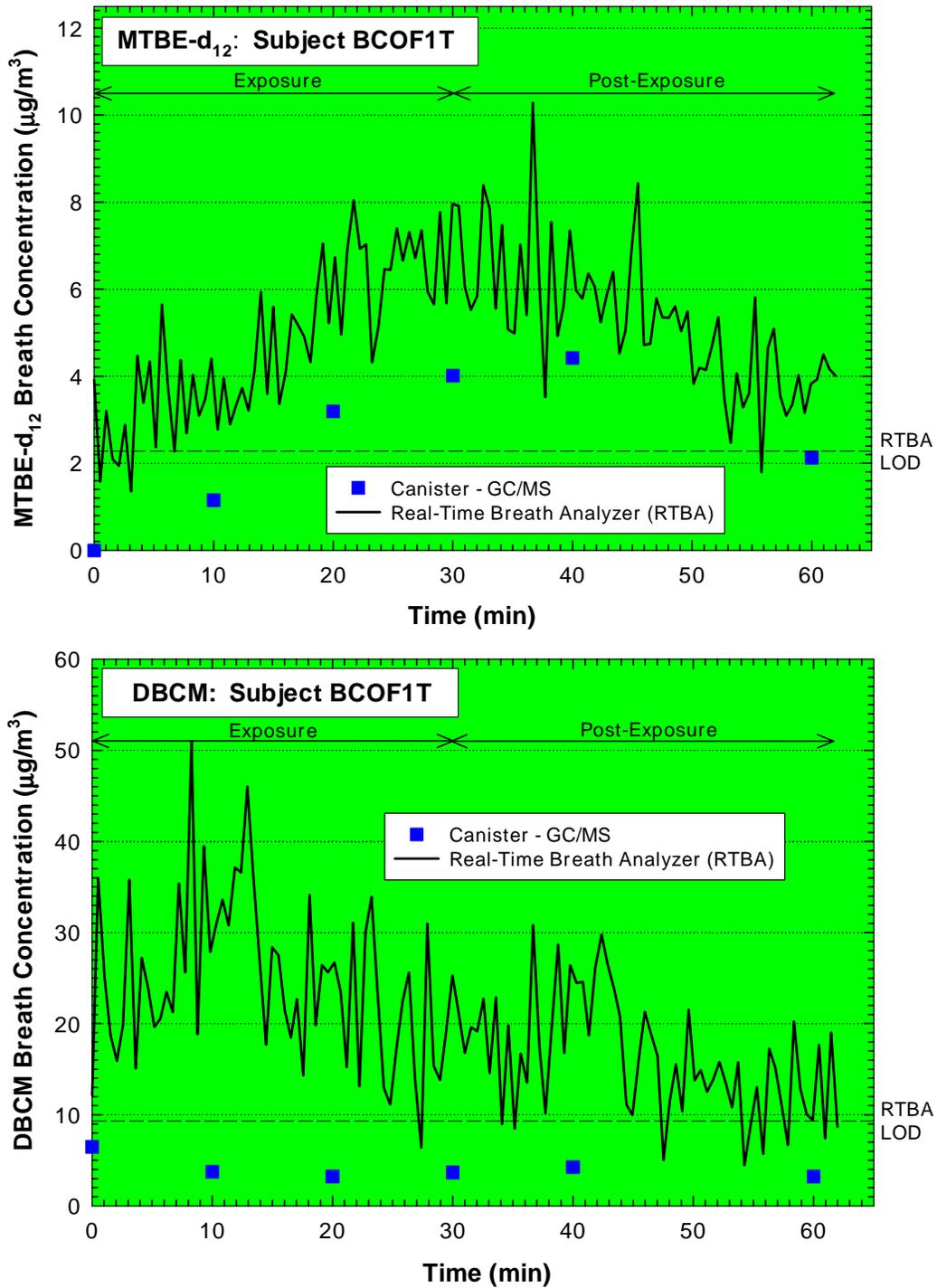


Figure 5-5. Continuous exhaled breath concentrations for MTBE-d₁₂ (upper plot) and DBCM (lower plot) as a function of time for Subject BCOF1T during and following dermal exposure while bathing. Exposure duration was 33.0 min; post-exposure monitoring continued for another 33.1 min. Water temperature was 39.0°C. Nominal concentrations were 150 µg/L for MTBE-d₁₂ and 40 µg/L for DBCM. RTBA LOD designates detection limit with real-time breath analyzer.

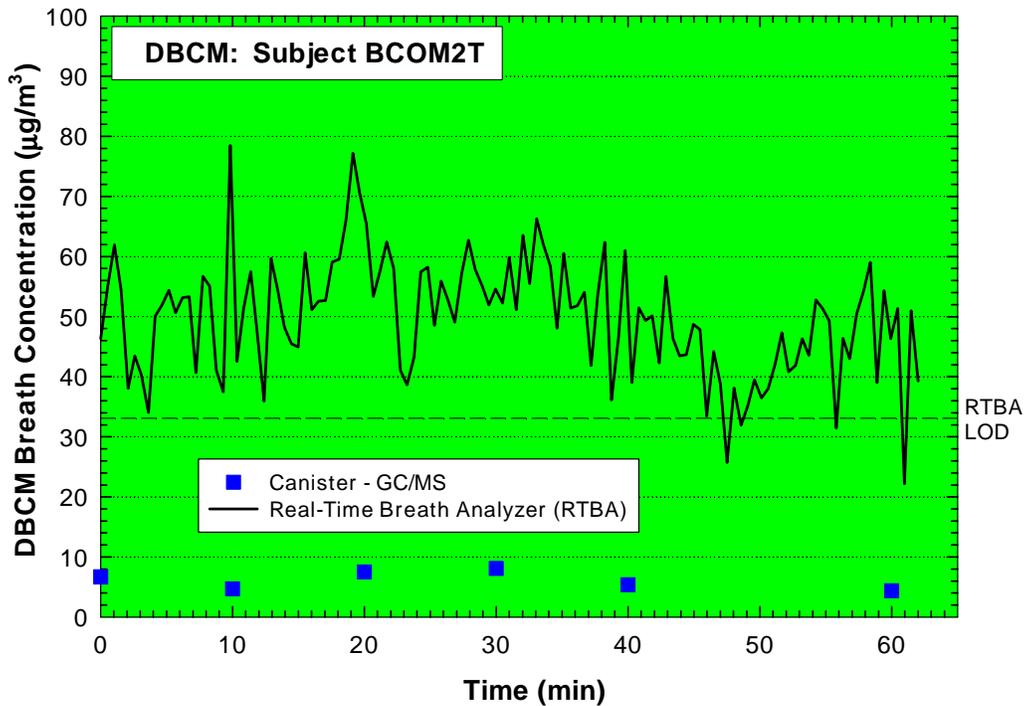
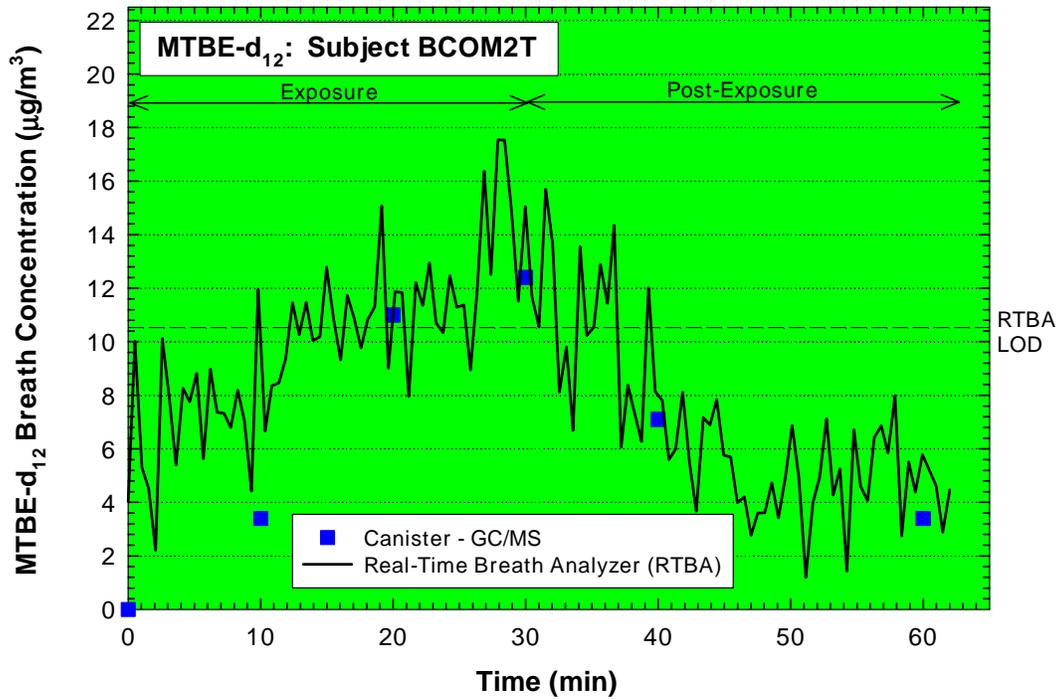


Figure 5-6. Continuous exhaled breath concentrations for MTBE-d₁₂ (upper plot) and DBCM (lower plot) as a function of time for Subject BCOM2T during and following dermal exposure while bathing. Exposure duration was 33.1 min; post-exposure monitoring continued for another 31.0 min. Water temperature was 38.8°C. Nominal concentrations were 150 µg/L for MTBE-d₁₂ and 40 µg/L for DBCM. RTBA LOD designates detection limit with real-time breath analyzer.

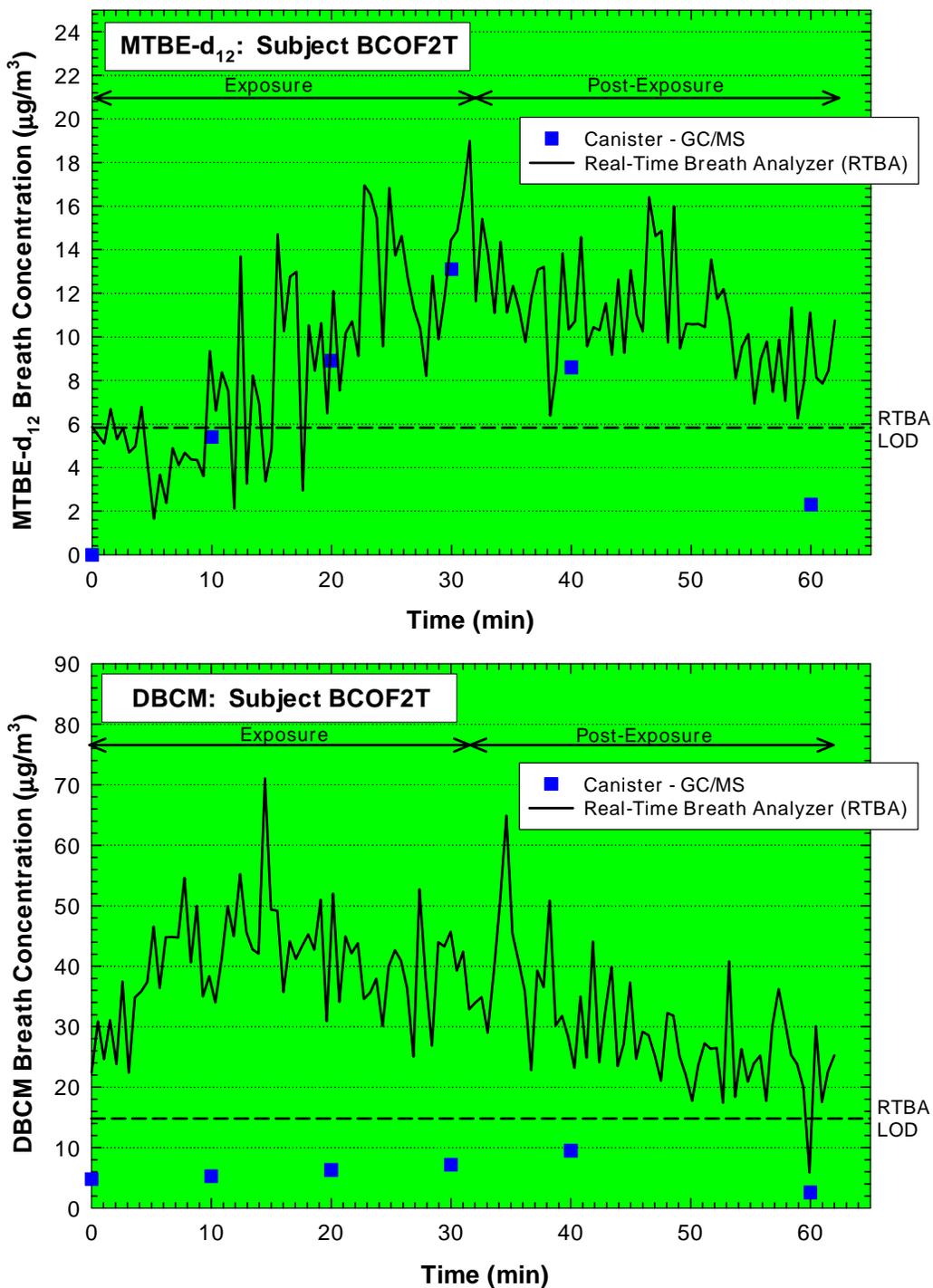


Figure 5-7. Continuous exhaled breath concentrations for MTBE-d₁₂ (upper plot) and DBCM (lower plot) as a function of time for Subject BCOF2T during and following dermal exposure while bathing. Exposure duration was 33.0 min; post-exposure monitoring continued for another 29.5 min. Water temperature was 39.8°C. Nominal concentrations were 150 µg/L for MTBE-d₁₂ and 40 µg/L for DBCM. RTBA LOD designates detection limit with real-time breath analyzer.

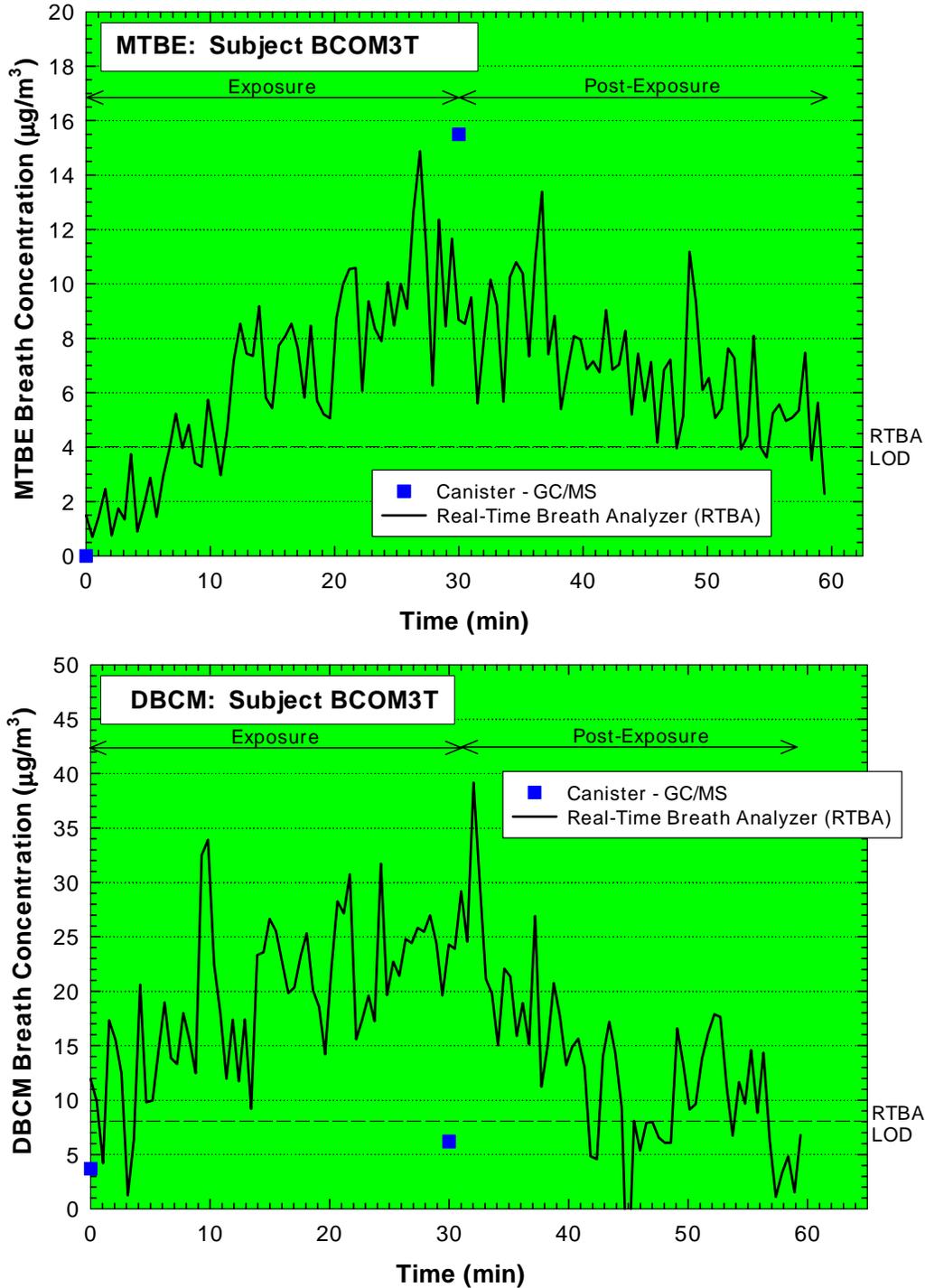


Figure 5-8. Continuous exhaled breath concentrations for MTBE (upper plot) and DBCM (lower plot) as a function of time for Subject BCOM3T during and following dermal exposure while bathing. Exposure duration was 29.5 min; post-exposure monitoring continued for another 30.4 min. Water temperature was 40.4°C. Nominal concentrations were 150 $\mu\text{g}/\text{L}$ for MTBE and 40 $\mu\text{g}/\text{L}$ for DBCM. RTBA LOD designates detection limit with real-time breath analyzer.

Table 5-1. Total exhaled dose of MTBE-d₁₂ or MTBE as a result of dermal absorption in bath water.

Parameter	Subj. BCOM1T	Subj. BCOF1T	Subj. BCOM2T	Subj. BCOF2T	Subj. BCOM3T	Mean	Std Dev
Target Analyte	MTBE-d ₁₂	MTBE-d ₁₂	MTBE-d ₁₂	MTBE-d ₁₂	MTBE	—	—
Nominal Water Concentration, C_{water} ($\mu\text{g/L}$)	150	150	150	150	150	150	0
Water Temperature ($^{\circ}\text{C}$)	39.7	39.0	38.8	39.8	40.4	39.5	0.6
Total Exposure Time (Uptake Period), T_{uptake} (min)	34.1	33.0	33.1	33.0	29.5	32.5	1.8
Total Elimination Time Monitored, T_{decay} (min)	31.0	33.1	31.0	29.5	30.4	31.0	1.3
Total (Uptake + Decay) Exhaled Air Volume (m^3)	0.593	0.531	0.648	0.537	0.590	0.580	0.048
Overall Ventilation Rate (L/min)	9.11	8.03	10.11	8.59	9.85	9.14	0.86
Alveolar Ventilation Rate, AVR (L/min)^a	6.10	5.38	6.77	5.76	6.60	6.12	0.58
Total Amount Exhaled During Uptake Period							
Area Under Uptake Curve ($\mu\text{g}\cdot\text{min}/\text{m}^3$) ^b	358	163	332	210	194	251	88
Total Amount Exhaled During Uptake (μg)	2.18	0.88	2.25	1.21	1.28	1.56	0.62
Total Amount Exhaled During Decay Period							
Area Under Decay Curve Over Monitored Period ($\mu\text{g}\cdot\text{min}/\text{m}^3$) ^c	404	159	183	215	205	233	98
Normalized Area Under Decay Curve ($\mu\text{g}\cdot\text{min}/\text{m}^3$) ^d	391	144	177	218	202	226	96
Total Amount Exhaled During Decay (μg)	2.38	0.77	1.20	1.26	1.33	1.39	0.60
Total Exhaled Dose							
Total Amount Exhaled During Uptake + Decay (μg)	4.6	1.7	3.5	2.5	2.6	3.0	1.1

^a Alveolar ventilation rate assumed to be 67% of ventilation rate.

^b Determined from fitted uptake curve using trapezoidal macro in SigmaPlot 8.0 over total monitored exposure time.

^c Determined from fitted decay curve using trapezoidal macro in SigmaPlot 8.0 over total monitored decay time.

^d Area under decay curve normalized to 30.0 min.

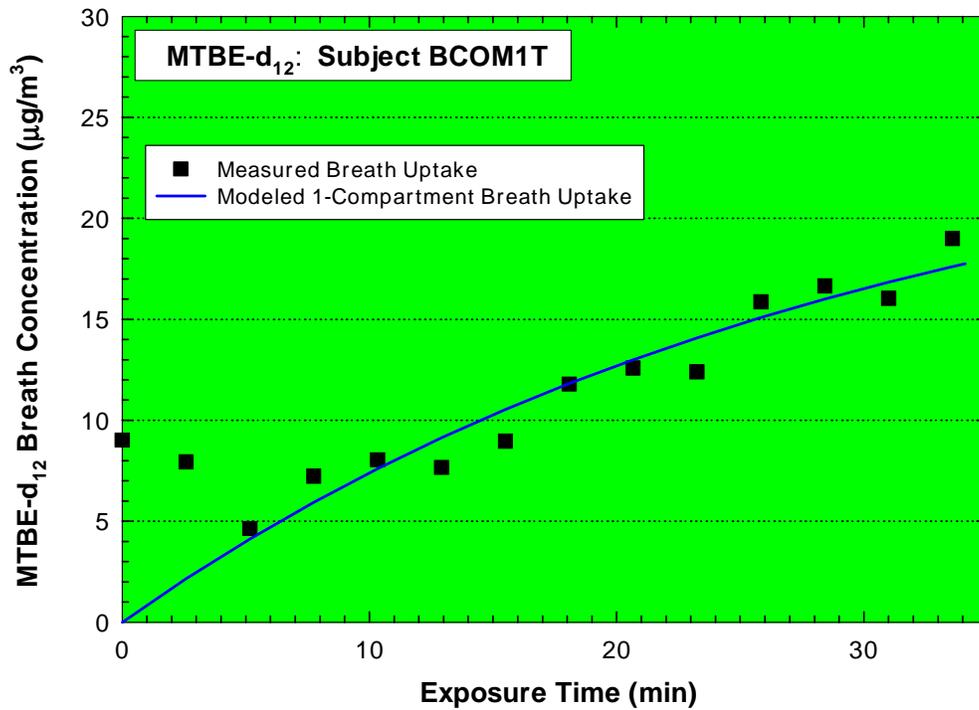


Figure 5-9. Measured MTBE-d₁₂ exhaled air exposure uptake plot for Subject BCOM1T compared with modeled curve. Bath exposure details as described in Figure 5-4. Data smoothed using 155-s block averaging time.

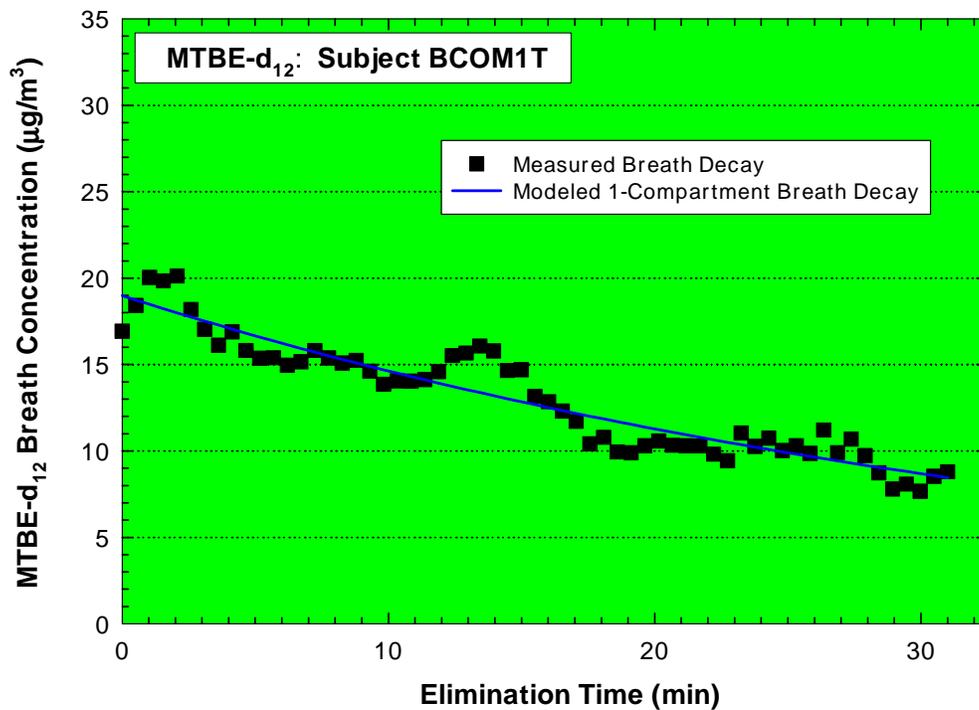


Figure 5-10. Measured MTBE-d₁₂ exhaled air exposure decay plot for Subject BCOM1T compared with modeled curve. Bath exposure details as described in Figure 5-4. Data smoothed using 155-s block averaging time.

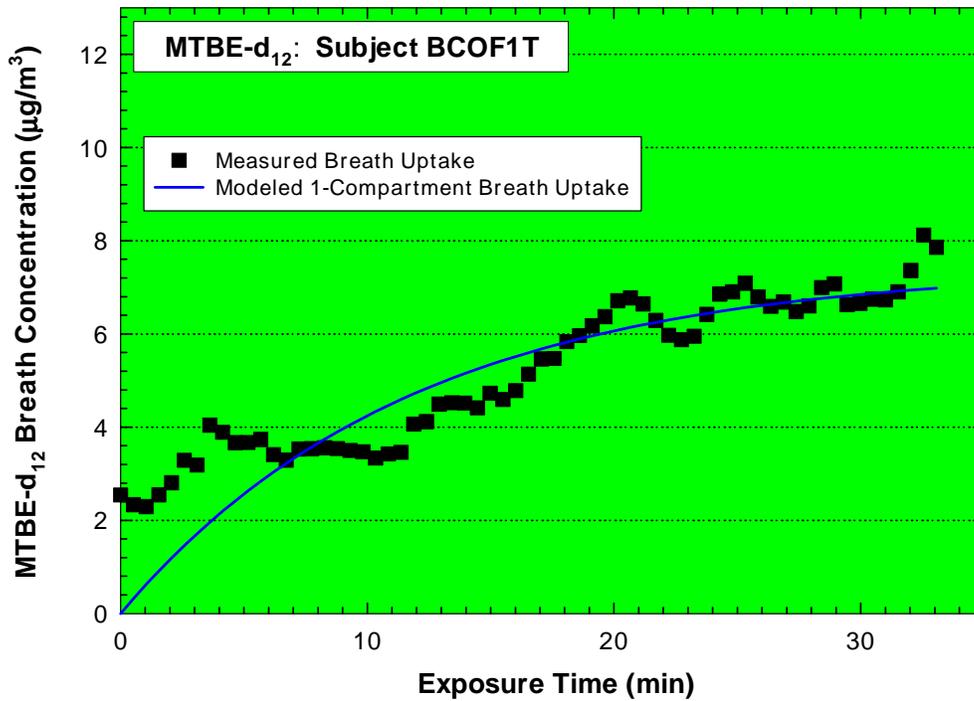


Figure 5-11. Measured MTBE-d₁₂ exhaled air exposure decay plot for Subject BCOF1T compared with modeled curve. Bath exposure details as described in Figure 5-5. Data smoothed using 5-point moving average.

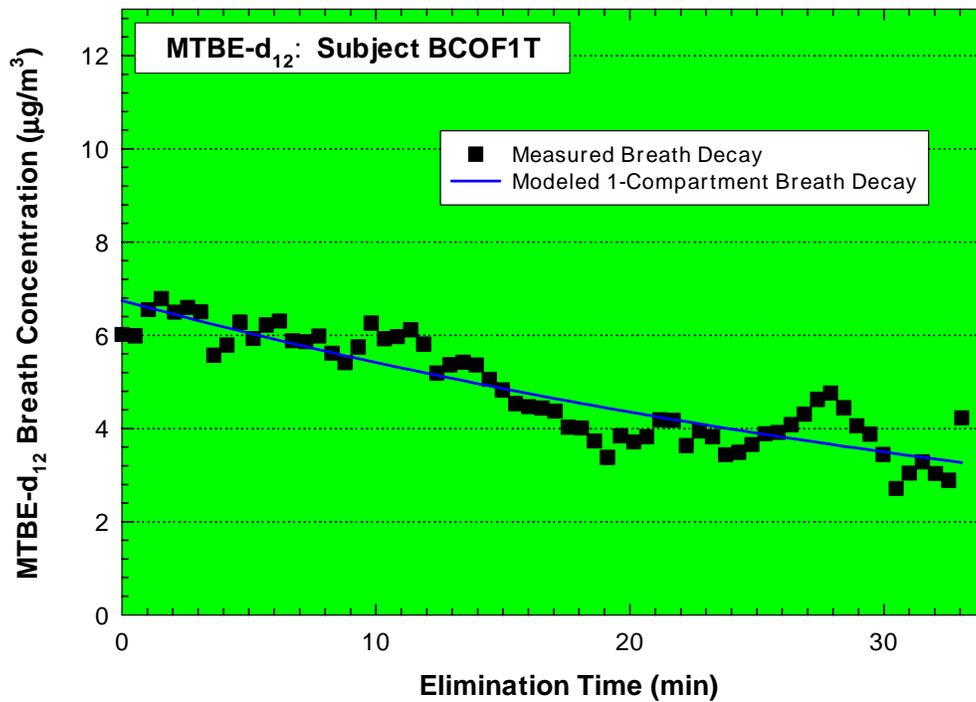


Figure 5-12. Measured MTBE-d₁₂ exhaled air exposure uptake plot for Subject BCOF1T compared with modeled curve. Bath exposure details as described in Figure 5-5. Data smoothed using 5-point moving average.

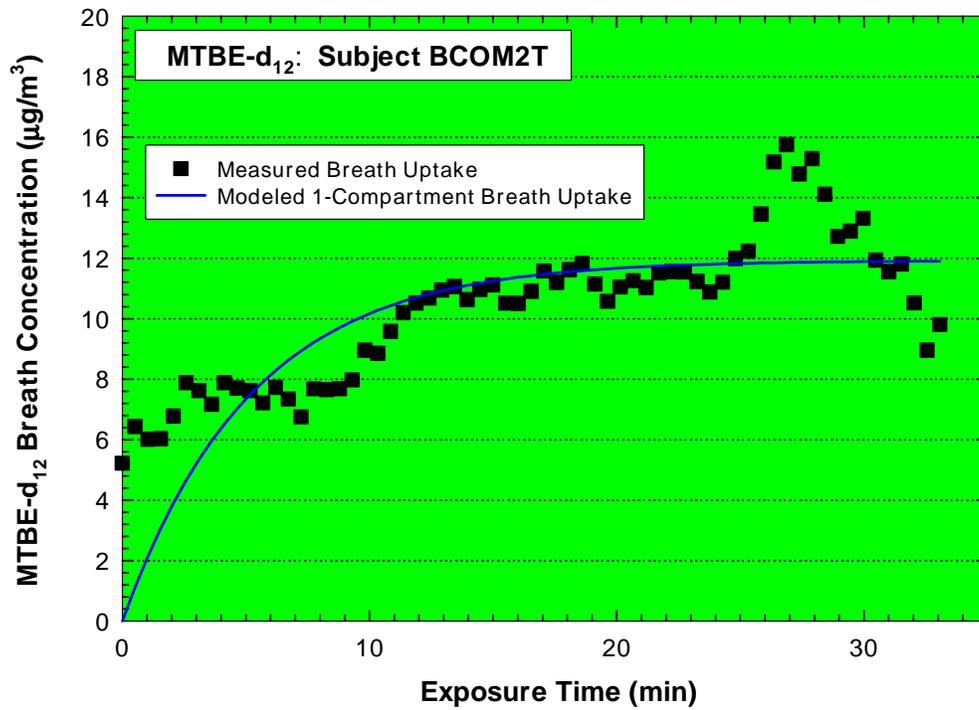


Figure 5-13. Measured MTBE-d₁₂ exhaled air exposure uptake plot for Subject BCOM2T compared with modeled curve. Bath exposure details as described in Figure 5-6. Data smoothed using 5-point moving average.

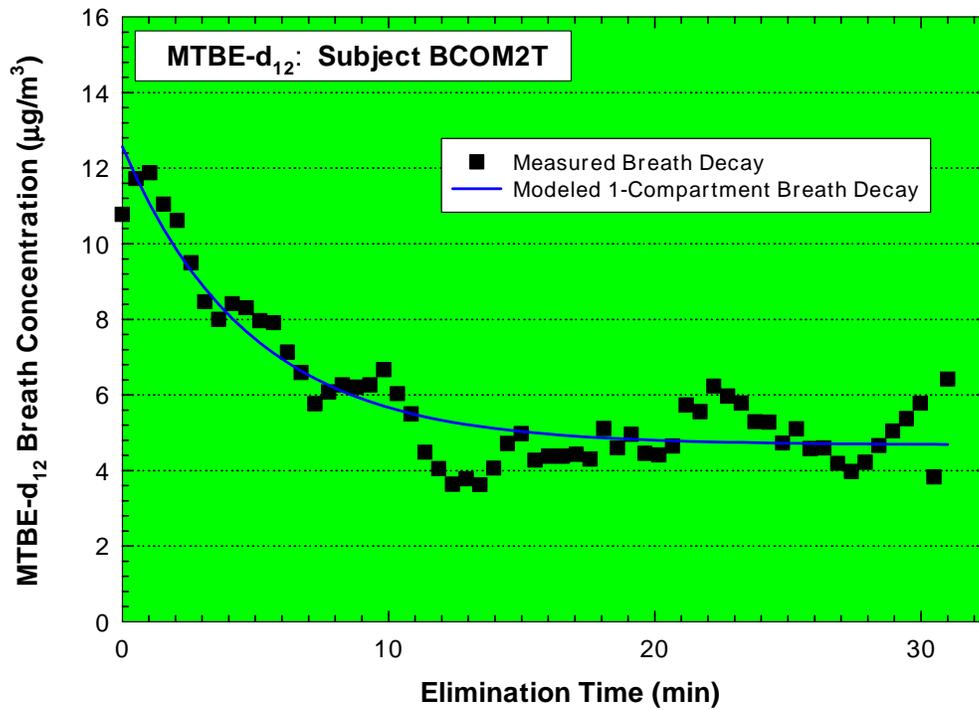


Figure 5-14. Measured MTBE-d₁₂ exhaled air exposure decay plot for Subject BCOM2T compared with modeled curve. Bath exposure details as described in Figure 5-6. Data smoothed using 5-point moving average.

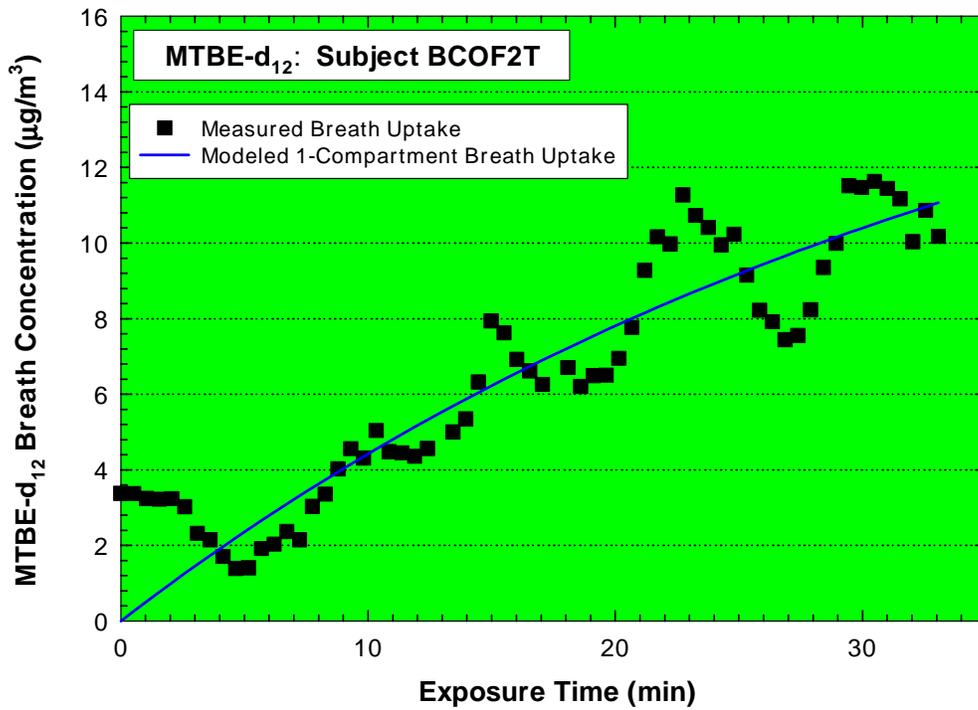


Figure 5-15. Measured MTBE-d₁₂ exhaled air exposure uptake plot for Subject BCOF2T compared with modeled curve. Bath exposure details as described in Figure 5-7. Data smoothed using 5-point moving average.

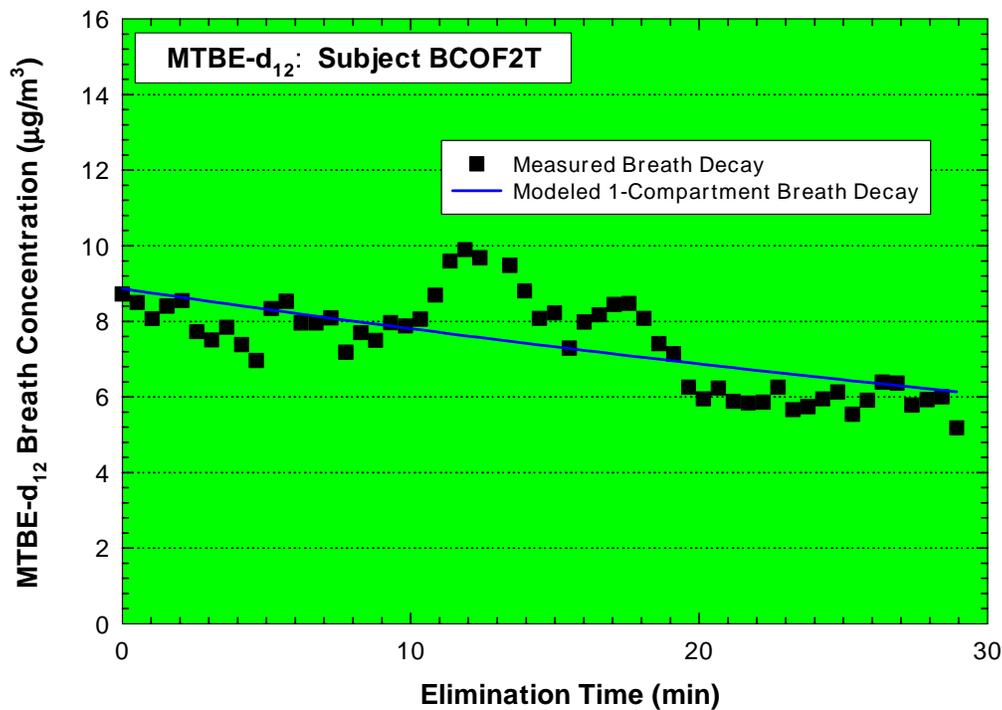


Figure 5-16. Measured MTBE-d₁₂ exhaled air exposure decay plot for Subject BCOF2T compared with modeled curve. Bath exposure details as described in Figure 5-7. Data smoothed using 5-point moving average.

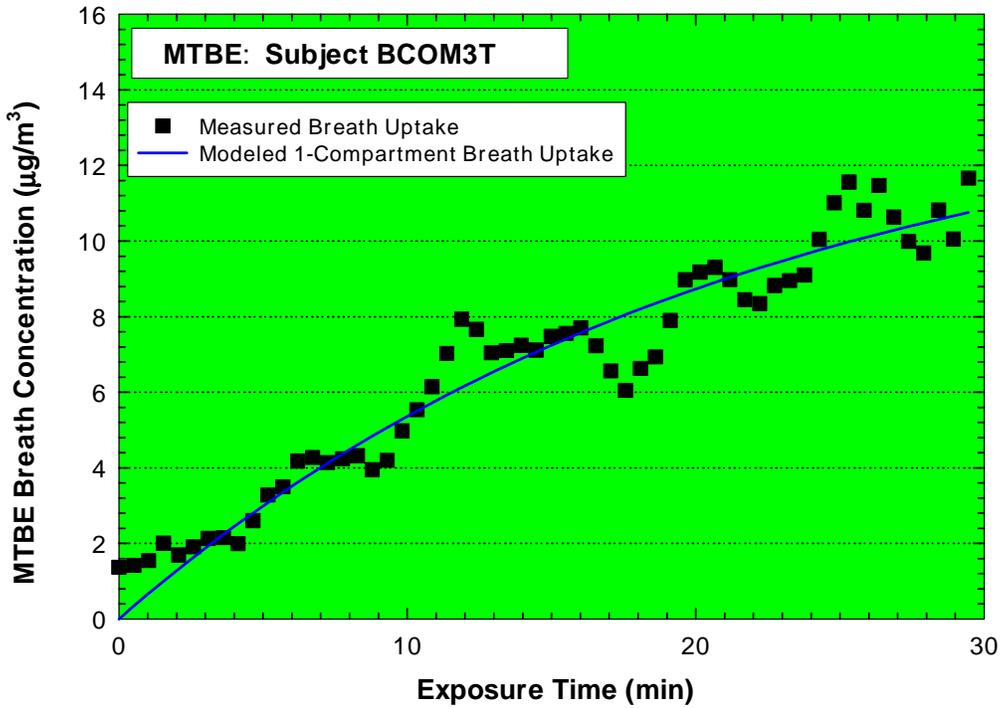


Figure 5-17. Measured MTBE exhaled air exposure uptake plot for Subject BCOM3T compared with modeled curve. Bath exposure details as described in Figure 5-8. Data smoothed using 5-point moving average.

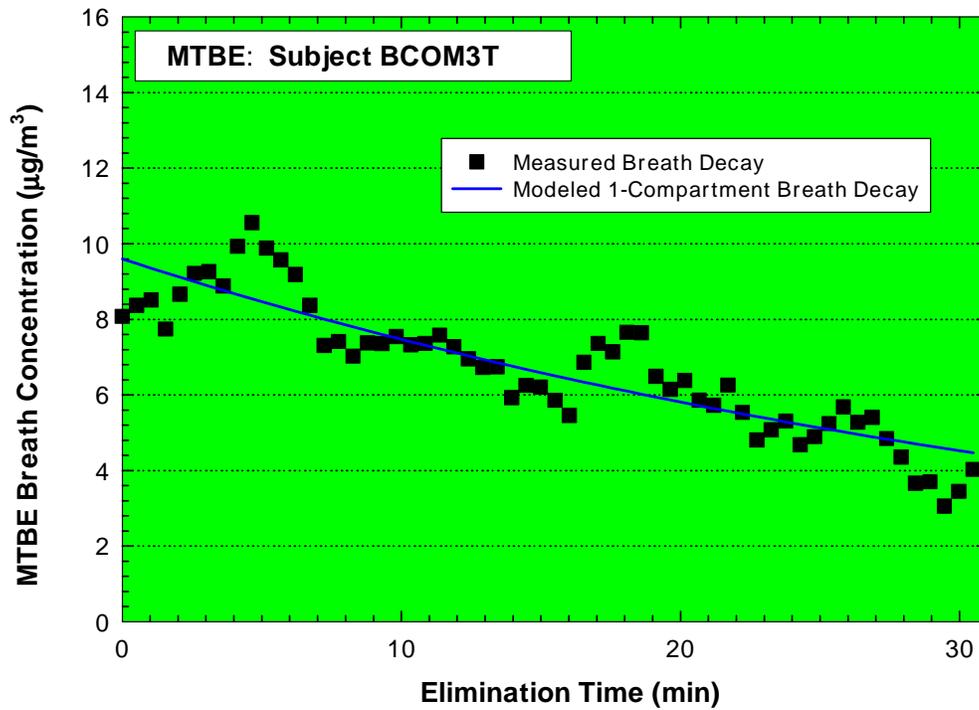


Figure 5-18. Measured MTBE exhaled air exposure decay plot for Subject BCOM3T compared with modeled curve. Bath exposure details as described in Figure 5-8. Data smoothed using 5-point moving average.

Table 5-2. Theoretical calculations of MTBE model parameters.

Parameter	Subj. BCOM1T	Subj. BCOF1T	Subj. BCOM2T	Subj. BCOF2T	Subj. BCOM3T	Mean	Std Dev
Target Analyte	MTBE-d ₁₂	MTBE-d ₁₂	MTBE-d ₁₂	MTBE-d ₁₂	MTBE	—	—
Nominal Water Concentration, C_{water} (µg/L)	150	150	150	150	150	150	0
Exposure (Uptake) Time, T (min)	34.1	33.0	33.1	33.0	29.5	32.5	1.8
Alveolar Ventilation Rate, AVR (L/min) ^a	6.10	5.38	6.77	5.76	6.60	6.12	0.58
f' (x10 ³)	0.19	0.06	0.08	0.12	0.10	0.11	0.05
One-Compartment Model (Uptake and Decay)							
Max. Breath Conc. (ng/L)							
Uptake ^b	26.2	7.4	11.9	18.9	14.4	15.8	7.2
Decay ^c	19.0	6.7	12.6	8.9	9.6	11.4	4.8
Residence Time (min)							
Uptake, τ_{uptake} ^b	30.2	11.8	5.2	37.5 ^h	21.5	21.2ⁱ	13.1ⁱ
Decay, τ_{decay} ^c	38.3	45.7	4.8	78.7	39.8	41.5^j	26.3^j
Adjusted R^2 ^d							
Uptake	0.424	0.701	0.433	0.827	0.930	—	—
Decay	0.884	0.814	0.858	0.462	0.785	—	—
Amount Exhaled During Uptake (ng-min/L) ^e	358	162	332	209	194	251	88
Amount Exhaled During Decay (ng-min/L) ^f	728	306	60	700	382	435	281
Normalized Mass Excreted (µg) ^g	6.5	2.4	2.6	5.3	3.8	4.1	1.8

^a Alveolar ventilation rate assumed to be 67% of ventilation rate.

^b All subjects, except Subject BCOM1T, had highly significant ($p < 0.0001$) values.

^c All subjects had highly significant ($p < 0.0001$) values.

^d Adjusted R^2 is the adjusted coefficient of determination, which takes into account the number of independent variables.

^e Calculated from Equation (4-8).

^f Calculated from Equation (4-9).

^g Calculated using measured ventilation rates, adjusted for alveolar contribution. Predicted dose normalized to 30 minutes decay period.

^h Subject had significant ($p < 0.005$) value.

ⁱ Mean \pm SD = 25.3 \pm 11.1 when Subject BCOM2T is excluded.

^j Mean \pm SD = 50.6 \pm 19.0 when Subject BCOM2T is excluded.

indicating that the two-exponent equation was “over-parameterized” and less suitable than the single-exponent equation. The adjusted R^2 values for the uptake data ranged from 42% to 93%; the adjusted R^2 values for the decay data were quite similar, ranging from 46% to 88%.

Quality Control Data

The determination of the precision of a continuous real-time system, such as the breath inlet/glow discharge/ion trap combination, is not well defined but, using a reasonably constant source such as an environmental chamber, the variation in ion signal with time can be measured. By averaging the results over a suitable time period, values of the means and standard deviations for the target compounds can be found, to provide an overall measure of system stability and reproducibility. Figure 5-19 shows the time course of the average signal for the MS/MS fragment ion at m/z 55, obtained from a calibration standard of 2-butanone that was prepared in a 186-L glass chamber at a level of $866 \mu\text{g}/\text{m}^3$ in zero-grade air. The ion current was sampled every 6 s and, at fixed intervals, the signal was averaged for 5 min. The ion intensity is almost constant over a 3½-h period, with a relative standard deviation of only 2.2%.

Quality control measures implemented in this study also included determining background levels and limits of detection for the compounds of interest. Background levels were estimated for the real-time breath measurements by passing humidified ultra-high purity air through the entire breath analyzer and measuring the signals at the masses used to monitor the target compounds. For the dermal exposure study, the mean background levels for MTBE- d_{12} at

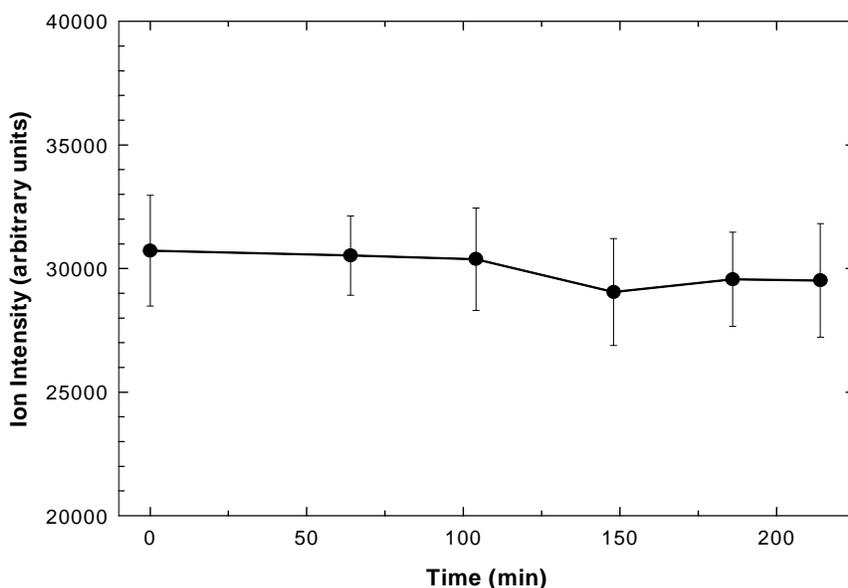


Figure 5-19. Plot of average ion signal (and standard deviation) at m/z 55 as a function of time, obtained from constant source of 2-butanone in glass chamber at a concentration of $866 \mu\text{g}/\text{m}^3$ in zero-grade air.

Table 5-3. Limits of detection (LOD) for MTBE-d₁₂ and DBCM in exhaled breath measured with the real-time breath analyzer (RTBA).

Subject	RTBA LOD ($\mu\text{g}/\text{m}^3$)	
	MTBE-d ₁₂	DBCM
BCOM1T	6.1	25.3
BCOF1T	2.3	9.1
BCOM2T	10.6	33.3
BCOF2T	5.8	14.3
BCOM3T	4.0 ^a	8.1
Mean \pm SD	5.8 \pm 3.1	18.0 \pm 10.9

m/z 82 and DBCM at m/z 129 were below the limits of detection, which were estimated by taking three times the standard deviation of the background (blank) mean concentration.⁴⁷ For MTBE-d₁₂, the detection limits averaged 5.8 ± 3.1 (SD) $\mu\text{g}/\text{m}^3$; for DBCM, the average detection limit was 18.0 ± 10.9 $\mu\text{g}/\text{m}^3$. The individually-measured detection limits for the real-time breath analyzer are summarized in Table 5-3.

Chapter 6 Discussion

Breath Concentration/Time Profiles

Multiple measurements of breath concentrations were made during and after dermal-only exposure to of MTBE-d₁₂ and DBCM while bathing in tap water contaminated with these chemicals at an elevated temperature. For MTBE-d₁₂ and MTBE, the plots in Figures 5-4 to 5-7 and in 5-8, respectively, show that the dermal exposure of the subjects to a nominal level of 150 µg/L for 30 minutes resulted in a relatively slow and small increase in the measured breath concentration from pre-exposure levels of 2 – 9 µg/m³ to peak levels of 7 – 15 µg/m³. After exposure ended, breath levels slowly decreased and tended toward the pre-exposure levels during the 30-minute elimination monitoring period. In all cases, except for Subject BCOM2T, the measured levels throughout the monitoring periods were above the limits of detection obtained with the real-time breath analyzer. The pre-exposure levels were roughly equal to the detection limits for MTBE-d₁₂, which ranged from 2.3 to 10.6 µg/m³.

Subjects also were dermally exposed at the same time to 40 µg/L of DBCM in water for 30 minutes. Detection limits for DBCM were significantly higher than for MTBE-d₁₂, averaging 18.0 ± 10.9 µg/m³ (range 8.1 – 33.3 µg/m³). Background breath levels for DBCM were approximately at or below the limits of detection. However, as noted earlier, the high initial breath concentrations as well as the lack of agreement between the breath analyzer and canister-GC/MS data in Figures 5-4 through 5-8 suggest that the measured breath analyzer signal at m/z 129 was probably due to an unknown contaminant with fragment ions at the same mass. We were unable to monitor DBCM in the MS/MS mode because none of the precursor masses examined (m/z 127, 129, and 131) fragmented by collision-induced dissociation in the glow discharge/ion trap mass spectrometer.

The RTBA background levels for MTBE-d₁₂ in pre-exposure breath samples were between 2 and 9 µg/m³. This concentration range is similar to that reported for background levels in previous studies that relied on batch collection and GC/MS analysis for the measurement of breath samples. As examples, in the inhalation exposure study of MTBE using the single breath canister method, Lindstrom and Pleil¹¹ obtained pre-exposure breath levels between 5.6 and 7.8 µg/m³. Similarly, in the inhalation exposure study conducted by Buckley et al.,²⁵ the background MTBE breath levels for two subjects were 3.6 and 12.6 µg/m³, and in the more recent inhalation study reported by Lee et al.,^{28,29} the mean pre-exposure breath level was 2.9 ± 4.3 µg/m³.

Breath Residence Times

The one-compartment model described by Equations (4-8) and (4-9) for the uptake and decay phases, respectively, was fit to the background-corrected uptake and decay data for all five subjects. The resulting curves are shown in Figures 5-9 to 5-18, and values obtained for f' , τ_{uptake} , and τ_{decay} are presented in Table 5-2. All of the τ_{uptake} and τ_{decay} estimates, except the τ_{uptake} value for Subject BCOM1T, were highly significant ($p < 0.0001$). The adjusted R^2 values associated with the one-compartment model fits ranged from 42 to 93% for the uptake data and from 46 to 88% for the decay data.

The mean residence times for the decay phase were roughly twice as long as the mean residence times for the uptake phase, viz., $\tau_{uptake} = 21.2 \pm 13.1$ min and $\tau_{decay} = 41.5 \pm 26.3$ min [mean \pm standard deviation]. These values are much greater than the residence times obtained in our earlier study of the dermal absorption of chloroform from bath water, for which the mean uptake residence time was 8.2 ± 3.1 min and the mean decay residence time was 7.7 ± 1.0 min.²¹ This may be due to the greater solubility of MTBE in water, which is reflected by their respective Henry's Law coefficients, namely, 1.6 mole/atm for MTBE vs. 0.26 mole/atm for chloroform.⁴⁸ These values also are significantly larger than the uptake and decay residence times for MTBE determined in our companion inhalation study. As proposed in the earlier study,²¹ this may be due to the obscuring effect that occurs as a result of continuous diffusion of MTBE through the stratum corneum for a time after exposure ends in the dermal absorption case. Because of this diffusion, the assumption of a single compartment is not strictly valid, and the continued influx of MTBE has the effect of increasing the observed residence time in the compartment.

Steady-State Ratio f' of Exhaled Breath to Water Concentration

The estimate of f' , the fraction of exhaled MTBE-d₁₂ to its water concentration, was fairly comparable among the five subjects, and was equal to $1.1 (\pm 0.5) \times 10^{-4}$. In one case (Subject BCOM2T), the uptake breath concentration/time profile appeared to reach equilibrium rapidly (see Figure 5-13) and the value for f' can be determined directly from the plot.

Our average value for f' is much smaller than the value calculated in our earlier inhalation study ($f = 0.29 \pm 0.04$), probably because of the more gradual dermal dose delivery and the fact that steady-state conditions may not have been attained here. It is, however, of the same order as the f' estimated by us in a similar experiment on the dermal absorption of chloroform from bath water, namely, 5.4×10^{-4} .²¹

Although lacking physiological significance, the parameter f' nevertheless plays an important role in compartmental models such as that used here to evaluate the data. From an exposure assessment perspective, it may often be the case that humans engaged in normal everyday activities are at or close to equilibrium with their immediate chemical environments. In these cases, it has been found that simply multiplying the measured breath concentration by the reciprocal of the parameter f' provides a reasonably good estimate of their average long-term normal exposure.⁴⁹

Total Exhaled Dose of MTBE

The total amount of MTBE-d₁₂ exhaled during the exposure and post-exposure periods was estimated by integrating the area under the curve. Measured ventilation rates (Table 5-1) for the subjects were used, and the alveolar ventilation rates were assumed to be 67% of the measured values. The mean amount of MTBE-d₁₂ exhaled at an average temperature of 39.5°C was 3.0 ± 1.1 (SD) µg (range: 1.7 – 4.6 µg). The mean exhaled amount obtained in our earlier bath water study of chloroform absorption at roughly the same temperature was 7.0 ± 2.0 µg. This indicates that the dermal uptake of MTBE from bath water is significantly smaller than that of chloroform under similar exposure conditions.

References

1. Squillace, P.J.; Zogorski, J.S.; Wilber, W.G.; Price, C.V. (1996). Preliminary assessment of the occurrence and possible sources of MTBE in groundwater in the United States, 1993-1994. *Environ. Sci. Technol.* **30**: 1721-1730.
2. ATSDR (August 1996). Toxicological Profile for Methyl Tertiary-Butyl Ether. Agency for Toxic Substances and Disease Registry, Centers for Disease Control (CDC), Atlanta, GA.
3. CalEPA (California Environmental Protection Agency). (June 1998). Public Health Goal for Methyl Tertiary-Butyl Ether (MTBE) in Drinking Water (Draft). Pesticide and Environmental Toxicology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.
4. U.S. EPA. (1993). Integrated Risk Information System (IRIS) on Methyl tert-Butyl Ether. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH.
5. Rao, H.V.; Ginsberg, G.L. (1997). A physiologically-based pharmacokinetic model assessment of methyl t-butyl ether in groundwater for a bathing and showering determination. *Risk Anal.* **17**: 583-598.
6. Williams, P.R.D.; Sheehan, P.J. (July/August 2002). Overview of MTBE and TBA exposures and human health risk in the U.S. *Contaminated Soil Sediment and Water* 93-103.
7. Johnson, M.L. Exposure of humans to MTBE from drinking water. In: *Health and Environmental Assessment of MTBE, Volume 5: Risk Assessment, Exposure Assessment, Water Treatment and Cost-Benefit Analysis*; Report to the Governor and Legislator of the State of California as Sponsored by SB 521; November 1998. Available at: <http://tsrtp.ucdavis.edu/>.
8. Wallace, L.A. (1997). Human exposure and body burden for chloroform and other trihalomethanes. *Crit. Rev. Environ. Sci. Technol.* **27**: 113-194.
9. Prah, J.D.; Blount, B.; Cardinali, F.L.; Ashley, D.L.; Leavens, T.; Case, M.W. (2002). The development and testing of a dermal exposure system for pharmacokinetic studies of administered and ambient water contaminants. *J. Pharmacol. Toxicol. Methods* **47**: 189-195.
10. Lioy, P.J.; Weisel, C.P.; Jo, W.K.; Pellizzari, E.; Raymer, J.H. (1994). Microenvironmental and Personal Measurements of Methyl-Tertiary Butyl Ether (MTBE) Associated with Automobile Use Activities. *J. Expos. Anal. Environ. Epidemiol.* **4**: 427-441.
11. Lindstrom, A.B.; Pleil, J.D. (1996). Alveolar breath sampling and analysis to assess exposure to methyl tertiary butyl ether (MTBE) during motor vehicle refueling. *J. Air &*

- Waste Manage. Assoc.* **46**: 676-682.
12. Vayghani, S.A.; Weisel, C.P. (1999). The MTBE air concentration in the cabin of vehicles while fueling. *J. Expos. Anal. Environ. Epidemiol.* **9**: 261-267.
 13. Mehlman, M.A. (2002). Carcinogenicity of methyl tertiary-butyl ether in gasoline. *Ann. N.Y. Acad. Sci.* **982**: 149-159.
 14. Moolenaar, R.L.; Hefflin, B.J.; Ashley, D.L.; Middaugh, J.P.; Etzel, R.A. (1994). Methyl tertiary butyl ether in human blood after exposure to oxygenated fuel in Fairbanks, Alaska. *Arch. Environ. Health*, **49**: 402-409.
 15. Prah, J.D.; Goldstein, G.M.; Devlin, R.; Otto, D.; Ashley, D.; House, D.; Cohen, K.L.; Gerrity, T. (1995). Sensory, symptomatic, inflammatory, and ocular responses to and metabolism of methyl tertiary butyl ether in a controlled human exposure experiment. *Inhalation Toxicology*, **6**, 521-538.
 16. Brown, S.L. (1997). Atmospheric and potable water exposures to methyl tert-butyl ether (MTBE). *Reg. Toxicol Pharmacol.* **25**: 256-276.
 17. Jo, W. K.; Weisel, C. P.; Lioy, P. J. (1990). Routes of Chloroform Exposure and Body Burden from Showering with Chlorinated Tap Water. *Risk Anal.* **10**: 575-580.
 18. Weisel, C.P.; Jo, W.K. (1996). Ingestion, inhalation, and dermal exposures to chloroform and trichloroethene from tap water. *Environ. Health Perspect.* **104**: 48-51.
 19. Giardino, N. J.; Andelman, J. B. (1996). Characterization of the emissions of trichloroethylene, chloroform, and 1,2-dibromo-3-chloropropane in a full-size, experimental shower. *J. Expos. Anal. Environ. Epidemiol.* **6**: 413-423.
 20. Keating, G. A.; McKone, T. E.; Gillett, J. W. (1997). Measured and estimated air concentrations of chloroform in showers: Effects of water temperature and aerosols. *Atmos. Environ.* **31**: 123-130.
 21. Gordon, S.M.; Wallace, L.A.; Callahan, P.J.; Kenny, D.V.; Brinkman, M.C. (1998). Effect of water temperature on dermal exposure to chloroform. *Environ. Health Perspect.* **106**: 337-345.
 22. Corsi, R. L.; Howard-Reed, C. (1998). *Volatilization Rates from Water to Indoor Air, Phase II Report*, US EPA Assistance Agreement No. CR 824228-01.
 23. Moya, J.; Howard-Reed, C.; Corsi, R. L. (1999). Volatilization of chemicals from tap water to indoor air while showering with contaminated water. *Environ. Sci. Technol.* **33**: 2321-2327.
 24. Wester, R.C.; Maibach, H.I. (1994). Percutaneous absorption of chemicals from water simulating swimming and bathing and from vapor exposure. *Environ. Sci. Pollut. Control, Ser 9*: 149-165.
 25. Buckley, T.J.; Prah, J.D.; Ashley, D.; Zweidinger, R.A.; Wallace, L.A. (1997). Body burden measurements and models to assess inhalation exposure to methyl tertiary butyl ether (MTBE). *J. Air Waste Manage. Assoc.* **47**: 739-752.
 26. Nihlén, A.; Lof, A.; Johanson, G. (1998). Experimental exposure to methyl tertiary-butyl

- ether. I. Toxicokinetics in humans. *Toxicol. Appl. Pharmacol.* **148**: 274-280.
27. Nihlén, A.; Wålinder, R.; Lof, A.; Johanson, G. (1998). Experimental exposure to methyl tertiary-butyl ether: II. Acute effects in humans. *Toxicol. Appl. Pharmacol.* **148**: 281-287.
 28. Lee, C.W. (1999). Biomonitoring of human exposure to methyl tertiary-butyl ether following controlled exposures using alveolar breath, blood, and urine analysis. Doctoral Dissertation, Rutgers University.
 29. Lee, C.W.; Mohr, S.N.; Weisel, C.P. (2001). Toxicokinetics of human exposure to methyl tertiary-butyl ether (MTBE) following short-term controlled exposures. *J. Expos. Anal. Environ. Epidemiol.* **11**: 67-78.
 30. Gordon, S.M. (July 1997). Application of Continuous Breath Sampling to Determine VOC Dose and Body Burden. Final Report under EPA Contract 68-D4-0023, Work Assignment No. 1-05; National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC.
 31. Gordon, S.M., Wallace, L.A., Pellizzari, E.D., O'Neill, H.J. (1988). Human breath measurements in a clean air chamber to determine half lives for volatile organic compounds. *Atmos. Environ.* **22**: 2165-2170.
 32. Raymer, J.H.; Pellizzari, E.D.; Thomas, K.W.; Cooper, S.D. (1991). Elimination of volatile organic compounds in breath after exposure to occupational and environmental microenvironments. *J. Expos. Anal. Environ. Epidemiol.* **1**: 439-451
 33. Kelly, T.J.; Kenny, D.V.; Spicer, C.W.; Sverdrup, G.M. (1989). Continuous Analysis of Human Breath Using Atmospheric Pressure Ionization MS/MS with a Novel Inlet Design. In: *Proceedings of the 1989 EPA/A&WMA International Symposium on Measurement of Toxic and Related Air Pollutants*, VIP-13; Air & Waste Management Association: Pittsburgh, PA; 478-483.
 34. Gordon, S.M.; Kenny, D.V.; Kelly, T.J. (1992). Continuous real time breath analysis for the measurement of half lives of expired volatile organic compounds. *J. Expos. Anal. Environ. Epidemiol.*, **Suppl. 1**: 41-54.
 35. McLuckey, S.A.; Glish, G.L.; Asano, K.G.; Grant, B.C. (1988). Atmospheric sampling glow discharge ionization source for the determination of trace organic compounds in ambient air. *Anal. Chem.* **60**: 2220-2227.
 36. McLuckey, S.A.; Glish, G.L.; Asano, K.G. (1989). The coupling of an atmospheric sampling ion source with an ion trap mass spectrometer. *Anal. Chim. Acta* **225**: 25-35.
 37. Asano, K.G.; McLuckey, S.A.; Glish, G.L. (1990). Comparison of atmospheric sampling glow discharge ionization with electron ionization. *Spectroscopy* **8**: 191-209.
 38. Gordon, S.M.; Callahan, P.J.; Kenny, D.V.; Pleil, J.D. (1995). Direct trace analysis of volatile organic compounds in air using ion trap mass spectrometers with filtered noise fields. In: *Proceedings of the 1995 EPA/A&WMA International Symposium on Field Screening Methods for Hazardous Wastes and Toxic Chemicals*, Vol. 1, VIP-47; Pittsburgh, PA: Air & Waste Management Association; 670-679.
 39. Winberry, Jr., W.T.; Murphy, N.T.; Riggan, R.M. (1990). Methods for Determination of Toxic

Organic Compounds in Air: EPA Methods, Noyes Data Corporation, Park Ridge, NJ.

40. Church, C.D.; Isabelle, L.M.; Pankow, J.F.; Rose, D.L.; Tratnyek, P.G. (1997). Method for determination of methyl tert-butyl ether and its degradation products in water. *Environ. Sci. Technol.* **31**: 3723-3726.
41. Wallace, L.A.; Pellizzari, E.D.; Gordon, S.M. (1993). A linear model relating breath concentrations to environmental exposures: application to a chamber study of four volunteers exposed to volatile organic chemicals. *J. Expo. Anal. Environ. Epidemiol.* **3**: 75-102.
42. Pleil, J.D. and Lindstrom, A.B. (1997). Exhaled human breath measurement method for assessing exposure to halogenated volatile organic compounds. *Clin. Chem.* **43**: 723-730.
43. Lindstrom, A.B.; Pleil, J.D. (1996). A methodological approach for exposure assessment studies in residences using volatile organic compound-contaminated water. *J. Air & Waste Manage. Assoc.* **46**: 1058-1066.
44. Yu, R. and Weisel, C.P. (1996). Measurement of benzene in human breath associated with an environmental exposure. *J. Expo. Anal. Environ. Epidemiol.* **6**: 261-277.
45. Wallace, L.A.; Nelson, W.C.; Pellizzari, E.D.; Raymer, J.H. (1997). Uptake and decay of volatile organic compounds at environmental concentrations: application of a four-compartment model to a chamber study of five human subjects. *J. Expo. Anal. Environ. Epidemiol.* **7**: 141-163.
46. Gordon, S.M. (September 1999). Application of Continuous Breath Sampling to Determine VOC Dose and Body Burden: Dermal and Inhalation Exposure to Chloroform. Final Report under EPA Contract 68-D4-0023, Work Assignment No. 3-09; National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC.
47. Long, G.L.; Winefordner, J.D. (1983). Limit of detection. *Anal. Chem.* **55**: 712A-724A.
48. Sander, R. (July 2001). "Henry's Law Constants" in NIST Chemistry WebBook, NIST Standard Reference Database Number 69, Eds. P.J. Linstrom and W.G. Mallard, National Institute of Standards and Technology, Gaithersburg MD, 20899 (<http://webbook.nist.gov>).
49. Wallace, L.; Buckley, T.; Pellizzari, E.; Gordon, S. (1996). Breath measurements as volatile organic compound biomarkers. *Environ. Health Perspect.* **104 (Suppl. 5)**: 861-869.