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INHALATION UPTAKE OF XENOBIOTIC VAPORS BY PEOPLE

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March 1988

Otto G. Raabe, Ph.D.
Principal Investigator

University of California
Davis, California

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UNIVERSITY OF CALIFORNIA
DAVIS, CA 95616

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16. Abstract (Limit: 200 words)
THE OBJECTIVE OF THIS STUDY WAS TO PROVIDE INFORMATION ON THE DEGREE TO WHICH THE BODY ABSORBS INHALED TOXIC SUBSTANCES FROM AIR CONTAINING AMBIENT CONCENTRATIONS. FOUR HUMAN SUBJECTS, TWO MEN AND TWO WOMEN, INHALED EACH TEST COMPOUND (^{14}C)LABELED BENZENE, CHLOROFORM, METHYL BROMIDE, TRICHLORETHYLENE, AND FORMALDEHYDE) TWICE, ONCE THROUGH THE NOSE AND ONCE THROUGH THE MOUTH. IN ADDITION, EACH SUBJECT INHALED BENZENE THROUGH THE MOUTH WHILE ENGAGED IN EXERCISE.
THE UPTAKE (% OF INHALED) OF EACH OF THE COMPOUNDS WAS AS FOLLOWS: CHLOROFORM 45.6% NASAL, 49.6% ORAL; TRICHLOROETHYLENE 53.9% NASAL, 55.3% ORAL; METHYLBROMIDE 55.4% NASAL, 52.1% ORAL; BENZENE 60.0% NASAL, 54.6% ORAL; FORMALDEHYDE 75.1% NASAL, 86.4% ORAL. THE UPTAKE OF BENZENE DURING EXERCISE WAS 41.6%

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RETENTION AND METABOLISM OF TOXICS

INHALATION UPTAKE OF XENOBIOTIC VAPORS BY PEOPLE

CARB Contract No. A5-155-33

Final Report
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Otto G. Raabe, Ph.D.
Principal Investigator
Department of Pharmacology and Toxicology-
School of Veterinary Medicine,
Department of Civil Engineering,
and Institute for Environmental Health Research
University of California
Davis, California 95616
Telephone (916) 752-7754

SUBMITTED TO THE BIOLOGICAL EFFECTS RESEARCH SECTION
CALIFORNIA AIR RESOURCES BOARD
P.O. Box 2815
Sacramento, California 95812

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ABSTRACT

When low concentrations of xenobiotic chemical vapors or gases are inhaled by people as in air pollution, the potential risk is dependent upon the systemic uptake, retention and metabolism. In this project quantitative measurements were made of the systemic uptake during nose-breathing and during mouth-breathing of very low concentrations ($\leq$25 ppb) in dry air of five selected ^{14}C-radiolabeled chemical vapors including benzene, chloroform, formaldehyde, trichloroethylene, and methyl bromide. The experimental subjects were paid volunteers, two adult women and two adult men. Typical exposures were two hours long with each of the two breathing modes (oral and nasal) including one oral exposure to benzene while exercising utilizing a bicycle ergometer. The concentration of the chemical vapor or gas under study was measured before and after inhalation to determine uptake efficiency.

The steady state fractional systemic uptake corrected for external dead space during nasal breathing at rest of inhaled vapor or gas in air at room temperature was found to be 45.6%$\pm$1.5%SE for chloroform, 53.9%$\pm$1.9%SE for trichloroethylene, 55.4%$\pm$3.6%SE for methyl bromide, 60.0%+3.2%SE for benzene, and 75.1%$\pm$2.1 %SE for formaldehyde. The uptake corrected for dead space during oral breathing at rest of the total inhaled vapor or gas was 49.6%$\pm$1.6%SE for chloroform, 55.4%$\pm$1.8%SE for trichloroethylene, 52.1%$\pm$3.4%SE for methyl bromide, 54.6%+2.1%SE for benzene, and 86.4%$\pm$0.8 %SE for formaldehyde. During oral breathing with exercise and more than doubling of inhalation minute volume, the uptake of benzene dropped to 41.6%$\pm$1.3%SE, significantly ($p<0.001$) lower than the at rest value. Although there was observed considerable intersubject variability, most could be accounted with simple linear models:
(a) Uptake (%) via mouth = 35.1 + 314 D - 1.56 RR - 0.0168 TV + 5.49 H, accounting for 93% of the variability among 23 experiments, and
(b) Uptake (%) via nose = 50.8 SE) + 193 D - 1.48 RR - 0.0232 TV + 9.73 H, accounting for 62% of the variability among 20 experiments, where D is the gas or vapor diffusivity (cm^2/s), RR the respiratory rate (breaths per minute), TV the tidal volume (ml), and H a head and/or upper airway uptake factor with H=1 for all vapors but chloroform for which H=0. These results indicate that inhalation uptake is limited by pulmonary ventilation and the diffusion of the respective relatively tissue-soluble vapors in air within the lung, since vapor in the lung is not completely mixed during breathing.

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Mohammed Al-Bayati - Toxicology and Physiology
Fiorella Gielow - Radioanalytical Chemistry
Stephen Teague - Inhalation Exposure Methodology
Dale Uyeminami - Toxicology

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DISCLAIMER

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SUMMARY AND RECOMMENDATIONS

Low concentrations of xenobiotic chemical vapors or gases in the atmosphere are inhaled by people and may pose a risk associated with lifetime chronic exposure. This potential risk is dependent upon the systemic uptake, retention and metabolism. This project focuses on the fractional uptake of these vapors by the body during normal breathing via nose or mouth. One set of experiments considered the effect of exercise on this process. Uptake fractions for people have previously been measured for a few chemicals at relatively high concentrations (>50 ppm), and none are available for low concentrations approaching environmental trace levels (<50 ppb).

Organic vapors of the types studied in this project are found in California air as reported for 1985 in the preliminary CARB Toxic Air Quality Data Base Report. The statewide average concentration for benzene was 2.6 ppb with one measurement as high as 15.6 ppb. The average for trichloroethylene was 0.8 ppb with a maximum of 12.4 ppb. The average for chloroform was about 0.1 ppb with a maximum of 3.5 ppb. Other vapor types have also been measured. Formaldehyde continues to be a major indoor air pollutant. All of the five vapors are themselves or are generically representative of chemical vapors that people in California are regularly inhaling in the ppb to 10 ppb concentration range. There is a clear need to understand accurately the uptake of these inhaled chemical vapors.

In this project quantitative measurements have been made of the systemic uptake during nose-breathing and during mouth-breathing of very low concentrations ($\leq$25 ppb) in air of five selected ^{14}C-radiolabeled chemical vapors including benzene, chloroform, methyl bromide, trichloroethylene, and formaldehyde. The experimental subjects were paid volunteers, two adult women and two adult men. Each volunteer was studied with each of the five vapors and with each of the two breathing modes (oral and nasal). In addition one additional oral exposure to benzene was performed with each subject while exercising utilizing a bicycle ergometer. There were, therefore, a total of 44 separate inhalation experiments in this project.

The special apparatus for the controlled inhalation exposure of individuals was designed for use in this project. It used a respirator demand-air breathing valve that separated inhaled and exhaled gases. The special method of concurrent flow spirometry was adapted to the system to measure the volumes of air inhaled and exhaled during the exposures and the breathing rate. Each person breathed normally via a SCUBA-type mouthpiece or nose shield at a comfortable and normal breathing rate. Each organic vapor/gas was produced from high specific activity ^{14}C-labeled xenobiotic chemicals at concentrations in the range from 2 ppb to 25 ppb and the assays of the material were done using radioanalytical techniques. The concentration of the chemical vapor or gas under study was measured before and after inhalation to determine uptake efficiency. Exhaled air and urine samples were used to measure the uptake and compare to metabolic behavior in the earlier beagle studies. The individual exposures were two hours long in thirty-minute monitoring sub-periods and there was a following separate thirty-minute respiratory clearance measurement while breathing clean air. The four exposures during exercise were conducted for only one hour, followed by a fifteen-minute clearance period.

The levels of radiation and chemical exposures to the subjects were both very low and did not involve special risks to the volunteers. The experimental protocol was approved by both the University of California, Davis, Human Subjects Administrative Advisory Committee and the UC Medical Center Radiation Use Administrative Advisory Committee.

The steady state fractional systemic uptake during nasal breathing at rest of the total inhaled vapor or gas in air at room temperature was 45.6%$\pm$1.5%SE for chloroform, 53.9%$\pm$1.9%SE for trichloroethylene, 55.4%$\pm$3.6%SE for methyl bromide, 60.0%+3.2%SE for benzene, and 75.1%$\pm$2.1 %SE for formaldehyde. The uptake during oral breathing at rest of the total inhaled vapor or gas was 49.6%$\pm$1.6%SE for chloroform, 55.4%$\pm$1.8%SE for trichloroethylene, 52.1%$\pm$3.4%SE for methyl bromide, 54.6%+2.1%SE for benzene, and 86.4%$\pm$0.8 %SE for formaldehyde. During exercise with oral breathing and more than doubling of inhalation minute volume from rest conditions, the steady state uptake of benzene dropped to 41.6%$\pm$1.3%SE; this average was significantly ($p<0.001$) lower than the at rest average values for either nose or mouth breathing.

The main results show that mouth inhalation uptake of chloroform was significantly higher than that by nose ($p<0.005$), and there was a strong tendency for by mouth inhalation uptake of formaldehyde to be higher than by nose ($p<0.01$). The average oral inhalation uptake of benzene vapor during exercise was significantly lower than for uptake at rest for either nose or mouth breathing ($p<0.001$).

For oral inhalation, the uptake of trichloroethylene (TCE) was significantly higher than chloroform ($p<0.005$) and lower than formaldehyde ($p<0.001$), but not statistically different from the results for methyl bromide or benzene. The oral uptake of chloroform was significantly lower than formaldehyde ($p<0.001$), benzene ($p<0.03$) or TCE ($p<0.005$). Oral uptake of methyl bromide was significantly lower than formaldehyde ($p<0.025$). The oral uptake of benzene was higher than chloroform ($p<0.025$) and lower than formaldehyde ($p<0.001$), but not statistically different from methyl bromide or TCE.

For nasal inhalation, the uptake of trichloroethylene was significantly higher than chloroform ($p<0.01$) and lower than formaldehyde ($p<0.025$), but not statistically different from the results for methyl bromide or benzene. The nasal inhalation uptakes of benzene and methyl bromide were not significantly different from the other vapors.

Although there was considerable inter-subject variability in the results, most of that variability may be explained by the physiological differences among subjects and among data of the same subject in different sessions. The variability among the data was studied with linear and logarithmic models utilizing the tidal volume (TV) and respiratory rate (RR) as the principal respiratory variables. In addition, the influences of sex, gas diffusivity (D), blood-to-air partition coefficient, and apparent upper respiratory and head airways uptake (H) for all the vapors but chloroform were also considered. It was found that a considerable portion of the variability could be explained with the simple linear models and no improvement was associated with multiplicative (logarithmic) models. Sex and partition coefficient had little influence on the regression correlation. However, the results should not be expected to apply to vapors of gases with blood-to-air partition coefficients that are very much smaller than unity.

The linear regression model for mouth-breathing is:

$$\text{Uptake (\%) via mouth} = 35.1(\pm 7.1\ \text{SE}) + 314(\pm 25\ \text{SE})\ D - 1.56(\pm 0.39\ \text{SE})\ RR - 0.0168(\pm 0.0037\ \text{SE})\ TV + 5.49(\pm 2.54\ \text{SE})\ H$$

where D is the gas or vapor diffusivity (cm^2/s), RR is the respiratory rate (breaths per minute), TV is the breathing tidal volume (ml), and H the head and/or upper airway uptake factor with H=1 for all vapors but chloroform for which H=0. This fit displayed a multiple correlation coefficient of 0.97 ($p<0.001$) and the regression equation accounted for 93% of the variability. Of this 93%, 79% was associated with vapor diffusivity, 6% with the respiratory rate, 6% with the tidal volume, and 2% with the head/upper tract effect. This equation provides reasonable predictions of both the at rest and exercise data.

The linear regression model for nose-breathing is:

$$\text{Uptake (\%) via nose} = 50.8(\pm 25.7\ \text{SE}) + 193(\pm 53\ \text{SE})\ D - 1.48(\pm 1.41\ \text{SE})\ RR - 0.0232(\pm 0.0260\ \text{SE})\ TV + 9.73(\pm 5.19\ \text{SE})\ H$$

This fit displayed a multiple correlation coefficient of 0.79 ($p<0.001$) and the regression equation accounted for 62% of the variability. Of this 62%, 47% was associated with vapor diffusivity, 4% with the respiratory rate, 2% with the tidal volume, and 9% with the upper tract effect. The prudent choice is H=1 for an untested chemical vapor, unless is is reason to believe that there is low head/nose uptake; a value between 0 and 1 could also be considered as appropriate in certain cases.

These results show that uptake increases with increased vapor diffusivity, and decreases with increased respiratory rate (decreased vapor residence time in lung) or increased tidal volume (greater lung expansion and increased diffusion distance). Thus, the diffusion of vapor in the lung is demonstrated to be the significant limiting process in determining vapor uptake into the body. Models of the uptake process usually assume complete mixing of vapor in the lung during breathing and rapid equilibration with the blood circulating through the lungs at the alveolar air/blood interface. Because all of the

vapors under study can be expected to be highly soluble in blood at very low concentrations, these models predict nearly quantitative absorption into the blood of vapor or gas from the lung parenchyma. The expected uptake on this basis should readily exceed 60% even if there is no upper respiratory tract absorption, and should approach 80% with modest upper tract absorption. Only the highly diffusive formaldehyde approached this uptake fraction. These results indicate that inhalation uptake is limited by the ventilation process dependent upon pulmonary ventilation and the diffusivities of the respective vapors in air within the lung. Exercise reduced uptake fraction (but not total uptake) by enlarging the lungs so that there is a bigger average vapor diffusion distance to reach the alveolar surface. Increased respiratory rates also decreased uptake by reducing the residence time of vapor for diffusion in the lung.

Previously reported uptake measurements for trichloroethylene and benzene by people at much higher concentrations (about 100 ppm) were in good agreement with the results of the uptake measurements in these studies for these two vapors at near environmental concentrations (less than 25 ppb). A previously reported study of the uptake of these same five chemical vapors by beagles (Raabe, 1986) showed beagle to have less variability than the people in this study and to have uptake fractions at the low end of the human range in each case. It appeared that the beagle uptake of benzene was about the same as for exercising people in this study.

Because the standard simulation models and the associated pharmacokinetic models do not adequately account for the finite transfer time associated with vapor diffusion in the lung to the air/alveolar membrane interface, the rate of transfer through that membrane and associated cells to reach the blood, and the conductive airway absorption-desorption phenomena, those models tend to overestimate the uptake. The experimental data reported in this study are values that can be used directly for risk assessment purposes, however. For xenobiotic chemicals not included in this study, comparison of molecular diffusivity in air, and blood/air partition coefficient with those chemicals that were studied provides a basis for estimation of uptake utilizing the linear regression equations as provided.

INTRODUCTION

Releases of various xenobiotic organic chemical vapors to the environment that occur as a consequence of the extensive use of chemicals in industrial, agricultural, governmental and private sectors result in the exposure of the general population to low concentrations of these vapors in the air that is breathed. These vapors may fall into one of various organic chemical classes including alkanes, alkenes, brominated alkanes, aromatic hydrocarbons, and oxiranes. When low concentrations of organic vapors are inhaled by people as in the case of environmental releases, the potential risk is dependent upon the systemic uptake and metabolic fate. Uptake fractions have been measured for certain chemicals at relatively high concentrations, but are not generally available for low concentrations approaching environmental trace ppb levels. The potential risk to the general public associated with these inhalation exposures at very low concentrations may be assessed with various dose-response models that require uptake dosage quantification based upon ambient concentration data (Elkins, 1967).

When organic vapors are inhaled, they are transferred from the respiratory tract to the systemic circulation at rates that depend upon respiratory tract ventilation efficiency, diffusivities of the vapors in air and in the warm, humid environment of the respiratory airways, gas solubility in body fluids, blood-to-air and tissue-to-air partition coefficients, alveolar concentration gradients, volumetric flow rate of blood through the lungs, and alternative fates of elimination or enzymatic metabolic chemical alteration (Leibman, 1983; Fiserova-Bergerova, 1983a; Fiserova-Bergerova, 1983b). Experimental measurements were made in this project to ascertain the relationship of these factors by measurement of the uptake, excretion, and exhalation of inhaled vapors at environmentally meaningful concentrations.

Several investigators have studied body retention of various chemicals instilled in blood and cleared via the lungs during breathing. For example, Wagner et al. (1974) and Wagner (1981) have developed a rather complete perfusion-ventilation model for chemicals in the body based upon their solubility in blood. The higher solubilities yield the higher retentions.

These results provide information of the blood-to-air partition coefficients but do not solve the lung-tissue and gaseous diffusion aspects of the process. For concentrations measured in ppb, most xenobiotic vapors should be relatively soluble in blood and body tissues.

Measurements have been made of the uptake, blood concentration with time, excretion of metabolic products, and retention and clearance with time after exposure for certain chemical vapors including anesthetics such as ether and halothane (Eger, 1963; Landry et al., 1983b, Leibman,1983), organic solvents such as toluene, acetone, and xylene, and other organic agents such as styrene, trichloroethylene, perchloroethylene, and vinyl chloride (Fiserova-Bergerova, 1983a; Fiserova-Bergerova, 1983b; Fiserova-Bergerova, 1983c; Astrand, 1975). However, these available data do not address the special problem of exposure at trace levels nor do they generally provide the needed information for different types of chemical agents now of environmental concern.

Previous inhalation studies with human subjects using benzene concentrations of 57 ppm (Nomiyama & Nomiyama, 1974) and 217 ppm (Astrand, 1975) yielded measured uptake fractions of 47% and 55%, respectively, for normal breathing at rest. Only Astrand (1975) who studied mouth-breathing people, collected all of the exhaled vapor. Likewise, trichloroethylene uptake in nose-breathing humans was found to be 55% at 316 ppm (Nomiyama & Nomiyama, 1974), 58% at 193 ppm (Bartonicek, 1962), 46% at 68 ppm (Monster, et al. 1976), and 44% at 100 ppm (Vesterberg et al., 1976). Astrand and Ovrum (1976), who studied mouth-breathing people, collected and measured the exhaled vapor and found 53% uptake at 100 ppm.

There are, in fact, very few reliable data on uptake of chemical vapors in people even at very high concentrations. As noted above, there is a mouth-breathing study of benzene in people at 217 ppm reported by Astrand (1975) and of trichloroethylene at 100 ppm ppm reported by Astrand and Ovrum (1976). Other human studies involving nose breathing allowed rebreathing of vapor and did not provide for definitive measurements of exhaled vapor for uptake determinations.

In earlier studies sponsored by the California Air Resources Board (Raabe, 1986), the uptake and early systemic distribution and clearance of low concentrations in air of six inhaled organic vapors were measured in individual nose-breathing awake dogs. The six selected chemical vapors included benzene, dimethylnitrosamine, chloroform, methyl bromide, trichloroethylene, and formaldehyde. The experimental subjects were three pedigreed adult female beagles obtained from the dog colony at UC Davis. A special apparatus for the controlled inhalation exposure of individual subjects was used. It consisted of a demand valve-based inhalation exposure system that separated inhaled and exhaled gases. The organic vapor was produced from high specific activity carbon-14 labeled chemicals at concentrations in the range from about 1.4 ppb to 594 ppb so that assays of the material could be done using radioanalytical techniques. The concentrations of the chemical vapor under study were measured before and after inhalation to determine uptake efficiency. Exhaled air, blood, urine, and fecal samples were utilized to measure the metabolic pattern of blood concentration and excretion of each chemical or its metabolites during and after exposure. The individual exposures were up to three hours long, and the metabolic behavior of the chemicals was followed for up to 120 hours after exposure.

The results in beagles (Raabe, 1986) show that the fractional systemic uptake rate relationship for each vapor with respect to time from beginning of exposure stabilized rapidly so that a steady-state uptake was achieved within the first 30 minute assessment period. The steady-state fractional systemic nasal inhalation uptake (corrected for equipment dead space) of the total vapor was 42.1%$\pm$2.2% SE for benzene, 39.8%$\pm$1.5% SE for chloroform, 48.0%$\pm$0.8% SE for trichloroethylene, 53.6%$\pm$2.1% SE for dimethylnitrosamine, 39.5%$\pm$1.0% SE for methyl bromide, and 54.4%$\pm$0.9 %SE for formaldehyde.

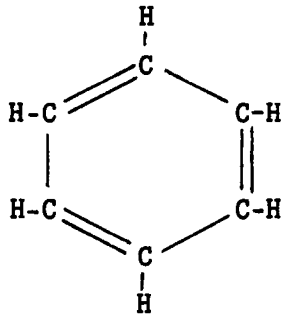
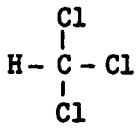
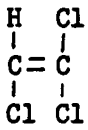
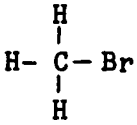
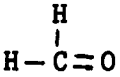
After the three-hour exposure the blood burdens as percentage of total inhaled vapor were 9.2%$\pm$5.4%SE for benzene, 3.3%$\pm$0.6%SE for chloroform, 2.5%$\pm$0.4%SE for trichloroethylene, 5.6%$\pm$0.4%SE for dimethylnitrosamine, 1.6%$\pm$0.1%SE for methyl bromide, and 12.4%$\pm$4.7%SE for formaldehyde. Clearance half-times after the exposure ended based upon the radiocarbon label were from less than 10 hours for dimethylnitrosamine to 41 hours for methyl bromide.

Among the laboratory animal data, the beagle data of Raabe (1986) are the most useful. Most of the other reported laboratory animal studies involved rebreathing of exhaled air. However, the dependence on ventilatory gas diffusion nature of the uptake process described by Raabe (1986) leaves unanswered questions about the extrapolation to people. Also, nose breathing dogs are uncertain models of mouth breathing people.

This study was conducted to provide definitive data on uptake in people for both nose-breathing and mouth-breathing of inhaled xenobiotic chemical gases to improve the estimation of exposure risks and the potential for adverse health effects of exposure of people to environmental trace levels of organic vapors. Although the word "vapor" is used herein to describe the mixture of low concentrations of these chemicals in air, methyl bromide is a gas at normal ambient conditions. The specific purpose of this project was to measure the pulmonary uptake during controlled inhalation over two hours of five selected chemical gases at trace levels (<25 ppb) via nose or mouth breathing in normal adult humans for environmental risk estimation. The five vapors are representatives of five different chemical classes and include benzene, methyl bromide, trichloroethylene, formaldehyde, and chloroform. Ancillary purposes include measurement of exhaled carbon dioxide produced as a result of the vapor metabolism, measurement of early pulmonary clearance up to thirty minutes post-exposure, and measurement of urinary clearance of the agent and its metabolites up to 24 hours post exposure. Properties of the five vapors are summarized in Table 1.

Organic vapors and gases of the types needing study are found in California air as reported for 1985 in the preliminary CARB Toxic Air Quality Data Base Report. The statewide average concentration for benzene was 2.6 ppb with one measurement as high as 15.6 ppb. The average for trichloroethylene was 0.8 ppb with a maximum of 12.4 ppb. The average for chloroform was about 0.1 ppb with a maximum of 3.5 ppb. Other vapor types have also been measured. Formaldehyde continues to be a major indoor air pollutant. All of the five vapors are themselves or are generically representative of chemical vapors that people in California are regularly inhaling in the ppb to 10 ppb concentration range. There is a clear need to understand accurately the uptake of these inhaled chemical vapors.

Table 1. Characteristics of the Chemical Vapors Studied in this Project

CHEMICAL	STRUCTURE	MOLECULAR WEIGHT (g/mole)	DIFFUSIVITY (at 37°C) (cm^2/s)	PARTITION COEFF.* (at 37°C) BLOOD/AIR	LUNG/AIR
BENZENE C_6H_6		78.11	0.14	6.5-9.0	10-12
CHLOROFORM $CHCl_3$		119.39	0.14	8.2-11.0	7-11
TRICHLOROETHYLENE C_2HCl_3		131.40	0.13	9.0-9.9	10-15
METHYL BROMIDE CH_3Br		94.95	0.16	(1)	(1)
FORMALDEHYDE CH_2O		30.03	0.24	(20)	(20)

* Blood/air and lung tissue/air partition coefficients from Fiserova-Bergorova (1983). Methyl bromide at low concentration was estimated from data on methyl chloride and formaldehyde values are estimated because of its high water solubility as being at least twice that for chloroform; these vapors and gas are all soluble in blood at ppb levels.

PROJECT OBJECTIVES

The overall objective of this project was to provide quantitative information measured in vivo that will reduce the current uncertainties in assessing the potential uptake and biological risk to the public associated with the inhalation of air containing low concentrations of certain xenobiotic and potentially toxic chemical vapors and gases.

The specific purpose of this project was to measure the pulmonary uptake during controlled inhalation of five selected chemical vapors in air at trace levels (<25 ppb) via nose or mouth breathing in normal adult humans for environmental risk estimation. The five vapors are benzene, methyl bromide, trichloroethylene, formaldehyde, and chloroform; these represent a diversity of different chemical classes. Ancillary goals included measurement of exhaled carbon dioxide produced as a result of the vapor metabolism, measurement of early pulmonary clearance up to 30 minutes post-exposure, and measurement of urinary clearance of the agent and its metabolites up to 16 hours post exposure.

The inhalation uptake and basic biological behavior of the five representative chemicals, including benzene, chloroform, methyl bromide, trichloroethylene, and formaldehyde, were measured during and after separate nasal inhalation or oral inhalation by four individual human volunteers at rest, including two adult women and two adult men to provide appropriate estimates of biological variability. In addition one study with benzene vapor was performed under conditions of exercise to observe its effect on uptake. The data were to provide the basis for future dosimetric analyses with available relevant interspecies and biochemical information to estimate the characteristic parameters in explanatory simulation models of uptake, retention, and metabolism (Eger, 1963; Fernandez, 1977; Fiserova-Bergerova and Hughes, 1983; Sato et al., 1977).

METHODS

Exposure System

The exposure system for the study of the uptake of inhaled vapors in air by human volunteers was designed and built utilizing a two-stage demand regulator-based inhalation exposure system that separated inhaled and exhaled air (Figures 1, 2 & 3). The exposure system was modified from the system previously used successfully for exposing dogs in the California Air Resources Board contract No. A3-132-33 (Inhalation Uptake of Selected Chemical Vapors at Trace Levels). This system was modified for the increased volume of air needed for inhalation studies with the human as compared to the beagle. The demand regulators used were designed for human sport self-contained underwater breathing air (SCUBA) diving and only the exhaust portion of the system was altered. The criteria for choosing a regulator was a low demand pressure required to open the valve, to avoid undue strain on the subject and the availability of an accessible port for drawing off the exhaust gas. Each air-vapor mixture was prepared and stored in a metallic gas cylinder of the type used as SCUBA tanks. Tanks of 80 cubic foot capacity were of sufficient volume for the two hours of breathing planned in this study plus the volume needed for the pre- and post-tests.

The entire exhaust gas portion leading to the bubbler collection system was insulated and heated to maintain a temperature above the body temperature of the subjects (>40^{o}C), as was the tubing serving as the surge volume leading to the spirometer. Vapor-air mixtures of both benzene and trichloroethylene (TCE) were stable in the SCUBA tanks after preparation and could be used on successive days after preparation. The other vapors, especially formaldehyde, were less stable and had to be prepared just before use and required precise temperature control for the pre-test and exposure to maintain the same vapor pressure. With all the exposures but benzene and TCE the tank was maintained at a constant 38^{o}C for the pre-test, exposure and post-test. However, the air delivered to the breathing valve did not exceed 28^{o}C after expansion in the pressure reduction valves.

Exposures were either mouth-only or nose-only connected to a second-stage demand regulator valve (Figure 1). This valve is designed to preclude rebreathing of inhaled and exhaled air and to minimize the external dead space (rebreathed air space). The subjects breathed the same vapor type by mouth and by nose after a sufficient amount of time had elapsed to insure their bodies had cleared all of the material from the previous exposure.

The mouth breathing method employed a standard mouthpiece used for SCUBA diving for which the mouth and lips are used to seal against ambient air. A nose clamp commonly employed by some for swimming was used to close off the nose. The volume of dead space (rebreathed air space) in the system was that space in the second stage regulator where air can be rebreathed was 7 ml, for the four subjects in this study this represents only 1.5% of the average tidal volume.

The nose breathing method employed a nose cone made of silicone rubber used for the administration of nitrous oxide or other anesthetic gases in dental applications. This nose cone was modified by filling the cone partially with silicone rubber to reduce the volume of dead space and plug up the holes used in the dental apparatus. The volume of the dead space depends on the size of the subjects nose but could be no more than 15 ml and was usually less, this represents less than 3% of the average at-rest tidal volume.

A strap with a rubber head band held on by Velcro cloth was used to keep the mouth piece or nose cone in the proper location or provide the pressure needed to insure proper sealing of the connecting fittings. Pressure balance in the system was maintained utilizing a concurrent flow spirometer (Raabe and Yeh, 1976) so that there was no unusual effort required by the subject to maintain normal breathing. A pressure differential of only about 1.0 cm water column was required to open the breathing valve, while the exhaust line was maintained near ambient pressure by the spirometer.

Small quantities of ^{14}C-labeled benzene (57 mCi/mmol), trichloroethylene (10 mCi/mmol), methyl bromide (13 mCi/mmol), and formaldehyde (44 mCi/mmol) were obtained from New England Nuclear, Boston, Massachusetts. The ^{14}C-labeled chloroform (11.9 mCi/mmol) was obtained from Pathfinder

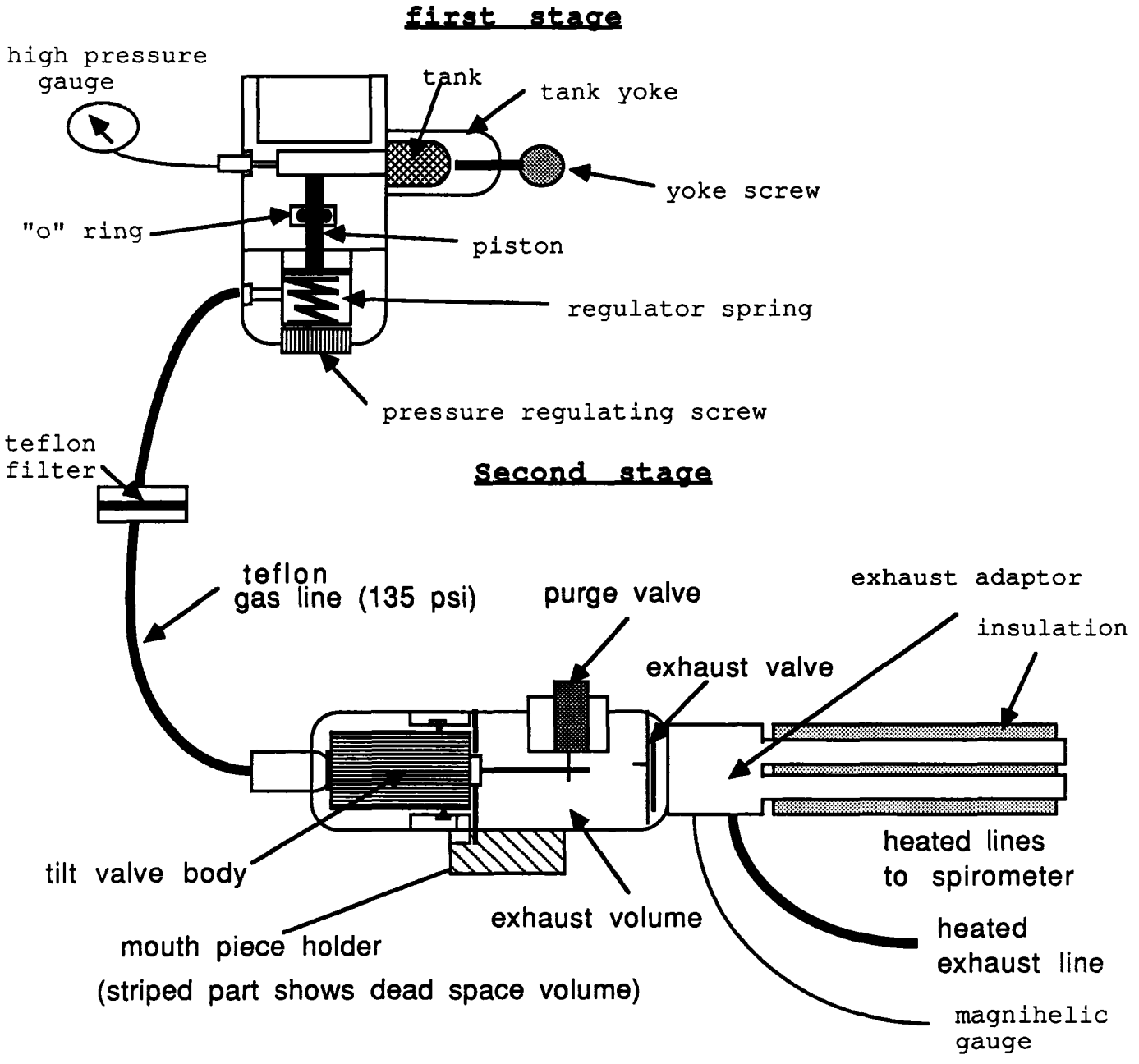
Laboratories Inc., St Louis, Missouri. For each compound all carbon positions were labeled and chemical purity exceeded 98%. Each ^{14}C-radiolabeled chemical vapor was first prepared by transferring the total contents of the suppliers ampule to a small "lecture bottle" (with the exception of the formaldehyde which was placed directly into the larger tank as described below) and pressurized utilizing argon gas as an inert carrier. This provided a stable inert source of the vapor for each exposure and minimized the possibility of degradation between exposures. Just prior to use, a small quantity of the selected chemical was transferred from the lecture bottle to a large compressed air cylinder (SCUBA tank) and mixed with very clean compressed air from a compressor used for filling SCUBA tanks; the air was filtered with activated charcoal and dried with desiccant. Air from this compressor was checked for total hydrocarbon and carbon monoxide content and found to be below detection limits. The tanks were filled to maximum pressure (3000 psi) to operate the breathing valve for two and one half hours at the chosen concentration. The relative humidity was less than 5% at the valve. The temperature at the mouth piece was no higher than 28^{o}C for any exposure.

The concentrations that were chosen for study depended primarily on the specific activity ^{14}C-labeled chemicals. The general goal was to use concentrations that were smaller than 30 ppb and as low as 5 ppb, if possible, to approximate environmental levels without sacrificing accuracy of radioassay. Since each chemical vapor was stored in a separate lecture bottle (in argon) from which a portion was taken to prepare for exposures, different concentrations resulted in successive exposures as the supply dwindled. This provided an opportunity to observe possible systematic differences in uptake that might be caused by differences in vapor concentration, at least over a limited range. Hence, successive exposures were conducted with vapor concentrations differing by up to a factor of about three over the course of the studies for each chemical.

The collection of the exhaled air during the exposure and the pure air and vapor before and after exposure was accomplished with three large bubblers containing vapor absorbing solvents. Acidified ethanol (5 mL concentrated HCl per gallon) was usually used in the first two bubblers as the trapping agent

Figure 1. Schematic illustration of the demand-regulator breathing valve used in this study to expose individual human subjects to selected chemical vapors.

Modified demand Tekna Regulator



AIR VOLUMES FOR EXPOSURE SYSTEM

Tekna T-2100 B/T second stage regulator.

Tilt valve secton = 5 ml

Mouth piece holder = 7 ml

Exhaust space = 36 ml

Nose adaptor = 8 ml

Exhaust line

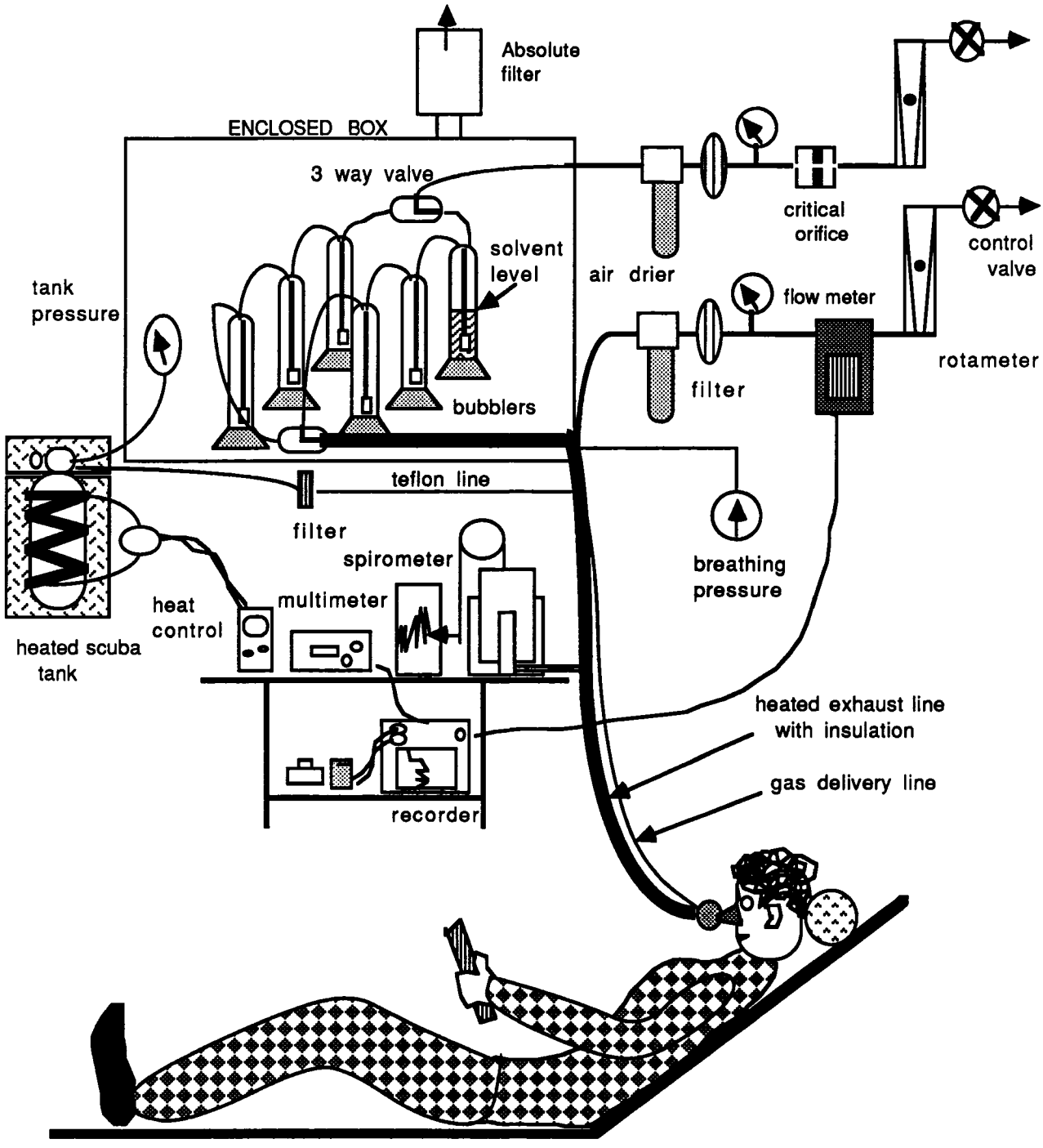
bubbler line = 250 ml

spirometer line = 1660 ml

spirometer internal =7000 ml

Figure 2. Schematic illustration of the inhalation exposure system designed and used in this study of the uptake of trace levels of organic vapors inhaled by individual human volunteers showing the position and relative placement of various components of the apparatus.

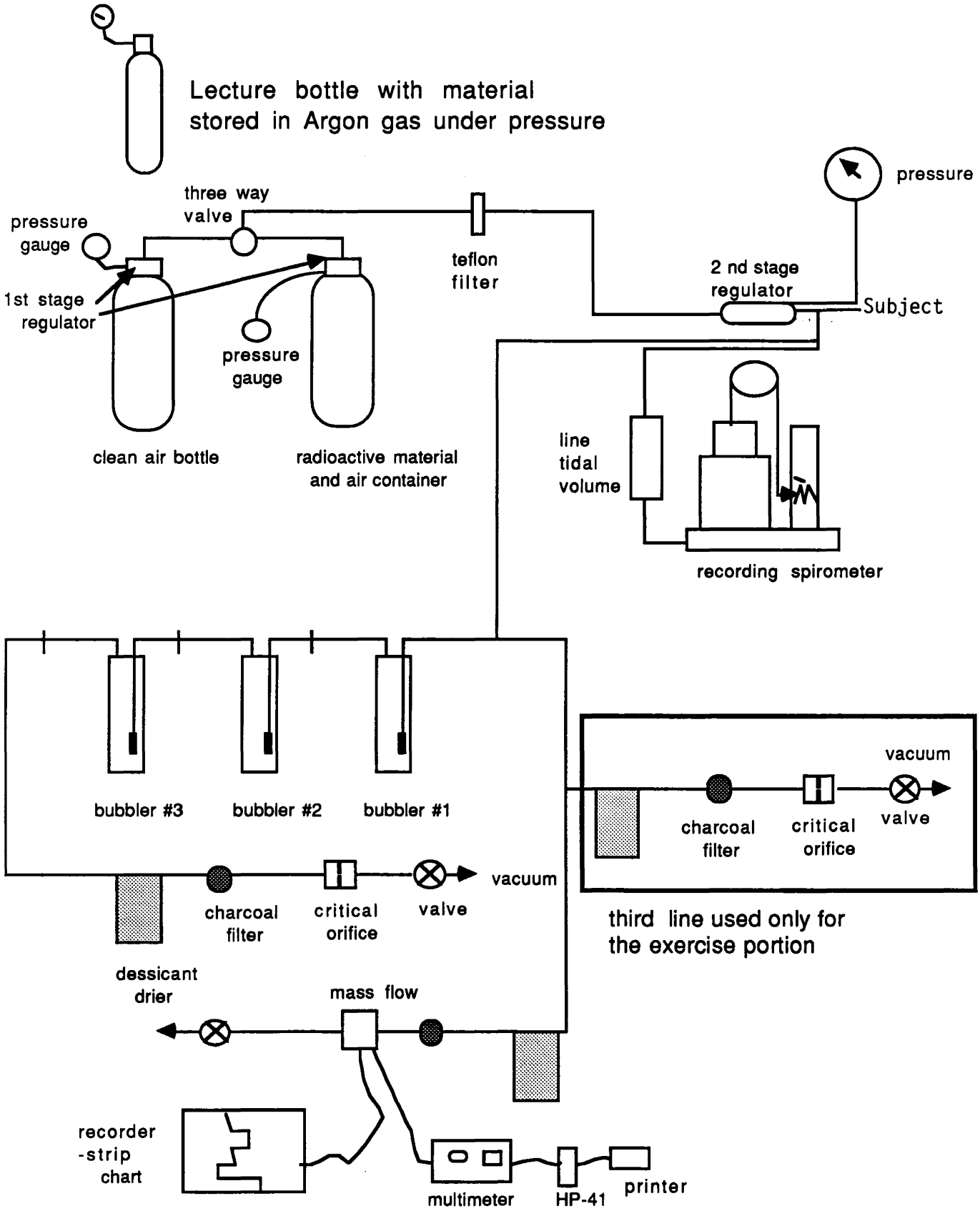
EXPOSURE SYSTEM CONFIGURATION



nose-only inhalation

Figure 3. Schematic representation of the human exposure system showing the third line used for the exposures involving exercise.

ARB HUMAN EXPOSURE SYSTEM



for formaldehyde, benzene, trichloroethylene and chloroform, while chloroform (unacidified) was used to collect methyl bromide. In every case the third bubbler contained a carbon dioxide ($^{14}CO_2$) collecting alkylamine organic cocktail (Harvey Carbon-14 Cocktail, R.J. Harvey Instrument Company, Hillsdale, New Jersey). Aliquots from the ethanol bubblers were combined with an appropriate scintillation cocktail (Complete Counting Liquid 3a70B, Research Products International Corp., Mount Prospect, Illinois) for radioassay utilizing a quench-correcting liquid scintillation counter (Packard Tri-Carb 300C, Packard Instrument Co., Downers Grove, Illinois). After the end of each two-hour exposure period the apparatus was switched to allow the individual to breathe only clean air, while the exhaled air was then monitored for 30 minutes longer.

The exposure apparatus delivered the gas or vapor of interest to the person using a demand regulator valve and provided for measurement of the respiratory minute volume of air and breathing frequency of the person. All parts of the exposure unit were clean metal, glass, high-density plastic, silicone rubber, or inert teflon (with the exception of the polyethylene pressure sensing hose) to preclude vapor losses. The compressed air cylinder (aluminum SCUBA tank, LUXFER CTC/DOT-3AL3000-S80; U.S. Divers, Pasadena, California) was connected by a 3-way stainless-steel ball valve to a first-stage pressure regulator (or alternately to the small lecture bottle that contained the source of the test material stored in an atmosphere of argon). The pressure at the outlet was maintained at 135 psig. The compressed air tank contained the radioactive test material mixed with clean filtered air. A second compressed air tank with regulator containing clean air was connected with a switching valve (shown schematically in figure 3) in place of the test material tank to provide clean air to the breathing valve system when needed. Air pressure in the tanks was monitored with test gauges (0-3000 psig) with 5 inch faces.

The first-stage pressure regulator was connected through a high pressure aerosol filter holder (stainless-steel, Millipore XX4404700, Millipore Corp., Bedford, Massachusetts) using a 47 mm diameter Millipore "FG" teflon membrane filter (0.2 micrometer pore size) with 1/4 inch teflon line to the second-stage stainless-steel demand regulator which was an integral part of the high density polycarbonate breathing valve shown schematically in Figure 1 (Model T-2100

B/t-2100, Tekna, Inc., Belmont, California). The breathing valve was modified by removing the exhaust port and screwing an adaptor into it made of stainless steel and connecting via two large teflon tubes to the 20 liter spirometer (Warren Collins Inc., Braintree, Mass.) having an inlet tube with volume of 1660 mL and a spirometer internal volume of 7000 ml. The total buffer volume between the exhaust flow line and the spirometer chamber was therefore 8.66 l. Because of the continuous exhaust flow, only about half of the individual's tidal volume passed into the spirometer buffer volume, so that this system could accommodate tidal volumes as large as 17 liters without losses occurring in the spirometer water bath. Two other teflon lines were used; the first line was connected from the valve exhaust to a three-way valve (Figure 2) that was used for changing the bubblers. The other line was used to measure breathing pressure at the exhaust by a Magnehelic gauge (1-0-1 inch WG, Dwyer Instruments Inc. Michigan City, Indiana). All exhaust lines carrying exhaled air were heated to 40^{o}C to prevent condensation by wrapping with heating tape and covering with closed-pore pipe insulation. Heating was controlled by 3 variac panels and monitored with a digital thermometer (Omega 2165A, Omega Engineering Inc.).

Another identical three-way valve connected the bubblers downstream to the vacuum air-metering system. These three way valves were connected to the bubblers using flexible stainless steel hoses to allow adjustments in placement of the bubblers. The line from this valve carried the exhaust through a desiccant bed (Nitrasorb-T Indicating, Multiform Desiccant Products, Inc., Buffalo, New York) to dry the air and through an activated charcoal filter (Motor Guard Corp., San Leandro, California) to remove residual vapor. The flow in this line was controlled by a critical orifice designed to operate at 1.65 liters per minute with the pressure monitored by a Magnehelic gauge. This method allowed a constant flow of exhaust gas to be pulled through the bubblers irrespective of the of the tidal and minute volumes.

The changing flow rate due to the individual breathing rates was monitored with a rotameter (Fischer-Porter FP 1/4-15.5 G 6 3/4 Model 10A1338, Lab-Crest Scientific Glass Co., Warminster, Pennsylvania) and the pressure was measured with a 0-5 psig Magnehelic gauge. Stamford, Connecticut). The flow was measured with a mass flow meter (Hastings Flowmeter model PR-4A 0-5 SLPM of air; Teledyne-Hastings-Raydist Hampton, Virginia). Flow rate was recorded by a

Hewlett-Packard 7100B strip chart recorder and a Hewlett Packard 3468A multimeter connected to a HP-41C calculator to integrate the flow rate over the exposure time (Hewlett-Packard Inc., Palo Alto, California). Flow rate was integrated into 3 minute intervals from 15 second recordings into a program on a HP-41C calculator and summed to give the half hour volumes.The program was printed out after the exposure by a printer for the calculator. The number of breaths per minute was also recorded as the average of 4-7 minute segments from each half-hour period. A check on the volume breathed by the individual was also obtained from the pressure drop of the SCUBA tank over each half hour period.

Exposure Procedure

Immediately before each exposure, complete maintenance was performed on the system. The filters were checked and replaced and desiccant replaced as needed. Bubblers were filled and labeled and the vapor was loaded into the exposure SCUBA tank from the lecture bottle (or loaded into the SCUBA tank directly in the case of the formaldehyde). The exhaust line heating system was turned on at least an hour in advance to allow the temperature to equilibrate to 40°C. A pretest was performed by starting the system vacuum and metering either 3.0 or 4.0 liters per minute from the clean air SCUBA tank until the flow stabilized and then switching via the three-way valve to the tank with the vapor to be tested. The radioactive ^{14}C collected in the bubblers was checked to ascertain that there was sufficient activity to perform each experiment.

A second set of replacement bubblers was connected and checked for leaks before the individual was placed on the system and all the temperature and pressure measurement systems were allowed to come to equilibrium. The tank temperature was held at a constant temperature for at least one half hour before the pretest was done. The individual inhaled on clean air for a few minutes until he or she started to breathe in a regular pattern.

The vapor was provided via the demand valve to the individual person for each inhalation and the exhaled air and vapor were bubbled through the bubblers for each one-half hour sub-period. The concurrent flow spirometer served to maintain the exhalation pressure exactly at ambient as well as providing a

buffer for the intermittent exhalations; likewise a record of each breath was made with the timed chart-recorder on the spirometer. The exhaust flow rate was maintained and adjusted as necessary to keep the spirometer trace in the center of the recording drum to prevent the spirometer from overfilling or emptying. The volumetric flow rate of air being pulled through the bubblers required to balance the subject exhalation rate (the average exhalation flow rate) was recorded on the strip chart recorder. The flow rate was measured every 15 seconds and the average was recorded every three minutes by a HP-41C calculator. This system of adjusting the flow rate to accommodate the human breathing variations and recording changes and breathing pattern by the spirometer was continued for a total time of two hours and for subsequent clearance measurements of one half hour.

After each half-hour sub-period the bubblers were changed by switching the valves and allowing the flow to be diverted to the next set of bubblers. After the full two-hour exposure was completed the tank selection valve was switched to clean air. The same set of bubblers was used for the next three minutes to insure that the gas or vapor in the lines were completely purged. The bubblers were then changed via the valving and the new bubblers collected samples for one half hour while the individual inhaled clean air to provide a sample of the exhaled vapor and carbon dioxide for 0.5 hour post-exposure. Shortly after the end of this sampling period, the individual was removed from the apparatus and another measurement of the concentration was made during a half-hour test period; this second test was performed to determine if the concentration had changed during the exposure.

Exercise Exposures

The exercise studies utilized a bicycle ergometer to maintain the chosen level of effort during uptake measurements via the mouth for a benzene vapor-air mixture. The exercise portion of the study differed from the other exposures in the modification of the physical configuration of the breathing valves and accommodation for the increased flow. In consideration for the subjects and from our experience with the time required to reach a steady state uptake it was decided to limit the test to a total of one hour and fifteen minutes with the first hour broken into four portions of fifteen minutes each

and one fifteen minute clearance portion. The subjects were able to maintain a constant level of exertion throughout the entire exposure. They began with five minutes of training without the breathing apparatus and were then put on the system and after several more minutes the exposure was started. None of the subjects had undue stress due to the test and felt fine but a little tired after the exercise; this was indicative of the excellent physical condition of each of the volunteers.

Modifications to the system for the exercise portion of the vapor tests required a reconfiguration so the participants could use both hands to hold onto the exercise cycle. A flexible copper pipe was used to hold the mouthpiece and teflon lines to the desired location for breathing. In order to accommodate the increased flow rate a larger critical orifice was installed to increase the flow while using the mass flow meter to measure the changing breathing rate as before. A desiccant canister and absolute filter with carbon was used to remove the water and organic vapors. The flow was metered for the bubblers with the same method as with the other exposures.

A metronome was used during the entire exposure to help the subjects maintain a constant pedal speed of 50 revolutions per minute. The tension on the ergometer was set at one kilo pound meter (KPM). Cycling at this speed is approximately equal to leisure cycling at 9.4 Miles per hour. The energy expenditure for this activity is equal to 0.100 Kcal/min/Kg body weight. This is equivalent to walking at a normal pace or light work. The respiratory minute volumes in the exercise experiments increased an average of about 2.5 times that measured in the prior exposures at rest.

Bubblers

The vapors were absorbed using sets of three glass 250 mL bubblers fitted with ball and socket joints and hooked in series with lockable pinch clamps. Each bubbler stem ended in a fritted glass cylinder having a nominal pore size range of 40-60 um (porosity "C"). The bubblers were leak sealed with silicone high vacuum grease (Dow Corning Corp., Midland, Michigan). Each bubbler was mated to a specific stem, pair of lockable pinch clamps and sealed end caps so that a tared weight was obtained. The bubblers were filled using repipettors.

The bubblers were numbered #1, #2 and #3 in the direction of vapor/gas flow (Figure 2). The first two bubblers in series each contained 120 mL of acidified ethyl alcohol (5 mL concentrated HCl/gallon of absolute ethyl alcohol). The third bubbler contained 120 mL of the carbon dioxide ($^{14}CO_2$) absorbing liquid-scintillation cocktail (alkylamine-based CO_2 absorber, Harvey ^{14}C Cocktail, R. J. Harvey Instrument Corp., Hillsdale, N. J.).

For methyl bromide two of the bubblers used chloroform and the third was filled with the carbon dioxide ($^{14}CO_2$) absorbing liquid-scintillation cocktail. The flow rate for the methyl bromide absorption by chloroform was reduced to 0.6 lpm because of bubbler overflow problems at the higher flow rate of 1.5 lpm normally used. For all exposures the bubblers were placed in plastic containers and surrounded with ice to minimize alcohol evaporation. Each set of three bubblers was replaced with a fresh set after each 30-minute interval. Each bubbler was then capped, removed from the ice, allowed to reach room temperature, wiped dry and weighed. The final volume in each bubbler was determined gravimetrically; based on the tare weight for each empty bubbler and the specific gravity of the alcohol or the $^{14}CO_2$-absorbing cocktail. The contents of each bubbler were transferred into 125 mL plastic bottles and two 1.0 mL samples were taken for separate liquid scintillation counting utilizing 19 mL each of 3a70B scintillation cocktail (Complete Counting Liquid 3a70B, Research Products International Corp., Mount Prospect, Illinois) for radioassay utilizing a quench-correcting liquid scintillation counter (Packard Tri-Carb 300C, Packard Instrument Co., Downers Grove, Illinois). The samples were each counted for 10 minutes or to achieve statistical coefficient of variation of 0.5% over a beta particle energy region of 0 to 156 KeV. (A 10 minute count of typical 50 dpm background yield a coefficient of variation of about 5%.) The plastic sample bottles for each bubbler were stored under refrigeration.

Carbon Dioxide

The minimization of $^{14}CO_2$ absorbed in the first two alcohol bubblers and the maximum efficient capture of exhaled $^{14}CO_2$ in the third bubbler was important to the success of the project. The carbon dioxide cocktail when used alone in special test measurements was found to be >99% efficient at flow rates measured up to 4.0 L/min for air containing 5% carbon dioxide; this concentration of carbon dioxide was used because it approximates the

concentration in exhaled air. In these tests acidified alcohol had only 39 nCi in the first bubbler and 16 nCi in the second bubbler while the third bubbler, which contained the CO_2 absorber, had 4074 nCi when exposed to air containing 34.4 nCi $^{14}CO_2$/L at 4.0 L/min for 30 minutes. This was <1.0% $^{14}CO_2$ in the first bubbler and <0.4% $^{14}CO_2$ in the second bubbler when exposed to air containing labeled $^{14}CO_2$ and 5% carbon dioxide (about the concentration in exhaled air). The data indicate that the exhaled $^{14}CO_2$ was essentially all collected by the third bubbler exclusively.

In the methyl bromide studies, chloroform was used in the first two bubblers as trapping agent for methyl bromide. The efficiencies of chloroform in collection of methyl bromide and CO_2 were 87.5% and 5%, respectively.

Table 2. Bubbler Collection Efficiencies in Vapor Inhalation Study

Vapor / gas	Solvent	Efficiencies (%) (Mean ± S.E)	Number of Measurements
Trichloroethylene	Acidified alcohol	92.8±0.5	8
Benzene	Acidified alcohol	92.9±0.7	12
Chloroform	Acidified alcohol	95.5±0.2	8
Formaldehyde	Acidified alcohol	99.8±0.3	8
Methylbromide	Chloroform	87.5±0.3	8
CO_2	Chloroform	5.0±1.2	4*
CO_2	Acidified alcohol	<1	4*
CO_2	^{14}C Cocktail	99.9±0.1	4*

*Special test measurements made with $^{14}CO_2$.

Analysis of Vapors Other Than Methyl Bromide

The efficiency, E, of collection of the respective vapors in the acidified alcohol in either bubbler #1 or bubbler #2 was determined during test runs before and after human exposures by drawing the respective vapors through the bubbler train at average flow rates of 1.5 l/ minute. This was calculated from the activities in bubbler #1 (B_1) and bubbler #2 (B_2) by:

$$E=(B_1-B_2)/B_1 \qquad (1)$$

These values are summarized in Table 2. This test efficiency, E, was the basis of the evaluation of the bubbler data. The ^{14}C activity, A, exhaled by the subject during a single 30 minute exposure period was calculated from the activity in bubbler #1 (B_1) and bubbler #2 (B_2) during the period by:

$$A= B_1 + B_2/E \qquad (2)$$

The exhaled activity, A, was divided by the total volume, tV_m, of air breathed during the specific 30-minute exposure (where t is the exposure time in minutes and V_m is the minute volume of the subject's breathing) to provide a measure of the average activity concentration of the exhaled air. The ratio of the average activity concentration of the exhaled air to the ^{14}C activity concentration, C, of the vapor to which the individual was exposed (determined as the average concentration in the test runs before and after the human exposure), provides the fraction of the inhaled vapor that was exhaled. The observed uptake fraction is this exhaled fraction subtracted from unity:

$$\text{Uptake Fraction} = 1.0 - A/tV_mC \qquad (3)$$

The activity collected in the third bubbler containing the special $^{14}CO_2$-absorbing cocktail is primarily associated with $^{14}CO_2$. However, some small portion of the vapor that penetrates both of the first two bubblers is partially collected in the third bubbler. Since the total exhaled activity was calculated and the activity in the first two bubblers was measured, it was possible to calculate the amount of vapor entering the third bubbler. By assuming the same collection efficiency for vapor collection in the third

bubbler as for the other bubblers, the amount of vapor collected in the third bubbler was predicted; this is reasonable since so little vapor gets to the the third bubbler that an estimation error will have little influence on the result. This was subtracted from the collected activity in bubbler #3 (B_3) to determine the $^{14}CO_2$ activity:

$$^{14}CO_2 \text{ (observed)} = B_3 - B_2(1-E) \qquad (4)$$

Also, trace degradation products or impurities if present may also be collected in the third. Although these background levels were small; they were determined during the test run and subtracted to correct the observed $^{14}CO_2$ activity during each exposure period .

$$^{14}CO_2\text{(actual)} = \text{observed}-(1-\text{uptake fraction})*B3(\text{mean of pre- \& post-tests}) \qquad (5)$$

The details of the full calculations are described in detail and illustrated in the Appendix.

Analysis of Methyl Bromide

Preliminary tests showed that ethyl alcohol was not a satisfactory absorber for low concentrations of methyl bromide vapor, having an efficiency of only 14% and chloroform was a good trapping agent (87.5% efficient). Methyl bromide has such a low boiling temperature, 3.6°C, that for a liquid to be an absorber it must react with methyl bromide if possible rather than just be a solvent for it. In this study, the first two bubblers were filled with chloroform to collect methyl bromide vapor and the third bubbler was filled with CO_2 absorber. The CO_2 absorber used in the third bubbler for the other vapors is primarily a solution of scintillators dissolved in a proprietary mixture of alkylamines (R.J. Harvey Instrument Corp., Hillsdale, NJ).

The efficiency of chloroform for trapping methyl bromide and CO_2 was determined by passing a known amount of ^{14}C labeled methyl bromide alone through bubbler #1 and #2 at flow rate of 0.6l/minute for 30 minute and repeating the same study with $^{14}CO_2$. The efficiencies were 87.5% and 5% for

methyl bromide and CO_2 respectively. The exhaled methyl bromide activity (A) and CO_2 were calculated using the following equations.

$$A + {}^{14}CO_2 = B_1+B2+B3 \quad (6)$$

$$0.875A + 0.05{}^{14}CO_2 = B1 \quad (7)$$

The uptake fraction for methyl bromide was calculated as described in equation 3 above. Also, trace degradation products or impurities if present may also be collected in the third. Although these background levels were small; they were determined during the test run and subtracted to correct the observed ${}^{14}CO_2$ activity during each exposure period (Equation 6) .

The details of the full calculations are described in detail and illustrated in the Appendix.

Dead-space Correction

Although the demand breathing valve used in this study was designed to minimize dead space, a volume, v_d, of about 15 mL was in effect an extension of the nose and 7 ml of the mouth of the human during the exposures. This dead space volume was filled by exhaled air during exhalation and this same volume was the first air entering the airways during the next inhalation breath. Also, this dead space volume is filled with fresh vapor-containing air at the end of inhalation that is the first portion of the exhaled air volume leaving the valve during each exhalation. Hence, the volume of ${}^{14}C$-vapor containing air that was inhaled in each breath of tidal volume V_T was actually only equal to V_T-v_d. Since the average tidal volume of the subject was about 500 mL, the systematic error in observed uptake fractions would be about 1.4 and 3.0% for mouth and nose exposure respectively. Hence, the observed uptake fractions and calculated inhaled activity were corrected for dead space using a dead space correction factor given by:

$$f=1.0/(1.0 - v_d/V_T) \quad (8)$$

where f is the dead space correction factor (always larger than unity), v_d is the dead space (7 ml for oral or 15 ml for nasal), and V_T is the average tidal volume measured for the individual subject during each separate two-hour exposure. A separate dead space correction factor was calculated from the average minute volume and breathing rate for each exposure experiment.

The corrected uptake fractions were obtained by multiplying the separate observed uptake fractions by the appropriate respective dead space correction factors. The total inhaled activity for each exposure experiment was calculated by reducing the calculated volume of inhaled air by dividing by the dead space correction factor.

Urine Sample

Urine samples were obtained at 0.5, 8, and 16 hours post-exposure from each individual to monitor the clearance rate of ^{14}C labeled chemical via the urine. Duplicate 0.2 mL urine samples were also analyzed for ^{14}C with the same scintillation cocktail used to analyze the ethanol bubblers. The samples were each counted for 10 minutes or to achieve a coefficient of variation of 0.5% over a beta particle energy region of 0 to 156 KeV. Pre-exposure background sample levels were subtracted to yield net post exposure activity values.

The ^{14}C activities measured in the urine samples were normalized by dividing in each case by the total inhaled activity during the separate two-hour human exposures. This allows the results to be readily applied to other exposure levels. The total urine burden of ^{14}C labeled compound at 0.5 hour post-exposure was calculated as follows:

$$\text{Urine burden (nCi)} = 2.5^{*} \text{ body weight (kg)} * 0.83 * \text{urine specific activity} \quad (9)$$

(for 2.5 hours) (nCi/ml)

where 0.83 is the rate of urine formation (ml/kg/hour) for people (Snyder, 1975).

Experimental Design

The experimental design of this project is summarized in Table 3. This design has allowed the same four individual volunteers to participate in the testing of all five chemical vapors so that biological factors remain the same throughout the project.

Table 3. Human Vapor/gas Inhalation Study Experimental Design

	Exposure Route				
	Mouth		Nose		Air Concentration (ppb)
Chemical	Female	Male	Female	Male	(Mean + S.D.)
Trichloroethylene	2	2	2	2	18±3
Benzene (N)	2	2	2	2	9±3
Benzene (E)	2	2	0	0	8±2
Methylbromide	2	2	2	2	18±6
Chloroform	2	2	2	2	13±5
Formaldehyde	2	2	2	2	5±2

Benzene (N) = Normal breathing rate.

Benzene (E) = With exercise (double breathing rate).

Human Subjects

Four healthy adult white human volunteers were involved in this study. Their physical status is listed Table 4. In addition, these subjects were non-smokers and in excellent physical condition. These individuals were also examined by a medical doctor at the begining of the project to determine their health status. In addition, urine and blood samples were also taken and were analyzed by the university health center clinical laboratory. Each subject was exposed twice to trace levels of each of the five vapors listed in this study. Each person was screened and questioned to make sure they were not on any medication or drug during the duration of the exposures and with the exception of colds all subjects were healthy for the entire sequence of exposures. Details about the four volunteers are found in Table 4

The levels of radiation and chemical exposures to the subjects were both very low and did not involve special risks to the volunteers. The experimental protocol was approved by both the University of California, Davis, Human Subjects Administrative Advisory Committee and the UC Medical Center Radiation Use Administrative Advisory Committee.

Exposures

The completed experiments are summarized in Table 5. There were a few repeat exposures necessitated by equipment malfunctions; these are designated by the "A" suffix to the exposure numbers.

Table 4. Human Volunteers Physical Status

PARAMETERS	HUMAN SUBJECT INITIAL			
	B.R.	B.L.	P.W.	M.G.
Sex	male	male	female	female
Body weight (kg)	75	76	75	57
Height (feet)	6.1	6.1	5.6	5.2
Age (years)	21	21	36	32
At rest (Mean ± S.E, n=10)				
Breathing rate (breath/min.)	14.1±0.5	14.6±0.4	12.1±0.5	13.4±0.5
Resp. Dead Space (ml)	150	170	150	130
Lung minute volume (L/min.)	7.0±0.2	8.3±0.3	6.0±0.2	5.8±0.1
Alveolar ventilation* volume (L/min.)	4.9±0.1	5.8±0.2	4.2±0.1	4.1±0.1
Bicycle exercise				
Breathing rate (breath/min.)	12	17	11	19
Lung minute volume (L/min.)	17.5	17.6	13.9	16.9
Alveolar ventilation* volume (L/min.)	15.7	14.7	12.3	14.4

* Calculated based on 30% Respiratory physiological dead space (Ganong, W.F. 1979)

Table 5. Schedule of Studies

Exposure #	Date of Exposure	Vapor/gas	Route	Subject	Sex
1	10 November 1986	benzene	mouth	P.W.	F
2	14 November 1986	benzene	mouth	B.L.	M
3	20 November 1986	benzene	nose	B.L.	M
4	21 November 1986	benzene	mouth	M.G.	F
5	25 November 1986	benzene	mouth	B.R.	M
6	2 December 1986	benzene	nose	B.R.	M
7	4 December 1986	benzene	nose	P.W.	F
8	10 December 1986	benzene	nose	M.G.	F
9	16 January 1987	TCE	mouth	B.L.	M
10	20 January 1987	TCE	mouth	P.W.	F
11	23 January 1987	TCE	mouth	M.G.	F
12	26 January 1987	TCE	nose	B.L.	M
13	29 January 1987	TCE	mouth	B.R.	M
14	3 February 1987	TCE	nose	P.W.	F
15	5 February 1987	TCE	nose	M.G.	F
1A	10 February 1987	benzene	mouth	P.W.	F
16	12 February 1987	TCE	nose	B.R.	M
17	17 February 1987	formaldehyde	mouth	M.G.	F
18	20 February 1987	formaldehyde	mouth	B.L.	M
19	24 February 1987	formaldehyde	mouth	P.W.	F
20	26 February 1987	formaldehyde	mouth	B.R.	M
21	2 March 1987	formaldehyde	nose	M.G.	F
22	6 March 1987	formaldehyde	nose	B.L.	M
23	10 March 1987	formaldehyde	nose	P.W.	F
24	12 March 1987	formaldehyde	nose	B.R.	M
17A	13 March 1987	formaldehyde	mouth	M.G.	F
25	19 March 1987	chloroform	mouth	P.W.	F
26	27 March 1987	chloroform	mouth	B.L.	M
27	1 April 1987	chloroform	mouth	M.G.	F
28	2 April 1987	chloroform	mouth	B.R.	M
29	7 April 1987	chloroform	nose	P.W.	F
30	13 April 1987	chloroform	nose	B.L.	M

Exposure #	Date of Exposure	Vapor/gas	Route	Subject	Sex
31	15 April 1987	chloroform	nose	M.G.	F
32	16 April 1987	chloroform	nose	B.R.	M
33	20 April 1987	methyl bromide	mouth	P.W.	F
34	28 April 1987	methyl bromide	mouth	B.L.	M
35A	2 June 1987	methyl bromide	mouth	B.R.	M
36	7 May 1987	methyl bromide	nose	B.L.	M
37	12 May 1987	methyl bromide	mouth	M.G.	F
38	14 May 1987	methyl bromide	nose	P.W.	F
39	26 May 1987	methyl bromide	nose	B.R.	M
40	1 June 1987	methyl bromide	nose	M.G.	F
41	9 June 1987	benzene	mouth+exercise	M.G.	F
42	11 June 1987	benzene	mouth+exercise	P.W.	F
43	15 June 1987	benzene	mouth+exercise	B.L.	M
44	17 June 1987	benzene	mouth+exercise	B.R.	M

Data Management

An exposure and data collection protocol was followed that including standardized data collection forms. All data was entered into a standard computer analysis and reporting system especially designed by us for these studies utilizing our in-house Data General MV-8000 computer. Details are found in Appendix.

RESULTS

Quantitative measurements were made of the systemic uptake by people during nasal and oral breathing of very low concentrations in air of the five selected chemical vapors including benzene, chloroform, methyl bromide, trichloroethylene, and formaldehyde. It was observed that the fractional systemic uptake rate relationship for each vapor/gas, with respect to time from beginning of exposure, stabilized rapidly so that a steady-state uptake was achieved within the first 30-minute assessment period. The steady state fractional systemic uptake of the total vapor (corrected for dead space) was based upon the last three 30-minute exposure sub-periods in each case. The respiratory characteristics of the subjects in these experiments are summarized in Table 6. The overall results of each inhalation study are summarized in Table 7. The detailed results for each chemical vapor or gas are given in Tables 8-13. The overall summary is found in Table 14. Clearance data are found in Table 15.

The steady state fractional systemic uptake (corrected for equipment dead space) during nasal breathing at rest of the total inhaled vapor or gas in air at room temperature was 45.6%$\pm$1.5%SE for chloroform, 53.9%$\pm$1.9%SE for trichloroethylene, 55.4%$\pm$3.6%SE for methyl bromide, 60.0%+3.2%SE for benzene, and 75.1%$\pm$2.1 %SE for formaldehyde. The uptake during oral breathing at rest of the total inhaled vapor or gas was 49.6%$\pm$1.6%SE for chloroform, 55.4%$\pm$1.8%SE for trichloroethylene, 52.1%$\pm$3.4%SE for methyl bromide, 54.6%+2.1%SE for benzene, and 86.4%$\pm$0.8 %SE for formaldehyde. During exercise with oral breathing and a more than doubling of inhalation minute volume from rest conditions, the steady state uptake of benzene dropped to 41.6%$\pm$1.3%SE.

The levels of radiation and chemical exposures to the subjects were both very low and did not involve special risks to the volunteers. The experimental protocol was approved by both the University of California, Davis, Human Subjects Administrative Advisory Committee and the UC Medical Center Radiation Use Administrative Advisory Committee.

Table 6. Human Inhalation Study Minute Volume During Rest and Exercise

SUBJECT	SEX	BODY WEIGHT (kg)	RESPIRATORY MINUTE VOLUME (L/min.) AT REST (X+SE, n=10)	WITH EXERCISE (X, n=1)	RATIO EXERCISE/ REST
B.L.	M	75.9	8.3±0.3	17.6	2.12
B.R.	M	74.8	7.0±0.2	17.5	2.50
P.W	F	74.5	6.0±0.2	13.9	2.32
M.G	F	56.8	5.8±0.1	16.9	2.91

Table 7. Human Vapor Inhalation Study Exposure Schedule and Data Summary

INHALATION EXPOSURE No.	DATE	SUBJECT	SEX	VAPOR OR GAS	ROUTE NOSE/ MOUTH	CONC. (ppb)	MIN. VOL. (LPM)	RR (BPM)	UPTAKE PERCENT (X ± S.E., N=3) OBSERVED	CORRECTED*
1A	02/10/87	P.W.	F	C_6H_6	M	12	6.80	10	62±4	63±4
2	11/13/86	B.L.	M	C_6H_6	M	10	8.20	15	47±3	48±3
3	11/20/86	B.L.	M	C_6H_6	N	5	7.54	14	57±3	59±3
4	11/21/86	M.G.	F	C_6H_6	M	12	5.84	15	56±3	57±3
5	11/25/86	B.R.	M	C_6H_6	M	6	6.44	12	50±2	51±2
6	12/02/86	B.R.	M	C_6H_6	N	12	6.23	13	64±3	66±3
7	12/04/86	P.W.	F	C_6H_6	N	12	4.70	12	68±4	71±5
8	12/10/86	M.G.	F	C_6H_6	N	6	5.70	15	44±2	46±2
41	06/09/87	M.G.	F	C_6H_6	M**	11	16.90	19	38±1	39±1
42	06/11/87	P.W.	F	C_6H_6	M**	8	13.92	11	47±2	47±2
43	06/15/87	B.L.	M	C_6H_6	M**	6	17.60	17	38±1	39±1
44	06/17/87	B.R.	M	C_6H_6	M**	6	17.46	13	42±2	42±2
9	01/16/87	B.L.	M	C_2HCL_3	M	17	8.54	13	51±1	51±1
10	01/20/87	P.W.	F	C_2HCL_3	M	17	5.82	12	61±2	62±2
11	01/23/87	M.G.	F	C_2HCL_3	M	17	5.31	13	53±4	54±4
12	01/26/87	B.L.	M	C_2HCL_3	N	22	9.05	13	53±4	54±4
13	01/29/87	B.R.	M	C_2HCL_3	M	15	6.78	15	53±5	54±5

INHALATION EXPOSURE No.	DATE	SUBJECT	SEX	VAPOR OR GAS	ROUTE NOSE/ MOUTH	CONC. (ppb)	MIN. VOL. (LPM)	RR (BPM)	UPTAKE PERCENT (X ± S.E., N=3) OBSERVED	CORRECTED*
14	02/03/87	P.W.	F	C_2HCL_3	N	13	5.40	11	49±1	50±1
15	02/05/87	M.G.	F	C_2HCL_3	N	22	6.53	16	58±3	60±4
16	02/12/87	B.R.	M	C_2HCL_3	N	17	7.79	16	49±4	51±4
17A	03/13/87	M.G.	F	CH_2O	M	3	6.24	12	83±1	85±1
18	02/20/87	B.L.	M	CH_2O	M	3	8.54	14	85±1	86±1
19	02/24/87	P.W.	F	CH_2O	M	4	6.74	12	88±2	89±2
20	02/26/87	B.R.	M	CH_2O	M	6	8.04	17	84±1	85±1
21	03/02/87	M.G.	F	CH_2O	N	2	5.91	13	78±1	81±1
22	03/06/87	B.L.	M	CH_2O	N	9	8.91	15	62±1	64±1
23	03/10/87	P.W.	F	CH_2O	N	5	6.97	13	75±2	77±2
24	03/12/87	B.R.	M	CH_2O	N	4	7.76	14	77±1	79±1
25	03/19/87	P.W.	F	$CHCL_3$	M	25	5.71	10	56±2	56±2
26	03/27/87	B.L.	M	$CHCL_3$	M	14	8.34	16	48±3	49±3
27	04/01/87	M.G	F	$CHCL_3$	M	11	5.85	14	49±2	50±2
28	04/02/87	B.R.	M	$CHCL_3$	M	12	7.20	14	43±1	43±1
29	04/07/87	P.W.	F	$CHCL_3$	N	13	6.39	14	48±2	50±2
30	04/13/87	B.L.	M	$CHCL_3$	N	10	8.60	16	40±1	41±1
31	04/15/87	M.G.	F	$CHCL_3$	N	10	5.63	14	48±2	50±2
32	04/16/87	B.R.	M	$CHCL_3$	N	7	6.52	13	41±1	42±1
33	04/20/87	P.W.	F	CH_3BR	M	23	6.02	12	54±0	54±0
34	04/28/87	B.L.	M	CH_3BR	M	18	9.32	16	56±1	57±1
35A	06/02/87	B.R.	M	CH_3BR	M	12	6.85	13	33±1	33±1
36	05/07/87	B.L.	M	CH_3BR	N	13	5.94	14	69±3	72±3
37	05/12/87	M.G.	F	CH_3BR	M	13	5.01	11	63±1	64±1
38	05/14/87	P.W.	F	CH_3BR	N	13	5.43	15	52±3	54±3
39	05/26/87	B.R.	M	CH_3BR	N	25	6.45	14	39±5	41±5
40	06/01/87	M.G.	F	CH_3BR	N	23	5.91	11	55±1	56±1

* STEADY STATE CORRECTED FOR DEAD SPACE

** WITH EXERCISE (double breathing rate).

Table 8. Behavior of Inhaled Trichloroethylene Vapor in Adult Human
(Steady State Uptake Percent of Inhaled: Mouth = 54.5±1.8, Nose = 52.2±1.8)[1]
(Corrected Uptake Percent of Inhaled: Mouth = 55.4±1.8, Nose = 53.9±1.9)

SUBJECT (SEX)	ROUTE NOSE/ MOUTH	PERCENT OF INHALED UPTAKE AT EXPOSURE INTERVAL (HOUR) 0-0.5	0.5-1	1-1.5	1.5-2.0	STEADY[2] STATE UPTAKE	TOTAL AT 2.5 HOURS[3] EXHALED as CO_2	EXCRETED in URINE	AIR CONC. (ppb)
B.L.(M)	M	55.3	52.4	51.1	48.8	50.8±1.0	2.61	0.69	17
B.R.(M)	M	49.9	49.1	62.4	47.8	53.1±4.7	0.87	1.08	15
M.G.(F)	M	54.6	52.3	60.0	47.1	53.1±3.8	0.80	2.20	17
P.W.(F)	M	65.6	61.2	63.6	57.5	60.8±1.8	4.41	0.97	17
B.L.(M)	N	57.3	50.6	60.3	48.2	53.0±3.7	0.65	1.57	22
B.R.(M)	N	50.6	45.8	56.9	44.8	49.2±3.9	N.D.	1.20	17
M.G.(F)	N	56.8	64.5	56.5	52.9	58.0±3.4	0.76	1.14	22
P.W.(F)	N	58.2	49.3	50.7	45.9	48.6±1.4	1.66	0.78	13

(1) Based on 12 measurements during the last 1.5 hours of the exposure of two males and two females.

(2) Total inhaled (ug): MOUTH B.L.= 94, B.R.= 64, M.G.= 58 , P.W.= 63
NOSE B.L.=128, B.R.= 86, M.G.= 93 , P.W.= 45

(3) For exposure time (2 hours) + 0.5 hour clearance.
N.D. = Not Detectable

Table 9. Behavior of Inhaled Benzene Vapor in Adult Human
(Steady State Uptake Percent of Inhaled: Mouth = 53.8±2.1, Nose = 58.1±3.1)[1]
(Corrected Uptake Percent of Inhaled: Mouth = 54.6±2.1. Nose = 60.0±3.2)

SUBJECT (SEX)	ROUTE NOSE/ MOUTH	PERCENT OF INHALED UPTAKE AT EACH EXPOSURE INTERVAL (HOUR) 0-0.5	0.5-1	1-1.5	1.5-2.0	STEADY[2] STATE UPTAKE	TOTAL AT 2.5 HOURS[3] EXHALED as CO2	EXCRETED in URINE	AIR CONC. (ppb)
B.L.(M)	M	53.0	50.5	49.0	42.0	47.1±2.7	N.D.	10.87	10
B.R.(M)	M	53.9	51.6	52.2	46.5	50.1±1.8	N.D.	2.61	6
M.G.(F)	M	57.4	52.9	61.8	52.9	55.9±3.0	0.02	7.61	12
P.W.(F)	M	66.0	60.5	69.9	55.4	61.9±4.2	0.30	16.20	12
B.L.(M)	N	64.8	56.1	61.9	52.9	57.0±2.6	0.07	7.17	5
B.R.(M)	N	81.0	69.2	60.4	60.8	63.5±2.9	0.57	2.93	12
M.G.(F)	N	47.3	40.4	46.9	43.9	43.7±1.9	0.07	2.93	6
P.W.(F)	N	83.6	75.7	68.3	60.4	68.1±4.4	0.04	2.50	12

(1) Based on 12 measurements during the last 1.5 hours of the exposure of two males and two females.

(2) Total inhaled (ug): MOUTH B.L.= 33, B.R.= 16, M.G.= 26 , P.W.= 32
NOSE B.L.= 15, B.R.= 27, M.G.= 14 , P.W.= 20

(3) For exposure time (2 hours) + 0.5 hour clearance.

N.D. = Not Detectable

Table 10. Behavior of Inhaled Benzene Vapor in Adult Human During Exercise[1]
(Steady State Uptake Percent of Inhaled: Mouth = 41.4±1.3)[2]
(Corrected Uptake Percent of Inhaled: Mouth = 41.6±1.3)

SUBJECT (SEX)	ROUTE NOSE/ MOUTH	PERCENT OF INHALED UPTAKE AT EACH EXPOSURE INTERVAL (HOUR) 0-0.25	0.25-0.5	0.5-0.75	0.75-1.0	STEADY[3] STATE UPTAKE	TOTAL AT 1.25 HOURS[4] EXHALED as CO_2	EXCRETED in URINE (ppb)	AIR CONC.
B.L.(M)	M	46.1	40.6	40.2	36.1	39.0±1.4	0.5	8.83	6
B.R.(M)	M	51.7	43.7	45.2	38.1	42.3±2.2	0.6	5.50	6
M.G.(F)	M	52.5	41.2	37.0	37.0	38.4±1.4	0.4	1.12	11
P.W.(F)	M	63.0	50.2	47.2	42.1	46.5±2.4	0.8	5.62	8

(1) With exercise (about double the at rest minute volume).
(2) Based on 12 measurements during the last 0.75 hours of the exposure of two males and two females.
(3) Total inhaled (ug): MOUTH B.L.= 21, B.R.= 20, M.G.= 36 , P.W.= 22
(4) For exposure time (1 hours) + 0.25 hour clearance.

Table 11. Behavior of Inhaled Methyl Bromide Vapor in Adult Human
(Steady State Uptake Percent of Inhaled: Mouth = 51.4±3.4, Nose = 53.7±3.5)[1]
(Corrected Uptake Percent of Inhaled: Mouth = 52.1±3.4, Nose = 55.4±3.6)

SUBJECT (SEX)	ROUTE NOSE/ MOUTH	PERCENT OF INHALED UPTAKE AT EACH EXPOSURE INTERVAL (HOUR) 0-0.5	0.5-1	1-1.5	1.5-2.0	STEADY[2] STATE UPTAKE	TOTAL AT 2.5 HOURS[3] EXHALED as CO_2	EXCRETED in URINE	AIR CONC. (ppb)
B.L.(M)	M	57.8	54.8	55.3	57.9	56.0±1.0	0.5	0.18	18
B.R.(M)	M	38.6	33.8	33.4	31.3	32.9±0.8	1.0	0.24	12
M.G.(F)	M	64.1	64.4	62.6	62.1	63.0±0.7	0.2	0.08	13
P.W.(F)	M	53.7	53.7	53.1	54.1	53.6±0.3	0.7	0.08	23
B.L.(M)	N	58.2	67.5	75.0	65.3	69.3±2.9	0.2	0.30	13
B.R.(M)	N	43.4	34.4	48.6	35.1	39.4±4.6	0.2	0.08	25
M.G.(F)	N	52.2	53.8	55.6	54.5	54.7±0.5	0.4	0.32	23
P.W.(F)	N	53.8	50.5	56.7	47.7	51.6±2.7	0.4	N.D.	13

(1) Based on 12 measurements during the last 1.5 hours of the exposure of two males and two females.

(2) Total inhaled (ug): MOUTH B.L.= 77, B.R.= 40, M.G.= 31 , P.W.= 65
NOSE B.L.= 35, B.R.= 74, M.G.= 62 , P.W.= 32

(3) For exposure time (2 hours) + 0.5 hour clearance.
N.D. = Not Detectable

TABLE 12. Behavior of Inhaled Chloroform Vapor in Adult Human
(Steady State Uptake Percent: Mouth = 48.9±1.6, Nose = 44.2±1.5)[1]
(Corrected Uptake Percent: Mouth = 49.6±1.6, Nose = 45.6±1.5)

SUBJECT (SEX)	ROUTE NOSE/ MOUTH	PERCENT OF INHALED UPTAKE AT EACH EXPOSURE INTERVAL (HOUR) 0-0.5	0.5-1	1-1.5	1.5-2.0	STEADY[2] STATE UPTAKE	TOTAL AT 2.5 HOURS[3] EXHALED as CO2	EXCRETED in URINE	AIR CONC. (ppb)
B.L.(M)	M	56.0	52.1	49.7	43.6	48.5±2.5	17.8	0.53	14
B.R.(M)	M	52.0	44.9	41.8	41.0	42.6±1.2	16.5	0.25	12
M.G.(F)	M	51.4	50.5	51.0	45.5	49.0±1.8	15.2	0.22	11
P.W.(F)	M	56.0	55.4	59.4	52.2	55.7±2.1	20.1	0.14	25
B.L.(M)	N	45.9	40.9	39.6	38.2	39.6±0.8	15.6	0.40	10
B.R.(M)	N	50.4	42.3	40.6	38.8	40.6±1.0	14.9	0.60	7
M.G.(F)	N	54.4	53.0	47.1	45.0	48.3±2.4	15.1	0.14	10
P.W.(F)	N	55.8	52.6	47.7	45.0	48.4±2.2	17.5	0.06	13

(1) Based on 12 measurements during the last 1.5 hours of the exposure of two males and two females.

(2) Total inhaled (ug): MOUTH B.L.= 68, B.R.= 52, M.G.= 40 , P.W.= 81
NOSE B.L.= 51, B.R.= 28, M.G.= 34 , P.W.= 50

(3) For exposure time (2 hours) + 0.5 hour clearance.

Table 13. Behavior of Inhaled Formaldehyde Vapor in Adult Human
(Steady State Uptake Percent: Mouth = 85.2±0.8, Nose = 72.8±2.0)[1]
(Corrected Uptake Percent: Mouth = 86.4±0.8, Nose = 75.1±2.1)

SUBJECT (SEX)	ROUTE NOSE/ MOUTH	PERCENT OF INHALED UPTAKE AT EACH EXPOSURE INTERVAL (HOUR) 0-0.5	0.5-1	1-1.5	1.5-2.0	STEADY[2] STATE UPTAKE	TOTAL AT 2.5 HOURS[3] EXHALED as CO_2	EXCRETED in URINE	AIR CONC. (ppb)
B.L.(M)	M	86.1	83.4	86.3	85.1	84.9±0.9	27.9	0.62	3
B.R.(M)	M	81.7	86.4	83.5	81.9	83.9±1.3	21.0	0.61	6
M.G.(F)	M	82.9	82.5	83.3	84.3	83.4±0.5	21.5	0.47	3
P.W.(F)	M	84.5	88.1	91.8	85.2	88.4±1.9	36.4	0.61	4
B.L.(M)	N	66.4	63.1	63.5	59.3	62.0±1.3	33.2	0.60	9
B.R.(M)	N	78.7	77.8	76.7	76.0	76.8±0.5	35.3	1.59	4
M.G.(F)	N	72.5	75.3	79.0	79.7	78.0±1.4	35.1	0.84	2
P.W.(F)	N	69.4	71.3	77.7	74.5	74.5+1.9	30.1	0.52	5

(1) Based on 12 measurements during the last 1.5 hours of the exposure of two males and two females.

(2) Total inhaled (ug): MOUTH B.L.= 3 , B.R.= 8 , M.G.= 3 , P.W.= 4
NOSE B.L.= 11, B.R.= 5 , M.G.= 2 , P.W.= 5

(3) For exposure time (2 hours) + 0.5 hour clearance.

Table 14. Overall Summary of the Corrected Uptake of Inhaled Vapors by People (Steady state uptake as percent of inhaled vapor/gas for three 30-min periods.)

Chemical	Exposure Route: Mouth (Mean ± S.E., n=12) PERCENT UPTAKE*	Exposure Route: Nose (Mean ± S.E., n=12) PERCENT UPTAKE*	Vapor/Gas Diffusivity (cm^2/s)	Concentration (ppb) (Mean ± S.D.)*
Trichloroethylene	55.4±1.8	53.9±1.9	0.13	18±3
Benzene (N)	54.6±2.1	60.0±3.2	0.14	9±3
Benzene (E)	41.6±1.3**	-	0.14	8±2
Methyl Bromide	52.1±3.4	55.4±3.6	0.16	18±6
Chloroform	49.6±1.6	45.6±1.5	0.14	13±5
Formaldehyde	86.4±0.8	75.1±2.1	0.24	5±2

Benzene (N) = Normal breathing rate.

Benzene (E) = With exercise (double breathing rate).

(-) : No exposure

* Uptake values after correction for external dead space in exposure system.

** n=8

Statistical Evaluation of Results.

Several types of statistical hypotheses were tested using the analysis of variance (ANOVA). These were :

1. Comparison of the percent uptakes from mouth and nose breathing within each of the five vapors.
2. Comparison of the effects on percent uptake due to exercise, for the benzene exposures only.
3. Comparison of the percent uptakes among the five vapors, on a pairwise basis, within each breathing type, i.e., within mouth-breathing only and within nose-breathing only.

In these analyses the "treatments" were considered to have been fixed in advance and not selected at random. The treatments were, then, following the scheme above : (1) mouth vs. nose, (2) exercise, and (3) chemical compounds, e.g., benzene vs. chloroform.

The subjects were required to meet certain criteria in order to be eligible for inclusion into the study. These criteria are discussed elsewhere, but included good health, and abstentions from smoking and from the use of drugs. It was assumed that the subjects represented a random selection from the population subset meeting the eligibility criteria, although they were not, in fact, selected strictly at random, e.g., by the use of a table of random numbers.

Thus, the two main effects - treatment and subjects (replications) - were fixed and random effects, respectively. The appropriate analytical model was, therefore, the two-way mixed model of the ANOVA (Anderson and Bancroft, 1952). The three null hypotheses tested in each ANOVA were : (1) that the two route-of-exposure means (taken over all four subjects) were equal; (2) that the four subject means (taken over both routes) were equal; and, (3) that the treatment versus subject interaction (potential inconsistency in behavior or response) was equal to zero.

In the experiments we carried out there were two experimental factors, namely, the route of exposure (nose or mouth) and the volunteer subject involved. We could and did test whether the mean uptake during mouth breathing equaled the mean uptake during nose breathing with each mean averaged over all four subjects. We also tested whether the mean uptakes of the four subjects, taken over both routes of breathing, were equal to each other.

If the two factors, breathing route and subject, were independent of each other, it should be possible to predict the uptake by mouth breathing given the uptake by nose breathing for any subject by simply adding the difference between mouth and nose breathing. For example, if mouth breathing produced an average uptake 10% greater than nose breathing uptake, it would be possible to add 10% to the nose breathing uptake to estimate the mouth breathing uptake for that subject.

When such a simple procedure is not workable, it is possible that the problem is due to "interactions," i.e., that the mouth-nose uptakes are not a consistent relationship over the set of four subjects. If, as did occur, three subjects had higher uptakes for one breathing mode, while the fourth had a lower uptake the statistical tests would detect a significant interaction (inconsistency). Also, as also did occur, if the difference in breathing modes was small but in the same direction for three subjects, while the fourth showed a large difference in the same direction, a statistically significant interaction would also be reported.

Thus, in commonly used terminology, interactions may be thought of as inconsistencies and unpredictability associated with various mixtures of synergisms and antagonisms. For a given subject breathing by nose or mouth, the uptake may be far greater than expected on the basis of the observations with the other subjects (synergism) or far less (antagonism). Similarly, when uptake following exposures to two gases or vapors are compared, e.g., chloroform and TCE, if the difference between the two uptakes for all subjects was consistent, there would be no reported interaction. However, if there was a greater uptake of TCE in some subjects and a lesser uptake in others, relative to their uptake of chloroform, a statistically significant interaction would be shown by the analysis of variance. Hence, it is useful to view the statistical term, interaction, as meaning inconsistency.

The presence of the interactions forces the investigator to be more prudent or conservative in drawing general conclusions, and indeed, is forced to do so by the statistical analysis. For this reason it may not be possible to make certain general statements such as whether nose breathing produces a higher uptake than mouth breathing for benzene, for, indeed that may depend upon the particular subject and experimental conditions.

Hence, the analysis of variance (ANOVA) provides information relative to the equality of means and the presence of interactions, but cannot provide any information as to why the observed results occurred. It is, in effect, blind to mechanisms. If an interaction is observed, and it is clear that it was caused by the behavior of one subject, it is necessary to ask why that subject performed in an unexpected fashion relative to the other subjects. The answers must be sought by means other than analysis of variance. In fact, the answers are largely associated with physiological differences in breathing rates and tidal volumes which vary among subjects and experiments.

For this reason, we used multiple linear regression analysis as well. In this analysis, variables or parameters which could have had an effect on uptake were explored to determine whether they were useful in predicting uptake. These factors included vapor diffusivity, respiratory rate, blood/air partition coefficients, sex, tidal volume, and apparent nasal/head uptake involvement.

In the mixed model the formation of the appropriate F statistics for testing the three null hypotheses is dictated by the expected mean squares. Here the test for interaction (inconsistency) is the ratio of the interaction (inconsistency) mean square to the error mean square ($= F_{3,16}$). If the interaction (inconsistency) is not significant both mean squares are estimates of the error mean square (MS_e) and may be pooled, so that the pooled MS_e has 19 degrees/freedom.

However, if the interaction (inconsistency) is significant (we used as the level of significance, $p=0.05$) then the treatment mean square divided by the interaction (inconsistency) mean square is the proper test for treatment effect. Without interaction (inconsistency) we have $F_{1,19}$. With interaction

(inconsistency) we have $F_{1,3}$ and demonstrations of significant differences between treatment means become much more difficult. The differences between means of subjects were tested by the ratio of the mean square for subjects divided by MS_e ($=F_{3,16}$ with interaction (inconsistency) or $F_{3,19}$ without interaction (inconsistency)).

The results of the ANOVA's (Tables 15, 16, and 17) clearly showed a weakened ability to demonstrate treatment differences, due to the presence of often large, highly significant interactions (inconsistencies) between subjects and route of inhalation. Unlike the earlier studies with beagles where the subjects showed consistently similar uptakes under similar conditions, the human volunteers showed erratic individual differences. The interaction (inconsistency) term is a measure of the responses of the same subjects to mouth vs. nose breathing or to benzene vs. formaldehyde while nose breathing, etc. Additivity is assumed. For example, if the mean uptake of benzene (B) is 50% and the mean uptake of formaldehyde (F) is 80%, then under strict additivity the curves connecting the four subjects should be parallel, with the formaldehyde curve offset upwards by 30% over that of benzene. If, for example, the difference (F - B) is not constant, but varies among subjects, and hence is non-additive, a significant interaction (inconsistency) may be observed. In even more serious instances some subjects will be observed in whom $F < B$, while in others $F > B$, so that a simple statement, (such as $F < B$), cannot be made about all subjects.

For nose breathing, intersubject versus vapor interactions (inconsistencies) were significant for all comparisons (Table 17) and for 4 out of 10 of the mouth breathing comparisons. There was a generally significant inconsistency between subjects and this affected the comparisons of chemicals. However, the observed intersubject variability was real and representative of the selected healthy population.

The main results show that mouth inhalation uptake of chloroform was significantly higher than that by nose ($p<0.005$), and there was a strong tendency for mouth inhalation of formaldehyde to be higher than by nose ($p<0.01$). There was not a statistically significant difference in route of exposure for the other vapors. The average oral inhalation uptake of benzene

vapor during exercise was significantly lower than for uptake at rest for either nose or mouth breathing ($p<0.001$).

For oral inhalation, the uptake of trichloroethylene was significantly higher than chloroform ($p<0.005$) and lower than formaldehyde ($p<0.001$), but not statistically different from the results for methyl bromide or benzene. The oral uptake of benzene was significantly higher than chloroform ($p<0.025$) and lower than formaldehyde ($p<0.001$), but not statistically different from methyl bromide or TCE. The oral uptake of methyl bromide was significantly lower than formaldehyde ($p<0.025$), but not different from the other vapors. The oral uptake of chloroform was significantly lower than formaldehyde ($p<0.001$), benzene ($p<0.025$), or TCE ($p<0.005$).

For nasal inhalation, the uptake of trichloroethylene was significantly higher than chloroform ($p<0.01$) and lower than formaldehyde ($p<0.025$), but not statistically different from the results for methyl bromide or benzene. The nasal inhalation uptakes of benzene and methyl bromide were not significantly different from the other vapors.

The assumption of randomly selected subjects allows more relevant extrapolations of the results to other persons similar to the subjects used, while the assumption that the subjects were "fixed" would restrict the application of results only to those subjects tested; hence the desirability of the assumption of randomness. The price paid for the assumption resulted from the perhaps unexpected variability among subjects and from their sometimes inconsistent responses.

Table 15. Result of Statistical Analyses of Vapor Uptake Data: Mouth vs. Nose
(Two-way analysis of variance, mixed model)

VAPOR/ GAS	TEST Description	TEST PARAMETERS AND VALUES: Subject versus Route Interaction	Differences Among Subjects	Mouth versus Nose
BENZENE	F value	F(3,16)=6.84	F(3,16)=9.83	F(1,3)=0.60
	p value	p< 0.005	p< 0.001	N.S
	Response type*	(1)	(2)	(3)
METHYL BROMIDE	F value	F(3,16)=9.16	F(3,16)=55.64	F(1,3)=0.24
	p value	p< 0.001	p< 0.001	N.S
	Response type*	(1)	(2)	(3)
CHLOROFORM	F value	F(3,16)=2.34	F(3,19)=10.6	F(1,19)=10.6
	p value	N.S	p< 0.001	p< 0.005
	Response type*	(4)	(2)	(5)
FORMALDEHYDE	F value	F(3,16)=18.61	F(3,16)=16.14	F(1,3)=9.53
	p value	p< 0.001	p< 0.001	0.05<p<0.10
	Response type*	(1)	(2)	(7)
TRICHLORO-ETHYLENE	F value	F(3,16)=3.3	F(3,19)=0.1	F(1,19)=2.19
	p value	0.05<p<0.10	N.S	N.S
	Response type*	(7)	(6)	(3)

*Response type: (1) : There is a significant subject by treatment interaction.
(2) : There are significant differences among subjects.
(3) : No significant difference due to route (mouth vs nose).
(4) : The subject by treatment interaction (inconsistency) did not differ significantly from zero.
(5) : Mouth uptake of vapor was significantly higher than nose.
(6) : The subjects did not differ relative to TCE uptake.
(7) : There is an interaction (inconsistency) tendency.

Table 16. Result of Statistical Analyses of Vapor Uptake Data for Mouth Breathing (Two-way analysis of variance, mixed model)

VAPOR/ GAS	(Mean ± S.E.)	TEST PARAMETERS AND VALUES		
		Subject vs. Chemical Interaction	Differences Among Subjects	Chemical A versus Chemical B
TRICHLOROETHYLENE	55.4 ± 1.8			
vs. BENZENE	54.6 ± 2.1	N.S.	$p < 0.01$	N.S.
TRICHLOROETHYLENE	55.4 ± 1.8			
vs. METHYL BROMIDE	52.1 ± 3.4	$p < 0.001$	$p < 0.001$	N.S.
TRICHLOROETHYLENE	55.4 ± 1.8			
vs. CHLOROFORM	49.6 ± 1.6	N.S.	$p < 0.005$	$p < 0.005$
TRICHLOROETHYLENE	55.4 ± 1.8			
vs. FORMALDEHYDE	86.4 ± 0.8	N.S.	$p < 0.05$	$p < 0.001$
BENZENE vs.	54.6 ± 2.1			
METHYL BROMIDE	52.1 ± 3.4	$p < 0.001$	$p < 0.001$	N.S.
BENZENE vs.	54.6 ± 2.1			
CHLOROFORM	49.6 ± 1.6	N.S.	$p < 0.001$	$p < 0.025$
BENZENE vs.	54.6 ± 2.1			
FORMALDEHYDE	86.4 + 0.8	N.S.	$p < 0.025$	$p < 0.001$
METHYL BROMIDE	52.1 ± 3.4			
vs. CHLOROFORM	49.6 ± 1.6	$p < 0.001$	$p < 0.001$	N.S.
METHYL BROMIDE	52.1 ± 3.4			
vs. FORMALDEHYDE	86.4 ± 0.8	$p < 0.001$	$p < 0.001$	$p < 0.025$
CHLOROFORM vs.	49.6 ± 1.6			
FORMALDEHYDE	86.4 ± 0.8	N.S.	$p < 0.005$	$p < 0.001$

Table 17. Result of Statistical Analyses of Vapor Uptake Data for Nose Breathing (Two-way analysis of variance, mixed model)

VAPOR/ GAS	(Mean ± S.E.)	TEST PARAMETERS AND VALUES		
		Subject vs. Chemical Interaction	Differences Among Subjects	Chemical A versus Chemical B
TRICHLOROETHYLENE	53.9 ± 1.9			
vs. BENZENE	60.0 ± 3.2	$p < 0.001$	N.S.	N.S.
TRICHLOROETHYLENE	53.9 ± 1.9			
vs. METHYL BROMIDE	55.4 ± 3.6	$p < 0.01$	$p < 0.001$	N.S.
TRICHLOROETHYLENE	53.9 ± 1.9			
vs. CHLOROFORM	45.6 ± 1.5	$p < 0.05$	$p < 0.005$	$p < 0.01$
TRICHLOROETHYLENE	53.9 ± 1.9			
vs. FORMALDEHYDE	75.1 ± 2.1	$p < 0.001$	$p < 0.005$	$p < 0.025$
BENZENE vs.	60.0 ± 3.2			
METHYL BROMIDE	55.4 ± 3.6	$p < 0.001$	$p < 0.001$	N.S.
BENZENE vs.	60.0 ± 3.2			
CHLOROFORM	45.6 ± 1.5	$p < 0.001$	$p < 0.001$	N.S.
BENZENE vs.	60.0 ± 3.2			
FORMALDEHYDE	75.1 ± 2.1	$p < 0.001$	$p < 0.001$	N.S.
METHYL BROMIDE	55.4 ± 3.6			
vs. CHLOROFORM	45.6 ± 1.5	$p < 0.001$	$p < 0.001$	N.S.
METHYL BROMIDE	55.4 ± 3.6			
vs. FORMALDEHYDE	75.1 ± 2.1	$p < 0.001$	$p < 0.025$	N.S.
CHLOROFORM vs.	45.6 ± 1.5			
FORMALDEHYDE	75.1 ± 2.1	$p < 0.01$	$p < 0.001$	$p < 0.01$

Uptake Regression Models

Although there was considerable inter-subject variability in the results, much of that variability may be explained by the physiological differences among subjects and among data of the same subject in different sessions. The variability among the data was studied with linear and logarithmic models utilizing the tidal volume (TV) and respiratory rate (RR) as the principal respiratory variables. In addition, the influences of sex, vapor diffusivity (D), blood-to-air partition coefficient, and apparent upper respiratory and head airways uptake (H) for all the vapors but chloroform were also considered. It was found that a considerable portion of the variability could be explained with the simple linear model and no improvement was associated with multiplicative (logarithmic) models. Sex and partition coefficient had little influence on the regression correlation, and were dropped from the analysis; however, male subjects tended to breath faster and have larger tidal volumes, and high correlations were observed for higher tidal volume in the male subjects during nose breathing ($p<0.05$) and higher respiratory rates in male subjects during mouth breathing ($p<0.025$). Also, of the 44 separate measurements, one experiment (35A) was inexplicably disparate and was omitted from the regression analysis.

The resulting linear regression model (with predictor standard errors) for oral inhalation is:

$$\text{Uptake (\%) via mouth} = 35.1(\pm 7.1\ \text{SE}) + 314(\pm 25\ \text{SE})\ D - 1.56(\pm 0.39\ \text{SE})\ RR - 0.0168(\pm 0.0037\ \text{SE})\ TV + 5.49(\pm 2.54\ \text{SE})\ H \quad (10)$$

for n=23 experiments (including exercise) with the gas or vapor diffusivity, D (cm^2/s), respiratory rate, RR (breaths per minute), tidal volume, TV (ml), and head and/or upper airway uptake factor, H, is 1 for all vapors but chloroform for which H is 0. This fit displayed a multiple correlation coefficient of 0.97 ($p<0.001$) and the regression equation accounted for 93% of the variability. Of this 93%, 79% was associated with vapor diffusivity, 6% with the respiratory rate, 6% with the tidal volume, and 2% with the head/upper tract effect. This equation provides reasonable predictions of both the at rest and exercise data.

The resulting linear regression model (with predictor standard errors) for nasal inhalation is:

$$\text{Uptake (\%) via nose} = 50.8(\pm 25.7\ \text{SE}) + 193(\pm 53\ \text{SE})\ D - 1.48(\pm 1.41\ \text{SE})\ RR - 0.0232(\pm 0.0260\ \text{SE})\ TV + 9.73(\pm 5.19\ \text{SE})\ H \quad (11)$$

for n=20 experiments with the gas or vapor diffusivity, D (cm^2/s), respiratory rate, RR (breaths per minute), tidal volume, TV (ml), and head/upper airway involvement factor, H, is 1 for all vapors but chloroform for which H is 0. This fit displayed a multiple correlation coefficient of 0.79 ($p<0.001$) and the regression equation accounted for 62% of the variability. Of this 62%, 47% was associated with vapor diffusivity, 4% with the respiratory rate, 2% with the tidal volume, and 9% with the upper tract effect.

These equations apply to xenobiotic chemicals of moderate to high solubility in body fluids, having blood-to-air partition coefficients that are generally greater than unity. In this study the range was about 1 for methyl bromide to about 20 for formaldehyde. Likewise, the lung alveolar membrane transfer rate is high for these vapors. Other volatile organic compounds can be expected to display similarly high solubility in body tissues. The regression analysis showed that the resulting uptake was relatively insensitive to partition coefficient, however. Apparently the uptake and metabolism of these xenobiotic volatile chemicals is very rapid compared to the speeds associated with ventilation and diffusion of vapor in the lung airways. Thus the regression equations are primarily controlled by these factors. However, it should be noted that the above equations are not applicable to vapors with low solubility in body fluids and having blood-to-air partition coefficients that are very much smaller than unity; in those cases the uptake will be much smaller than observed in these studies and will be limited by transfer from air to alveolar membrane and to blood rather than by ventilation.

These results show that uptake increases with increased vapor diffusivity, and decreases with increased respiratory rate (decreased vapor residence time in lung) or increased tidal volume (greater lung expansion and increased diffusion distance. The consequence is that diffusion of vapor in the lung is

demonstrated to be the limiting process in determining vapor uptake into the systemic circulation. Thus, during exercise, the uptake fraction dropped because of increased tidal volume and increased rate.

For general purposes, Reference Man (Snyder, 1975) with RR=15 breaths per minute for resting (TV=500 ml), light work (TV=750 ml), and moderate work (TV=1450 ml) can be used with the two regression equations to estimate the uptake for each vapor under these varied conditions (Table 18).

Table 18. Calculated Uptake Percentages for Example Tidal Volumes (15 Breaths/min Based Upon Reference Man: Snyder, 1975)

Vapor/Gas	Tidal Volume (ml)	Oral (%)	Nasal (%)
Benzene	500	55	54
	750	49	48
	1450	37	32
Trichloroethylene	500	50	52
	750	45	46
	1450	34	30
Chloroform	500	47	44
	750	43	38
	1450	31	22
Methyl bromide	500	59	58
	750	55	52
	1450	43	36
Formaldehyde	500	84	73
	750	80	67
	1450	68	51

Biological elimination of vapors

The clearance data of the inhaled vapors (benzene, trichloroethylene, methyl bromide, formaldehyde, and chloroform) are summarized in Table 19. These results, based upon clearance during the first half hour after exposures ended, show that chloroform and formaldehyde are eliminated rapidly by the way of oxidation to CO_2. Moderate amounts of these vapors were also excreted unchanged via the lung into the exhaled air. Trace levels of ^{14}C-labeled metabolites and/or the parent compound were detected in the urine.

In summary, the lung was the major route for chloroform and formaldehyde elimination with their metabolites. The elimination of benzene ^{14}C-equivalents was also rapid (biological half life about 12 hours). It was eliminated as benzene via the lung and as mainly metabolites in the urine. Benzene is metabolized by the liver to water soluble compounds by conjugation and oxidation to phenol, catechol, hydroquinol, and hydroxyhydroquinol (Bergman, 1979). The amount of benzene eliminated by the lung was 0.4 times the amount of benzene conjugated or oxidized by the liver. The rate of benzene oxidation to CO_2 is very slow as indicated by the amount of CO_2 measured in the exhaled air. The clearance rates of ^{14}C-equivalents for trichloroethylene was moderately rapid (biological half life was about 25 hours). A large portion was excreted via the lung as the parent compound and as CO_2. Trichloroethylene is also metabolized in the liver by oxidation to trichloroethanol and trichloroacetic acid (National Academy of Sciences, 1980) and these products were eliminated in the urine. Methyl bromide ^{14}C-equivalents showed the highest body retention among the compounds studied (biological half life was about 72 hours). It was eliminated mainly via the lung as the parent compound and as CO_2, measured during the first half hour after exposure. Trace levels of ^{14}C-labeled parent compound and/or metabolites were detected in the urine.

Unfortunately, urine samples collected up to 16 hours after exposure showed extreme variability in volume and activity indicating that the subjects did not provide complete samples. Although these samples indicated that clearance was proceeding as expected, they did not provide reliable quantification of the amount cleared during the period.

Table 19. Biological Elimination of Vapors (Both Routes)

VAPOR TYPE	PARAMETER	PERCENT OF INHALED (AT 0.5 HOURS POST INHALATION) TOTAL EXCRETED IN URINE	TOTAL EXHALED AS CO_2	TOTAL EXHALED AS VAPOR	NET BODY RETENTION	(hr) $T_{1/2}$	PULMONARY/ URINARY*
Benzene	AVERAGE	6.16	0.28	2.47	42.1	12.2	0.4
	S.E.,n=12	1.25	0.08	0.31	3.2	2.5	
Trichloro-	AVERAGE	1.20	1.47	1.15	49.5	25.2	1.0
ethylene	S.E.,n=8	0.17	0.50	0.10	1.3	2.5	
Methylbromide	AVERAGE	0.16	0.45	0.89	51.1	71.9	5.6
	S.E.,n=8	0.04	0.10	0.19	4.4	11.7	
Formaldehyde	AVERAGE	0.73	30.1	1.48	46.7	3.5	2.0
	S.E.,n=8	0.13	2.2	0.17	4.1	0.4	
Chloroform	AVERAGE	0.29	16.6	1.51	28.2	3.5	5.2
	S.E.,n=8	0.07	0.6	0.12	1.5	0.2	

(*) Calculations based on single exponential clearance equation fit to data.

The half-time estimates in Table 19 were made by assuming a simple exponential clearance process during each two hour exposure and half-hour post exposure using:

$$\ln A_1 = \ln A_2 + \lambda(t_2 - t_1) \qquad (12)$$

where A_1 is the average uptake, A_2 id the total body retention of inhaled vapor at 2.5 hours after the beginning of exposure, t_1 is the time at the beginning of the exposure, and t_2 is 2.5 hours after the beginning of the exposure. The value of A_2 is obtained by subtracting the measured urinary excretion at 2.5 hours, the amount exhaled as CO_2, and the observed exhaled parent or metabolites during the first half hour after the two hour exposure from the measured average uptake of the parent vapor. The clearance half-time is calculated from the clearance rate constant, λ, by $\lambda = \ln_e 2/T_{1/2}$.

DISCUSSION

Models of Inhalation Uptake of Vapors and Gases

The use of simulation or pharmacokinetic models of the processes associated with inhalation uptake, distribution, metabolism, and excretion of xenobiotic vapors and gases provides a convenient basis for predicting the uptake of a vapor or gas without actually measuring it over an extended period (Fiserova-Bergerova, 1983). It also provides a basis for understanding the results of experimental measurements such as performed in this study. The basis of this model in the context of this study relates to the continuous, chronic exposure of people to very low concentrations. The saturation of all body compartments with the vapor does not occur because of metabolic degradation and excretion of the chemicals by the body. Also, the low concentrations involved avoid saturation of the relevant biochemical and physiological pathways.

Models of uptake usually treat the lung as the principle route of entry into the body and as a specific body compartment into which vapor in transported with inhaled air and out of which the chemical is removed by the pulmonary blood flow and possibly exhaled air. The key parameter for evaluating this process is the the blood-to-air volumetric partition coefficient, $L_{bl/air}$, which depends in general upon the solubility of the chemical vapor in the blood. In this current study, the solubility was relatively high, and the partition coefficients were usually about 10 or higher, because of the chemical properties of the chemicals that were studied and also because of the very low concentrations involved. This means that one ml of blood will contain ten times as much of the chemical than one ml of air when at equilibrium. In such a case, the capacity of the blood to take up the vapor is great, and a significant fraction of the vapor in the deep lung should be transfered to the blood for distribution to other body organs and tissues.

If the body volume in 42 liters (for a 70 kg person, Snyder, 1975), then the body volume at equilibrium could hold 420 liters of the inhaled vapor. The typical respiratory minute volume for a person at rest is 9 liters. Therefore,

the body could be saturated with the chemical vapor after 420/9=47 minutes assuming fairly good mixing in body compartments. With only the approximately 5 liters of blood involved, the blood would be saturated after 50/9=6 minutes. With such saturation, the uptake fraction would drop to a low value as the metabolic clearance processes clear the chemical. In fact, no such saturation or even a tendency to saturation was observed in these studies, and it seems clear that the metabolism of these chemicals in the body occurs at a rate that exceeds the uptake rate during inhalation. Thus, since the capacity of the body reservoirs and the metabolic processes are not being saturated, it would be be expected that the air-to-blood transfer is the rate limiting process. This conclusion further supports the regression analysis showing ventilatory and vapor or gas diffusion to be the principal predictors of inhalation uptake.

During inspiration the air entering the alveolar (gas exchange) region of the lung is air remaining in the conductive airways of the respiratory tract from the previous inhalation. These conductive airways represent a respiratory dead space since no gas exchange and minimal vapor uptake occurs in them. The volume of this respiratory dead space in people is estimated at 30% of the resting tidal volume, or about 150 ml (Fiserova-Bergerova, 1983c). The first 150 ml of each inspiration is air from the dead space, followed by the fresh breath which may have a volume of from 350 ml to 2150 ml depending upon level of physical exertion.

If the alveolar (gas exchange) region of the lung is treated as a simple body compartment and ventilation is treated as a continuous process, the amount of vapor entering equals the product of the vapor concentration, c_{exp}, and the alveolar ventilation flow rate, V_{alv}. When the partial pressures of the vapor in alveolar air and blood in alveolar capillaries equilibrates, the concentration in the alveolar air becomes:

$$c_{alv} = c_{exp} V_{alv} / (V_{alv} + QL_{bl/air}) \qquad (13)$$

where Q is the pulmonary blood flow rate. Since Q is about 6.7 L/min in a 70 kg person, V_{alv} is about 4.8 L/min at rest, and the partition coefficient is about 10 for the chemicals in this study (Table 1), the alveolar concentration is estimated from this simple model as (Fiserova-Bergerova, 1983c):

$$c_{alv} = c_{exp}/(1 + 1.4L_{bl/air}) = 0.067c_{exp} \qquad (14)$$

If at rest 30% of the exhaled air is from the dead space at concentration c_{exp} and 70% is alveolar air at $0.067c_{exp}$, the exhaled air would have a concentration of $0.35c_{exp}$. The observed uptake would be 65%. Considering that some vapor should be taken up in the nose or lining of the conductive airways, uptake should have exceeded 65%. Many of the observed measurements were well below 65%, indicating incomplete alveolar equilibration and mixing of the vapors.

Oral inhalation of benzene had an uptake of about 55%. Further, under exercise conditions, the dead space becomes a much smaller factor in the process, and the uptake fraction should increase since the dead space has a smaller influence upon the respiratory process at higher tidal volumes. Blood flow increases along with tidal volume. For the average alveolar flow rate (minute volume) of 14 liters under exercise, the alveolar concentration from Equation 14 is $0.17c_{exp}$. The dead space is only 15% of the inhaled air, so that the predicted uptake fraction would be 70%. In fact, the observed uptake fraction under exercise for benzene vapor was about 42%, and significantly lower than at rest.

Clearly, the assumption of complete mixing in the alveolar space during breathing is not valid. The air in the lungs is not well mixed, and the passage of vapor from the incoming air to the walls of the alveoli is a function of vapor diffusivity, which is the proportionality constant describing the rate of flow of gases from regions of high concentration to regions of low concentration. The vapor in this study with the highest diffusivity is formaldehyde, and the observed uptake fractions that exceed 75% are indicative of this higher diffusivity. The other vapors in this study have similar and much lower diffusivities and much lower uptake fractions as well. The lower uptake fraction for benzene vapor during exercise can be explained by the greater inflation of the lung; this means the distance that vapor must diffuse to reach the walls of the alveoli is greater, and with somewhat increased breathing rate the time available for diffusion is less, so that less vapor

contacts the alveolar membrane and less is, therefore, available to be absorbed by the blood.

Another phenomenon that also needs to considered is uptake of vapor by the mucous membranes of the nose and other conductive airways. The volume of liquid lining the surface of the airways in too small to account for much uptake after initial equilibration. Where circulation is good, as in some parts of the nose, uptake into the blood stream can occur, however. This will increase the uptake fraction. On the other hand, it has been suggested that some vapor that is absorbed at the surface of the upper airways, desorbs into the exhaled air stream (Fiserova-Bergerova, 1983a). This can be one of the causes of the lower uptake observed in people for chloroform vapor in this study. The assignment of H=0 to chloroform in the regression model is primarily associated with this real but unclear phenomenon.

The lower uptake of chloroform (45.6%$\pm$1.5%SE) compared to benzene (60.0%$\pm$3.2%SE) via the nose was unexpected since previous beagle uptake studies yielded very similar results for these two vapors (39.8%$\pm$1.5%SE for chloroform versus 42.1%$\pm$2.2%SE for benzene). The human nose and head region does not appear to absorb chloroform as readily as other vapors, and for this reason was assigned a head airways uptake factor H=0. This phenomenon may relate to an absorption/desorption process such that chloroform is absorbed by the nasal membranes during inhalation and they give up excess vapor to the exhaled air during exhalation. Whether delayed absorption, less effective surface adsorption, or desorption is involved, the H=0 factor for chloroform was found to be an important part of the resulting regression equations, and was particularly important in the case of nose breathing.

Although the uptake fraction of benzene is lower during exercise, and the uptake fractions for the other vapors is predicted also to be lower during exercise, the total amount of xenobiotic chemical that enters the systemic circulation is higher because the total amount inhaled is more than double during exercise. The ratio of the uptake fractions during oral breathing at rest to the that during exercise was about 1.3. On the other hand, the volume of air inhaled was about 2.5 time more, so that the net uptake of benzene was 2.5/1.3=2 times greater per unit time during exercise than at rest in this study.

Comparison to other studies

Previous inhalation studies with human subjects using benzene concentrations of 57 ppm·(Nomiyama & Nomiyama, 1974) and 217 ppm (Astrand, 1975) yielded measured uptake fractions of 47% and 55%, respectively, for normal breathing at rest. Only Astrand (1975) who studied mouth-breathing people, collected all of the exhaled vapor. The results for the beagle studies at concentrations from 10 ppb to 46 ppb were about 42%. The uptake in these human studies varied from about 42% to 60% for people depending upon breathing rate and inhalation route. These results spanning from man to dog for concentrations that vary up to a factor of about 20,000 are remarkably similar (Figure 4). The short exposure duration may explain the observed higher uptake associated with the Astrand (1975) measurements (Figure 5), since the blood concentration is lowest at the beginning of and exposure, and the uptake should thus be maximum at that time.

Likewise, trichloroethylene uptake in nose-breathing humans was found to be 55% at 316 ppm (Nomiyama & Nomiyama, 1974), 58% at 193 ppm (Bartonicek, 1962), 46% and 48% at 68 ppm and 140 ppm, respectively (Monster, et al., 1976), and 44% at 100 ppm (Vesterberg et al., 1976). Astrand and Ovrum (1976), who studied mouth-breathing people, collected and measured the exhaled vapor and found 53% uptake at 150 ppm. The results for the beagle studies at concentrations from 85 ppb to 250 ppb were about 48%. The results in these human studies at even lower concentrations were about 55% regardless of route. Bergman (1979) had similar results for mice. These results show about the same uptake over a wide range of concentrations (Figure 6) and exposure times (Figure 7).

Medinsky et al. (1985) measured the uptake of ^{14}C-labeled methyl bromide by Fischer-344 rats for six hours at concentrations from 1.6 to 310 ppm. They found that in their apparatus the fractional uptake of methyl bromide vapor ranged from 37% to 27% at the highest concentrations to about 48% at the lower concentrations. The results of the beagle studies was about 40% uptake compared to about 55% in humans in this study. These results are compared in Figures 8 and 9. Medinsky et al. (1985) collected excreta and exhaled carbon dioxide for 66 hours after exposure and found about 50% of the ^{14}C to be eliminated as

exhaled $^{14}CO_2$ with 85% having a clearance half-time of 4 hours; this was much faster than observed for beagles or people.

Other human studies involving nose breathing allowed rebreathing of vapor and did not provide for definitive measurements of exhaled vapor for uptake determinations. No other unequivocal human data have been located for any of the chemical vapors in this study. It is particularly remarkable that no reports could be found for the uptake of chloroform in people when utilized as an anesthetic. Most of the reported laboratory animal studies involved rebreathing of exhaled air, and the results are, therefore, difficult to evaluate.

The beagle studies (Raabe, 1986) yielded uptake fractions for nasal inhalation that tended to be about 10% to 30% lower than the observed uptakes in people in this study. This may be explained by respiration and respiratory tract differences. Formaldehyde uptake in beagles was only about 54% (5-12 ppb), but was about 75% (about 5 ppb) in people. Because of its high water solubility, the uptake of formaldehyde might be expected to be closer to 100%. Formaldehyde in a natural metabolic product whose concentration in blood may be higher in beagles than in people, with reduced blood capacity. Heck et al. (1985) show that the normal concentration of formaldehyde in the blood of people and rats is from 2.2 to 2.6 ppm (by mass). This gradient between body tissue levels and the inhaled air may have influenced the result, although the radioactively labeled formaldehyde should exhibit an independent behavior.

If the vapors studied in this project were readily absorbed into body fluids at the surface of all parts of the respiratory tract, uptake would have approached 100% for these vapors. This is because the high diffusivities (Table 1) would lead to an efficient convective diffusional transport in the conductive airways during breathing. Diffusivity (also called diffusion coefficient, cm^2/s) is the constant of proportionality between the rate of diffusion (molecules/cm^2 per s) and a concentration gradient (molecule/cm^3 per cm). Aerosol particles with diffusivities less than those of these vapors are known to be nearly quantitatively deposited in the conductive airways and alveolar region of the lung during normal breathing in dogs and man (Raabe, 1982). For example, radon decay products are metallic aerosols with diffusivities about 0.054 cm^2/s (about 40% of the diffusivity of the vapor

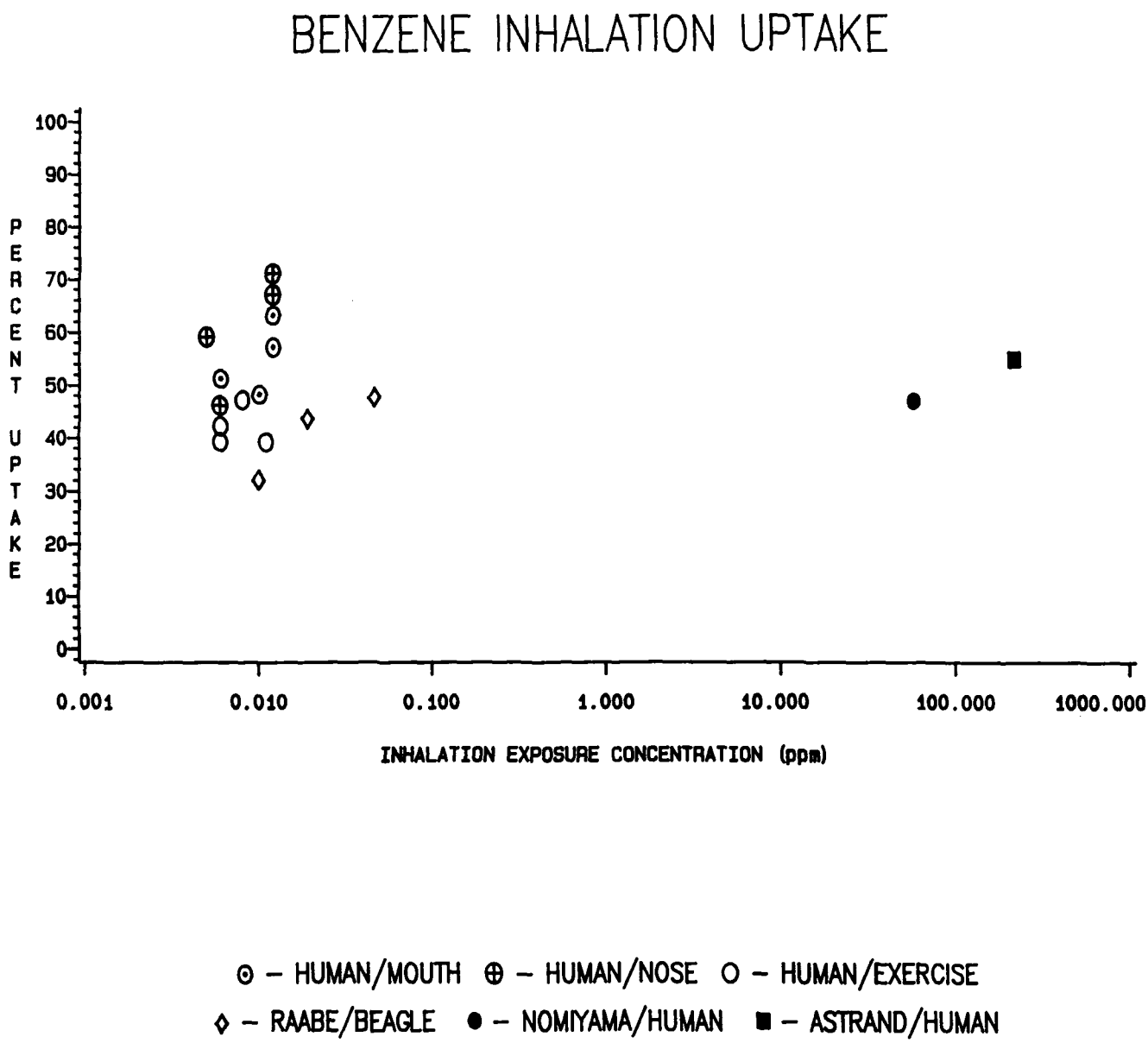


Figure 4. Comparison of observed uptake fractions of benzene vapor in human volunteers by this study, in beagles by Raabe (1986), and in human volunteers by Astrand (1975) and Nomiyama and Nomiyama (1974) with respect to exposure concentration.

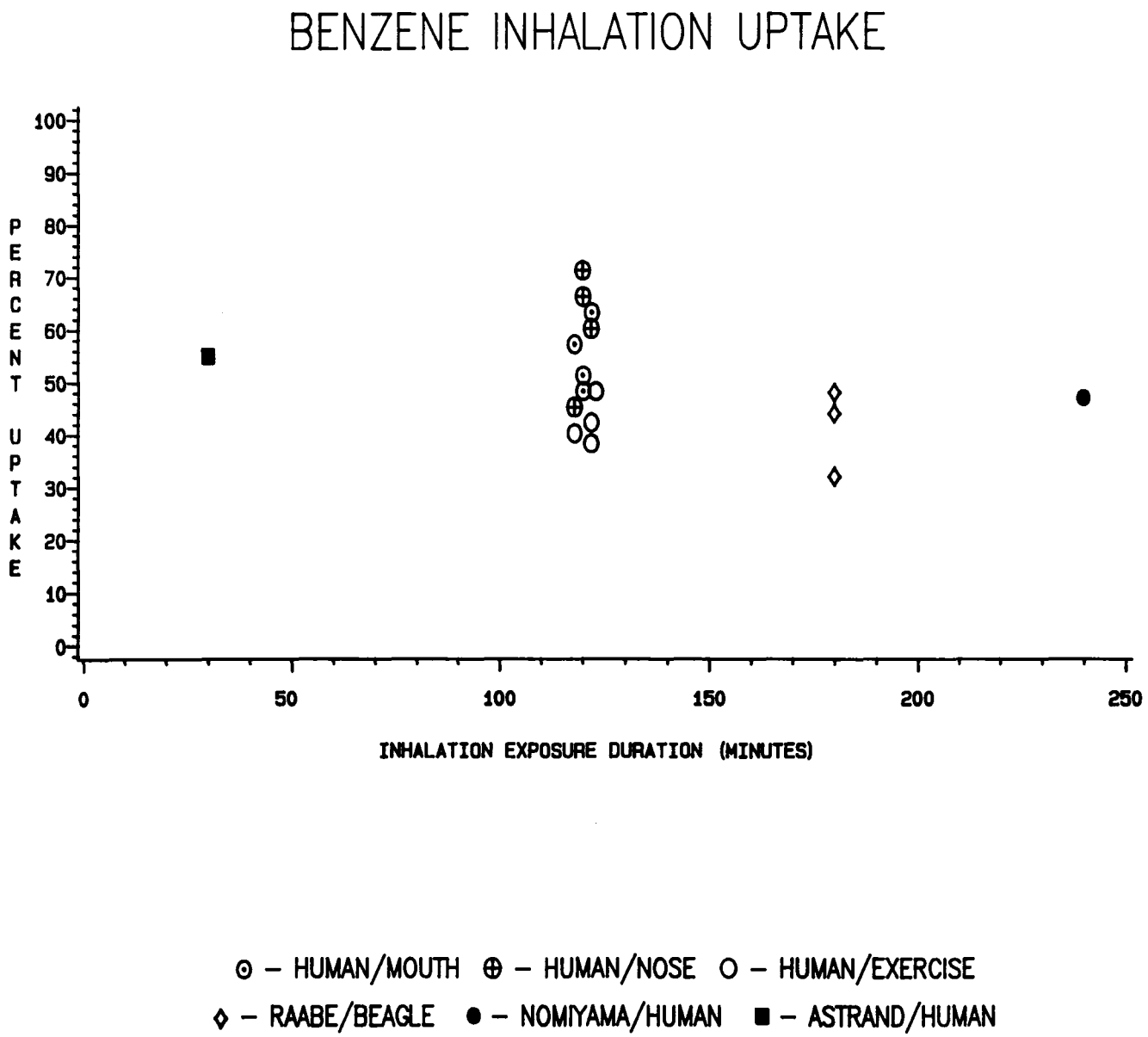


Figure 5. Comparison of observed uptake fractions of benzene vapor in human volunteers by this study, in beagles by Raabe (1986), and in human volunteers by Astrand (1975) and Nomiyama and Nomiyama (1974) with respect to duration of exposure.

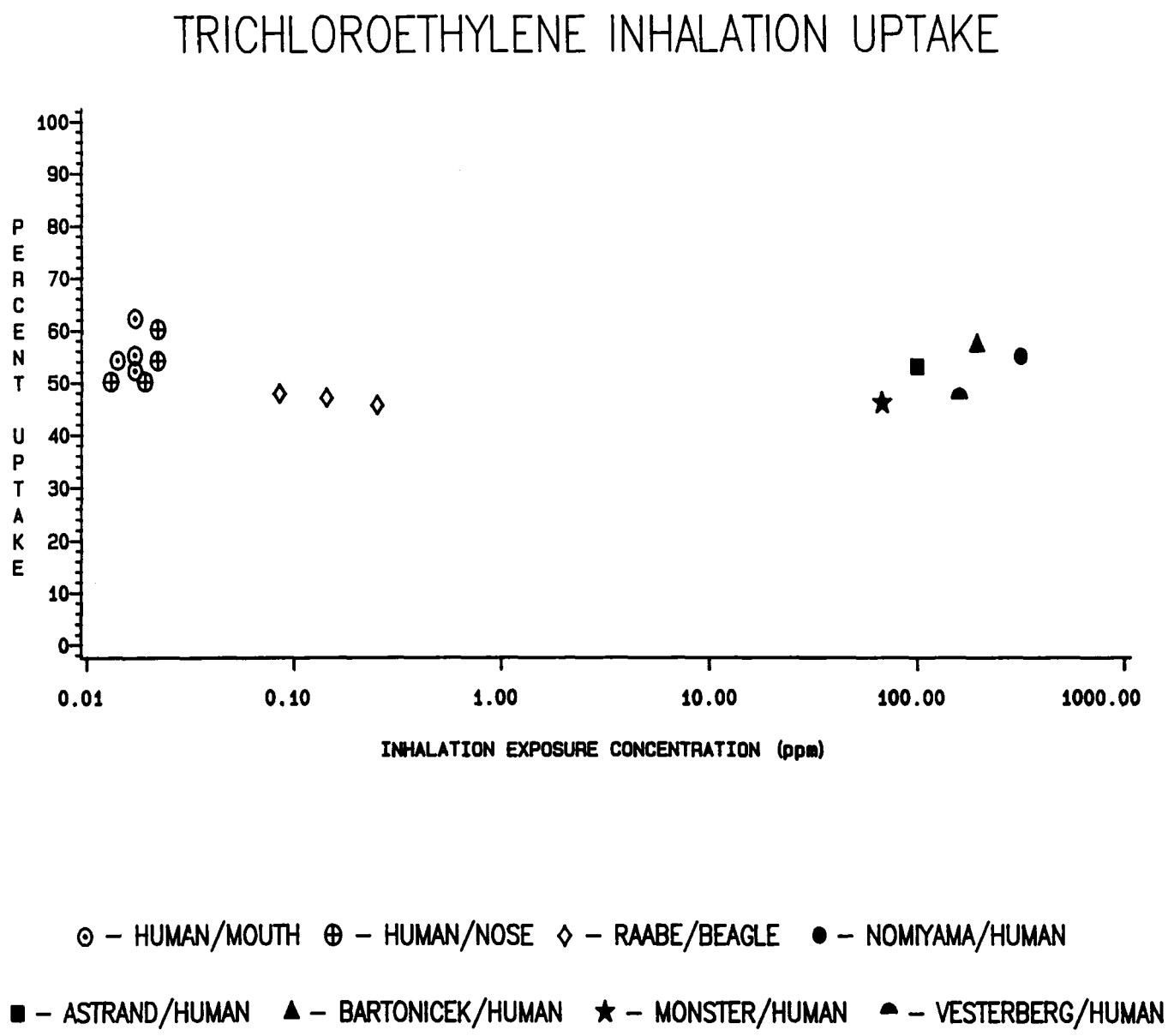


Figure 6. Comparison of observed uptake fractions of trichloroethylene vapor in human volunteers by this study, in beagles by Raabe (1986), and in human volunteers by Astrand and Ovrum (1976), Nomiyama and Nomiyama (1974), Bartonicek (1962), Monster et al. (1976), and Vesterberg et al. (1976) with respect to exposure concentration.

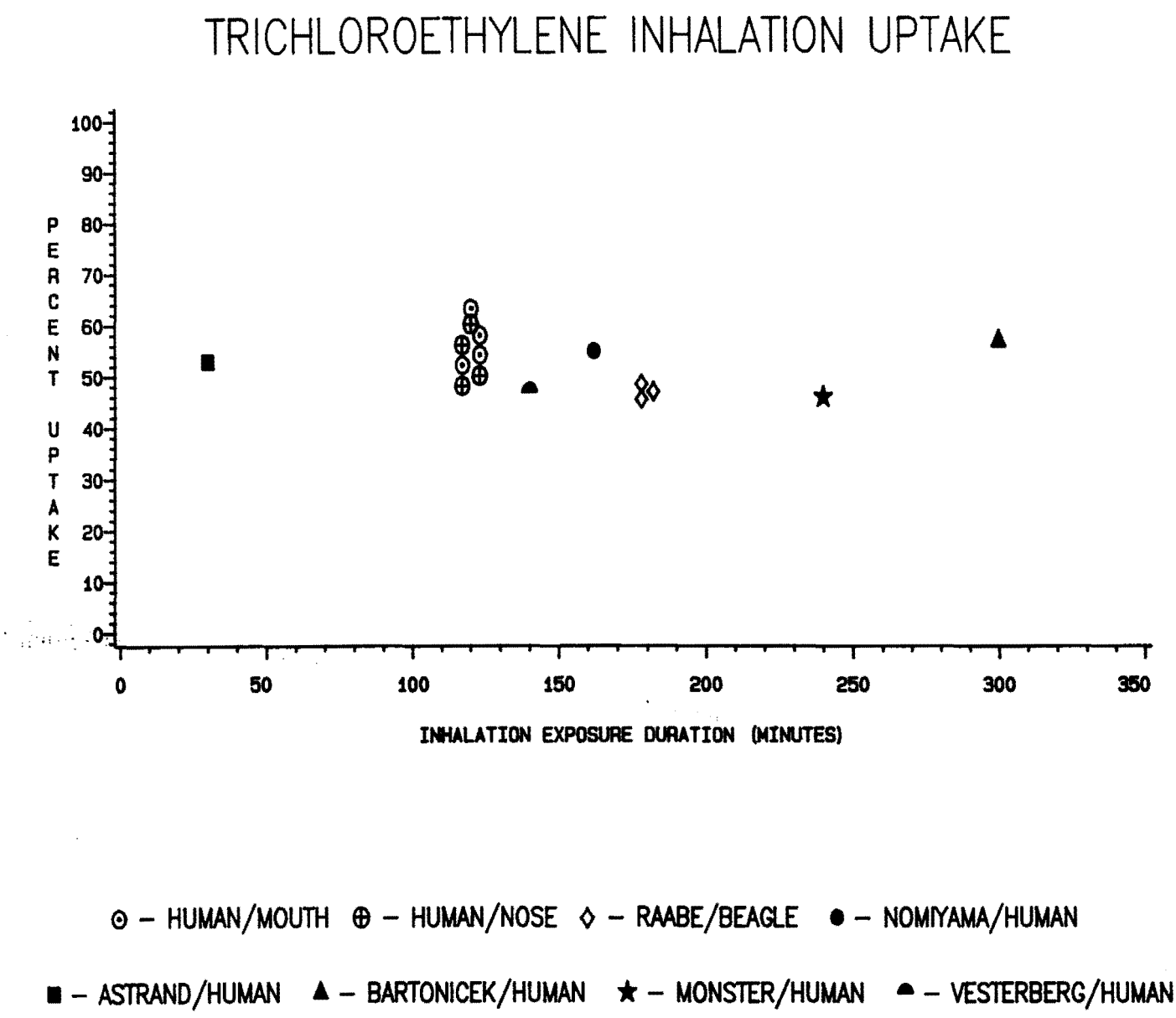


Figure 7. Comparison of observed uptake fractions of trichloroethylene vapor in human volunteers by this study, in beagles by Raabe (1986), and in human volunteers by Astrand and Ovrum (1976), Nomiyama and Nomiyama (1974), Bartonicek (1962), Monster et al. (1976), and Vesterberg et al. (1976) with respect to duration of exposure.

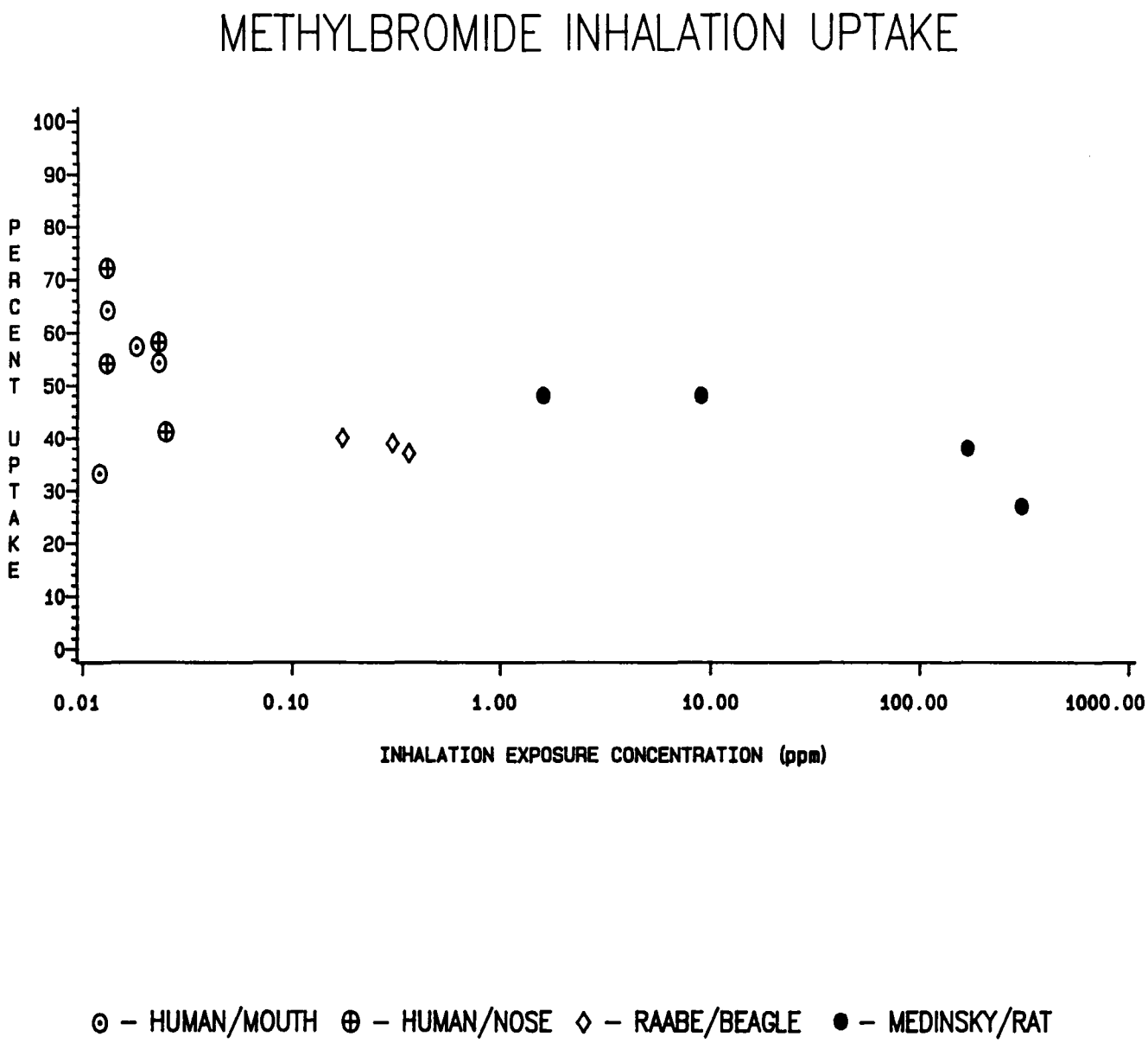


Figure 8. Comparison of observed uptake fractions of methyl bromide vapor in human volunteers by this study, in beagles by Raabe (1986), and in reported studies with Fischer-344 rats by Medinsky et al. (1985) with respect to exposure concentration.

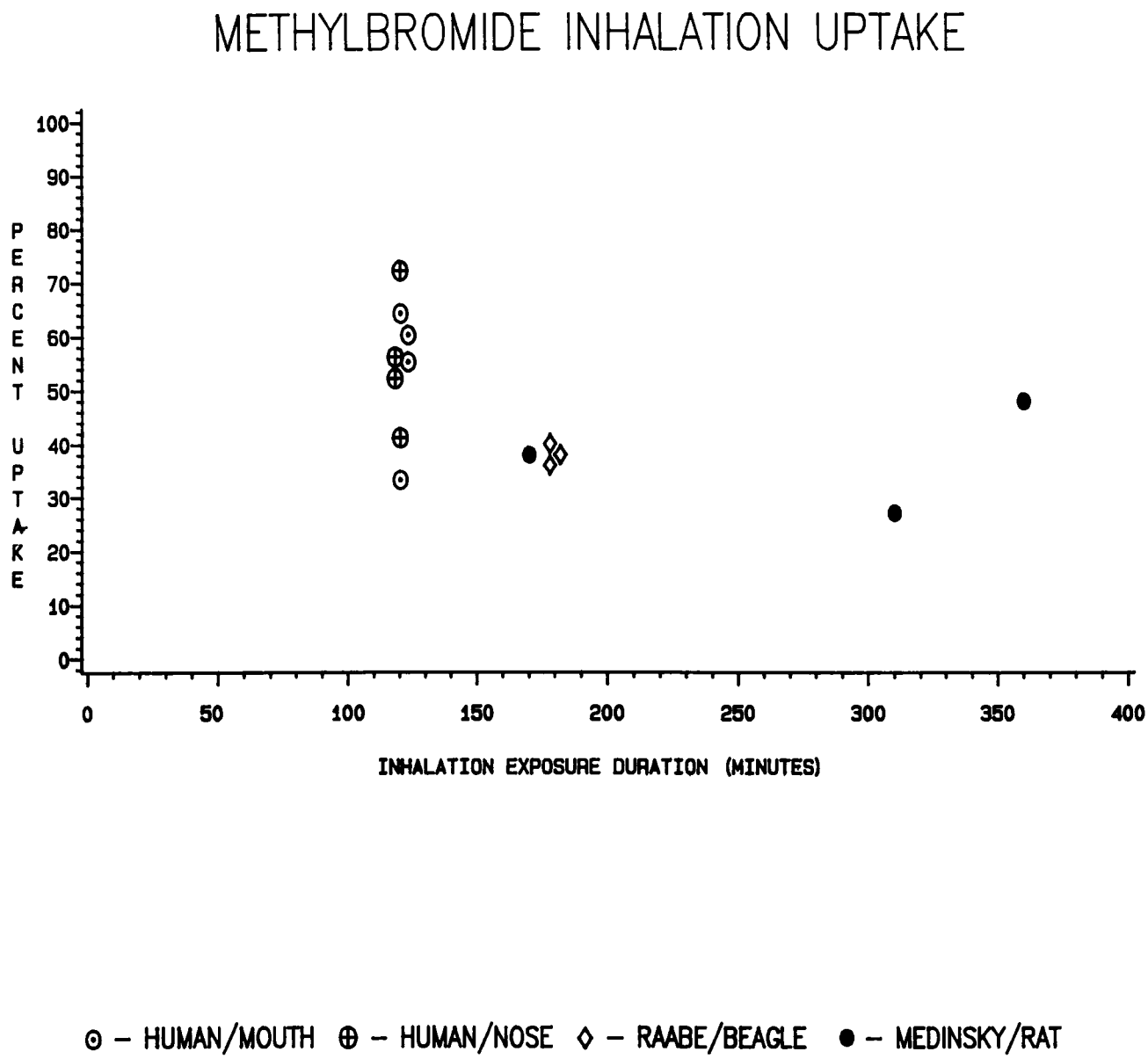


Figure 9. Comparison of observed uptake fractions of methyl bromide vapor in human volunteers by this study, in beagles by Raabe (1986), and in reported studies with Fischer-344 rats by Medinsky et al. (1985) with respect to duration of exposure.

molecules in this study); inhalation of these small particles has been calculated and measured to lead to essentially 100% deposition in the respiratory airways (Harley and Pasternack, 1972). Uptake of xenobiotic vapors at the respiratory epithelium is apparently limited to regions of ready transport and circulation such as in certain nasal membranes and primarily in the alveolar region of the lung. The effective accommodation coefficient (fraction of molecules hitting surface that adsorb) for diffusive adsorption must be much less than unity for these vapor molecules contacting the moist epithelium of the respiratory airways. In contrast, the accommodation coefficient is unity for aerosol particles contacting the moist wall of the respiratory tract. Alternatively, adsorbed vapor molecules readily desorb from the airway epithelium after collection.

These results indicate that inhalation uptake is primarily a ventilation process dependent upon pulmonary ventilation and the diffusivities of the respective vapors in air within the lung. The lung is not a well mixed compartment as has been assumed in some mathematical models, but has diffusion gradients from the incoming vapor flow to the alveolar surface where the concentration is lowest. Metabolic processes determine the extent of clearance of each chemical in the body which is reflected in the concentration in blood coming via the pulmonary artery to the lungs. Higher residual blood concentration will tend to yield lower uptake fractions. However, the low concentrations involved in this study should result in efficient metabolic clearance, so that the rate limiting process is the diffusion within the lung. This is shown during exercise in which the more than double minute volumes resulted in increased tidal volumes and enlarged lung parenchymal air spaces during inhalation. Because the diffusion distances were larger, the uptake fraction was lowered, even though the blood flow increased as minute volume increased. The formaldehyde with its much higher diffusivity than the other vapors, had the highest uptake, about equal to the maximum expected in the total respiratory tract.

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APPENDIX : Sample Worksheets for Uptake Measurement

The sample worksheets presented are for trichloroethylene (C_2HCl_3) exposure #9 identified as ARB_HUMAN_TCE_EXP#9 and for methyl bromide (CH_3Br) exposure #38 identified as ARB_H_METHYLBROMIDE#38. The file-names for each worksheet included the vapor and exposure number. The worksheets were developed using the spread-sheet program C-CALC on the Data General MV-8000 at LEHR. The data and results for each exposure were separated into 15 titled columns; columns A to O. The area bounded by rows 1 and 6 and columns A and C identify the subject's initials, compound name, exposure date and time, and exposure route. Rows (1-3) columns F and G were labeled "BLANK DPM". The data for control blanks in DPM for duplicate samples of 1.0 ml ethyl alcohol or chloroform + 19.0 ml 3a70B liquid scintillation cocktail appear in columns F and G . Data for 1.0 ml of $^{14}CO_2$-absorbing cocktail + 19.0 ml Carbon-14 cocktail were virtually identical so only the alcohol blank was used . The C_2HCl_3#15ABS worksheet represented the way in which trichloroethylene, benzene, formaldehyde, and chloroform vapors were studied; the first two bubblers had acidified ethyl alcohol and the third bubbler had Carbon-14 cocktail in each case. The methyl bromide studies utilized chloroform in the first two bubblers instead of alcohol.

DESCRIPTION OF DATA SHEET

Column (A): Bubbler #

A total of 21 bubblers were used per exposure in a set of three bubblers per interval. The first two bubblers were filled with vapor alcohol or chloroform and the third bubbler with Carbon-14 cocktail.

Column (B): Exposure interval

The experiment times were divided into seven collection intervals, 30 minutes each. The vapors were collected for 30 minutes before and after the exposure to measure the concentration of vapor in the inhaled air. During the exposure, the exhaled vapor and CO_2 were collected for two hours during

the exposure and for 30 minutes immediately after the exposure (clearance time). In the benzene exercise study, the collection time was 15 minutes instead of 30 minutes.

Column (C): Bubbler tare weight (g)

Bubbler weight (g) empty.

Column (D): Bubbler final weight (g)

Bubbler weight (g) with vapor or CO_2 trapping agents.

Column (E): Bubbler total volume (ml)

Volume (ml) = {bubbler final weight (g) - bubbler tare weight (g)} / Density
Density of trapping agents: Alcohol = 0.8065, Chloroform = 1.4459, and Carbon-14 cocktail = 0.9256.

Ex: Vol (ml) of alcohol in bubbler # 13 = (496.76 -401.16) / 0.8065 = 120.54

Column (F) & Column (G): DPM / ml for aliquot A and B respectively

Two one ml aliquots were taken from each bubbler and were counted with 19 ml of 3a70B liquid scintillation cocktail.

Column (H): Bubbler nCi / ml

nCi/ml = { Average sample (DPM/ml) - Average blank (DPM/ml) } / 2220

Ex: nCi/ml = (5345.35 + 5332.95 - 28 - 31) / 4440

Column (I): Total bubbler nCi without correction

Total nCi = Total volume (ml) x nCi/ml

Ex: Total nCi = 120.54 x 2.39 = 288.30

Column (J): Bubbler efficiency (TCE and other vapors except methyl bromide)

E= (nCi bubbler #1 - nCi bubbler #2) / nCi bubbler #1

Ex: E= (288.3 - 25.64) / 288.3 = 0.911

Column (J): Total methyl bromide (2) & Total CO_2 (3)

For methyl bromide and CO_2 calculation, the following equations were used.

M + C = Activity nCi (b1 + b2 + b3) (1)

87.5 M + 5C = b1 x 100 (2)

C = Activity nCi (b1 + b2 + b3)- M (3)

(M= Methylbromide, C= CO_2, b= bubbler)

Ex: M + C = (48.08 + 6.54 + 0.87) = 58.98 (1)

87.5 M + 5C = (48.08) x 100 (2)

M = 54.92 nCi

C = (48.08 + 6.54 + 0.87) - 54.92 = 0.08 nCi (3)

Column (K) : Corrected nCi/ bubbler (TCE & others except methyl bromide)

C.b (nCi) = bubbler nCi/ Average efficiency of bubblers for pre and post-test run.

Ex: Corrected nCi (b1) = 288.3/0.909 = 317.18

Column (K): nCi vapor or CO_2 / liter (Methylbromide data sheet)

nCi/liter = Total nCi per 30 minutes / total air breathed per 30 minutes

Ex: nCi/liter methyl bromide = 54.92 / 163.4 = 3.05

Column (L): nCi Vapor or CO_2 / liter (TCE data sheet)
(Same calculation as column (K) methyl bromide data sheet)

Column (L): Volume of air (l) breathed / interval (methyl bromide data sheet)

Total amount of air breathed by the subject per 30 minute interval during the exposure = Lung minute volume (l) x breathing rate x 30 (breaths/minute)

EX: Total air breathed (l) = 0.363 x 15 x 30 = 163.4 (0-0.5 hours)

Column (M): Volume of air (l) breathed/ interval (TCE data sheet)
(Same calculation as column (L) methyl bromide data sheet)

Column (M): Total nCi Exhaled vapor (1) and CO_2 (2) (methyl bromide data sheet)

Total exhaled vapor per interval nCi = total air breathed (ml) x nCi/l
nCi = 163.4 x 3.051= 498.53

Total CO_2 Exhaled per interval nCi = { A - (BxC)} x 30 , where
A = nCi CO_2 without correction during the exposure.
B = nCi/l based on the average activity in the third bubbler in pre and post-exposure test.
C = 1 - uptake fraction.

Ex: CO_2 (nCi) / first interval = { -0.02 - 0.06 (1-0.582)} x 30 = 4.35

Column (N): Total vapor exhaled or CO_2 per interval (TCE data sheet)
(Same as column (M) methyl bromide data sheet)

Column (N): % uptake (methyl bromide data sheet)

% uptake = (A - B) x 100 / A

Where A = Average nCi/l pre & post-test (Air concentration of vapor without the subject)

B = nCi/l (air concentration of vapor during the exposure)

EX: % Uptake (0-0.5 hours) = (7.44 - 3.33) x 100 / 7.44 = 55.2

Column (O): % Uptake (TCE data sheet)
(Same calculation as column (N) methyl bromide data sheet)

Worksheet: (186) ARB_H...AN_TCE_EXP#9 Range: A1..O52

EXPOSURE#	9	EXPOSURE	ARB		BLANK(A)	BLANK(B)		AVERAGE				Alcohol	14C COCK.	
DATE	1/16/1987	ROUTE	HUMAN		DPM/ml	DPM/ml		PRE AND				density	density	
TIME	10:30 AM	MOUTH	STUDY		28	31		POST-TEST				0.8065	0.9256	
NAME:	B.L.							EFFIC %						
COMPOUND:	TCE							90.90						
(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)	(K)	(L)	(M)	(N)	(O)
								Total(nCI)	BUBBLER	CORRECTED	nCI/L Vapor(1)			
BUBBLER	EXPOSURE	BUBBLER TARE WEIGH	BUBBLER FINAL	BUBBLER TOTAL	BUBBLER ALIQUOT(A)	BUBBLER ALIQUOT(B)	BUBBLER nCI/	BUBBLER WITHOUT	EFFIC.	nCi/	CO2(2)	VOLUME OF AIR(L)	TOTAL(NCI) EXHALED	% UPTAKE
#	INTERVAL	(g)	(g)	VOL.(ml)	(DPM/ml)	(DPM/ml)	(ml)	CORRECTION	%	BUBBLER	(Without Correction	/INTERVAL BREATHED	VAPOR(1) CO2(2)	
13.00	PRE	401.16	496.76	180.54	5,345.35	5,332.95	2.39	298.30	91.11	317.18	7.03	45.00		
14.00	TEST	399.40	497.21	123.28	483.60	498.90	0.21	25.64		28.21				
15.00		400.85	529.03	140.48	324.65	323.95	0.13	18.66		-6.99	-0.16			
16.00	0.5	396.80	491.30	117.17	2,701.00	2,095.90	1.07	125.03	91.10	137.56	3.05	262.22	799.90	55.27
17.00	HOUR	401.20	501.23	124.03	226.00	231.20	0.09	11.12		12.24			-0.07	
18.00		399.80	527.05	137.48	165.90	154.80	0.06	8.10		-3.02	-0.07		-0.17	
19.00	1	400.00	495.10	117.92	2,508.60	2,503.80	1.12	131.55	89.97	144.73	3.25	248.45	80 .44	52.40
20.00	HOUR	400.65	496.00	118.23	280.30	274.10	0.11	13.19		14.51			-0.07	
21.00		400.15	533.15	143.69	243.20	237.80	0.10	13.66		0.47	0.01		0.14	
22.00	1.5	400.70	495.20	117.17	2,591.80	2,593.30	1.15	135.28	89.96	148.83	3.34	260.32	86 .03	51.05
23.00	HOUR	400.70	496.10	118.29	283.80	285.10	0.11	13.58		14.95			-0.07	
24.00		400.60	533.70	143.80	298.80	282.90	0.12	16.60		3.02	0.07		6.41	
25.00	2.0	399.45	494.20	117.48	2,698.70	2,677.20	1.20	140.68	89.42	154.77	3.49	264.29	92.41	48.82
26.00	HOUR	403.20	498.70	118.41	309.40	307.70	0.13	14.88		16.38			-0.09	
27.00		400.85	533.60	143.42	354.30	345.70	0.14	20.71		5.82	0.13		4.29	
28.00	CLEARANCE	404.10	498.85	117.48	298.20	293.00	0.12	13.92		15.32	0.44	245.22	107.90	
29.00		393.20	488.65	119.35	189.70	189.70	0.05	5.34		5.88				
30.00		395.70	528.50	143.47	197.80	190.60	0.07	10.64		5.30	0.12		38.89	
31.00	POST-	399.95	498.90	115.25	5,224.20	5,221.80	8.34	269.62	90.69	296.63	6.61	45.00		
32.00	TEST	403.60	498.90	118.16	506.80	495.90	0.21	25.12		27.63				
33.00		390.85	520.70	140.29	309.10	322.60	0.13	18.73		-6.39	-0.14		% UPTAKE	(0.5,1,1.5
														2.0 hours)
							PRE &							
						Bubbler#3	Post	AVERAGE	CONTAM.	nCI/l	-0.15		AVE=	51.89
							VAPOR	AVERAGE	VAP.CON	nCI/l	6.82		SE=	1.35
							VAPOR	TOTAL	L/2 hrs	BREATHED	1,035.28		TCA	S.P
							VAPOR	TOTAL	nCI	INHALED	7,060.21		mCi/mmol	10.00
							VAPOR	TOTAL	nCi	EXHALED	3,397.78		AIR CONS.	
							VAPOR	AVERAGE	UPTAKE	%	51.87		(PPb)=	16.78
						TOTAL	CO2	2 HOURS	%	INHALED	1.57		INHALED	
						CLEARANCE	CO2	0.5 HOURS	%	INHALED	0.41		ug=	94
												% UPTAKE	1.0, 1.5,	2.0 hours)
													AVE:	50.76
													SE:	1.04

Worksheet: (180) ARB_H_METHYLBROMIDE#38 Range: A1..O50

EXPOSURE#	38	EXPOSURE	ARB		BLANK(A)	BLANK(B)		PRE AND			CHCL3	14C COCK.		
DATE	5/14/87	ROUTE	HUMAN		DPM/ml	DPM/ml		POST-TEST			density	density		
TIME	1:26 pm	NOSE	STUDY		26	31		EFFICIENCY			1.4459	0.9256		
NAME:	P.W.						%	87.52						
COMPOUND:	METHYL BROMIDE (CH3BR)													
(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)	(K)	(L)	(M)	(N)	
BUBBLER #	EXPOSURE INTERVAL	BUBBLER TARE WEIGHT	B.FINAL WEIGHT	BUBBLER TOTAL VOL.(ml)	BUBBLER ALIQUOT(A) (DPM/ml)	BUBBLER ALIQUOT(B) (DPM/ml)	BUBBLER nCi/ (ml)	Total(nCi) BUBBLER WITHOUT CORRECTION	TOTAL 1.M.B+CO2 2.M.B 3. CO2	nCi VAPOR OR CO2/ LITER	VOLUME OF AIR(L) /INTERVAL BREATHED	TOTAL(NCI EXHALED VAPOR(1) CO2(2)	% UPTAKE	
34.00	PRE	397.80	566.70	118.81	1,934.03	1,977.20	0.87	103.14	117.71		18.00			
35.00	TEST	396.70	571.60	122.96	268.34	257.84	0.11	12.99	117.88	6.55				
36.00		396.50	522.50	138.13	53.73	54.05	0.01	1.58	-0.17	-0.00				
16.00	0.5	396.70	566.85	117.68	922.70	948.51	0.41	48.08	55.49		163.40	0.03	53.82	
17.00	HOUR	401.10	582.00	125.11	147.64	141.32	0.05	6.54	54.92	3.05		498.55		
18.00		399.60	535.15	146.45	41.81	41.64	0.01	0.87	0.57	-0.02		4.26		
19.00	1	399.90	574.20	120.55	981.31	974.05	0.43	51.54	58.98		155.50	0.03	50.47	
20.00	HOUR	400.40	581.35	125.15	140.48	144.69	0.05	6.43	58.90	3.27		508.83		
21.00		400.15	536.00	146.77	43.43	44.00	0.01	1.01	0.08	-0.05		4.35		
22.00	1.5	400.40	573.75	119.89	858.99	863.29	0.38	44.97	50.40		165.50	0.02	56.74	
23.00	HOUR	400.65	582.30	125.63	111.61	115.23	0.04	4.81	51.45	2.86		473.06		
24.00		400.75	533.45	143.37	39.41	37.14	0.00	0.63	-1.05	-0.11		4.05		
25.00	2.0	399.30	573.70	120.62	1,028.02	1,038.12	0.45	54.58	64.62		171.20	0.03	47.66	
26.00	HOUR	404.65	584.35	124.29	177.48	181.82	0.07	8.46	62.24	3.46		591.99		
27.00		400.75	537.95	148.23	54.07	50.10	0.01	1.57	2.38	0.08		5.06		
28.00	CLEARANC	403.90	579.70	121.59	85.14	80.39	0.03	3.19	4.51		159.40			
29.00		393.05	571.40	123.35	38.89	43.35	0.01	0.70	3.59	0.20		31.83		
30.00		395.70	532.05	147.31	34.46	41.21	0.00	0.62	0.92	-0.01		-0.88		
31.00	POST-	399.95	570.80	118.16	1,999.12	2,005.89	0.89	105.07	122.08		18.00			
32.00	TEST	403.40	584.20	125.04	303.35	289.56	0.12	15.09	119.96	6.66				
33.00		390.75	529.50	149.90	55.72	58.11	0.01	1.92	8.12	0.12				
												%UPTAKE	(0.5,1,1.5	,2HOURS)
					THIRD	BUBBLER	Pre & Post	AVERAGE	CONTAM.	0.06		AVE=	52.17	
							VAPOR	AVERAGE	VAP.CON.	6.61		SE=	1.97	
							VAPOR	TOTAL	L/2 hrs	655.60		CH3BR	S.P	M.W
						INHALED	VAPOR	TOTAL	nCi	4,331.31		mCi/mmol	13.00	94.94
						EXHALED	VAPOR	TOTAL	nCi	2,072.43		AIR CONC.		
							VAPOR	AVERAGE	UPTAKE	52.15		(PPb)=	12.50	
						TOTAL	CO2	2 HOURS	%	0.41		INHALED		
						CLEARANCE	CO2	0.5 HOURS	%	-0.02		ug=	32	
												% UPTAKE	(1,1.5,2	HOURS)
												AVE:	51.62	
												SE:	2.68	