UCD-472-507

INHALATION UPTAKE OF SELECTED CHEMICAL VAPORS AT TRACE LEVELS

Final Report
to the CALIFORNIA AIR RESOURCES BOARD

CARB Contract No. A3-132-33
Project Term: 27 July 1984 to 27 January 1986

Otto G. Raabe, Ph.D.
Principal Investigator
Laboratory for Energy-related Health Research
School of Veterinary Medicine
University of California
Davis, California 95616

May 1986

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

ABSTRACT

When low concentrations of xenobiotic 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 for certain chemicals have previously been measured at relatively high concentrations, but have not generally been available for low concentrations approaching environmental trace levels. This project developed a methodology for assessing the potential inhalation uptake fractions and metabolic fate of chemical vapors at low concentration utilizing adult nose-breathing beagles as surrogates for people.

Quantitative measurements were made of the systemic uptake during nasal breathing of very low concentrations in dry air of six selected chemical vapors: benzene, dimethylnitrosamine, chloroform, methyl bromide, trichloroethylene, and formaldehyde. Attempted measurements of the uptake of ethylene oxide were unsuccessful because of the rapid degradation of this reactive chemical. The experimental subjects were three adult female beagles obtained from the dog colony at UC Davis; each beagle was studied with each of the six vapors. The beagles suffered no harm or pain, and they were returned to the dog colony in good health at the end of the study.

A special apparatus for the controlled inhalation exposure of individual beagles was designed, built and tested. 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 individual unanesthetized dog was immobilized in foam rubber padding and fitted with a latex mask to prevent oral breathing. Each dog was comfortable and awake during the exposures and the spontaneous breathing was normal for the resting state. Each organic vapor was produced from high specific activity radioactive carbon-14-labeled chemicals at concentrations in the range from 1.4 ppb (formaldehyde) to 594 ppb (chloroform) and the assays of the materials were done using radioanalytical techniques. The concentrations of each chemical vapor under study were measured before and after inhalation to determine uptake efficiency. Exhaled air, blood, urine, and fecal samples were used to measure the metabolic pattern of blood concentration and excretion of each chemical or

its metabolites during and after exposure. The individual exposures were three hours long in 30 minute monitoring sub-periods and the metabolic behavior of the chemicals was followed for 117 hours after exposure.

The steady state fractional systemic uptake of the total vapor was 39.5%±1.0%SE for methyl bromide, 39.8%±1.5%SE for chloroform, 42.1%+2.2%SE for benzene, 48.0%±0.8%SE for trichloroethylene, 53.6%±2.1%SE for dimethylnitrosamine, and 54.4%±0.9 %SE for formaldehyde. 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. Similar resting uptake fractions are expected for people with somewhat lower uptake fractions with increased activity and breathing.

After the three-hour exposure the ^{14}C blood concentrations as percentage of total inhaled vapor were 1.6%±0.1% SE for methyl bromide 3.3%±0.6% SE for chloroform, 9.2%±5.4% SE for benzene, 2.5%±0.4% SE for trichloroethylene, 5.6%±0.4% SE for dimethylnitrosamine, and 12.4%±4.7% SE for formaldehyde. Clearance half-times after exposure based upon the radiocarbon label ranged from about 10 hours or less for dimethylnitrosamine, chloroform, and formaldehyde to about 40 hours for methyl bromide.

Previously reported uptake measurements for trichloroethylene and benzene by people at much higher concentrations (about 100 ppm) agreed within about 15% with the results of the uptake measurements in beagles for these two vapors at near environmental concentrations (about 0.1 ppb). A previously reported study of the uptake of methyl bromide by rats measured uptake of 48%±2%SE at 1.6 ppm compared to 39.5%±1.0%SE for beagles at about 0.3 ppm.

The results indicate that the respiratory uptake of the inhaled xenobiotic vapors at concentrations from about 0.1 ppb to about 100 ppm depended primarily on respiratory ventilation and vapor diffusivity with uptake primarily in the lung parenchyma. Similar uptake is therefore expected for all mammalian species under dynamically similar conditions. Increased or altered respiratory patterns are expected to alter uptake, such as reducing uptake fraction during exercise.

ACKNOWLEDGEMENTS

The principal technical staff who contributed to this project are listed below along with their major area of expertise and involvement:

Mohammed Al-Bayati - Toxicology and Laboratory Animal Science
Fiorella Gielow - Radioanalytical Chemistry
David Silberman - Analytical Chemistry
Stephen Teague - Inhalation Exposure Methodology

In addition several other staff members and students also contributed including Scott Folwarkow, Dale Uyeminami, Debbie Johnson, and Moire Robertson. Don Ballard and Ed Hinz provided mechanical, electrical, and electronic support. Steve Maslowski supervised the animal care, and Dr. Gary Cain was the project veterinarian. Victor Pietrzak provided computer expertise. Cecilia Bauernhuber and Sue Schafer handled administrative and fiscal matters. Charles Baty and Pam Carroll typed reports, tables, protocols and correspondence. Personnel of the Laboratory Services Section, Aerometric Data Division, California Air Resources Board, Robert Kuhlman (Manager), Debbie Okamoto, Kevin Mongar, and Bruce Oulrey, measured background room concentrations of vapors.

This report was submitted in fulfillment of California Air Resources Board Interagency Agreement No. A3-132-33 entitled "Inhalation Uptake of Selected Chemical Vapors at Trace Levels" with the University of California, Davis, under the sponsorship of the Air Resources Board. The beneficial guidance, support, and contributions of Mr. Dane Westerdahl and Dr. Joan Denton of the Biological Effects Research Section, Research Division of the California Air Resources Board, is gratefully acknowledged. Work was completed on 27 January 1986.

DISCLAIMER

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SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

The uptake and early systemic distribution and clearance of six inhaled organic vapors was measured in individual awake, adult female beagles. The vapor concentrations in dry air were all at trace levels less than one ppm, and as low as 1.4 ppb for formaldehyde. The steady state fractional systemic uptake of the total vapor was 39.5%±1.0% SE for methyl bromide, 39.8%±1.5% SE for chloroform, 42.1%±2.2% SE for benzene, 48.0%±0.8% SE for trichloroethylene, 54.4%±0.9 %SE for formaldehyde, and 53.6%±2.1% SE for dimethylnitrosamine. Attempted measurements of the uptake of inhaled ethylene oxide were unsuccessful because of the extremely rapid degradation or polymerization of this reactive chemical.

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. Even for formaldehyde, the vapor with the highest diffusivity of those studied, the nasal uptake was apparently a small fraction of that which was inhaled. This may be explained in part for formaldehyde by the fact that the normal concentration in body fluids is higher than the concentration in air in these studies (or in typical environmental exposures). Similar resting uptake fractions for these six vapors are expected for people. The uptake fractions are also expected to be lowered by about one-fifth in the case of higher ventilation rates and volumes associated with strenuous activity in people.

After the three-hour exposure the blood concentrations as percentage of total inhaled vapor were 1.6%±0.1%SE for methyl bromide, 3.3%±0.6%SE for chloroform, 9.2%±5.4%SE for benzene, 2.5%±0.4%SE for trichloroethylene, 12.4%±4.7%SE for formaldehyde, and 5.6%±0.4%SE for dimethylnitrosamine. Clearance half-times after exposure, based upon the radiocarbon label, ranged from about 10 hours or less for dimethylnitrosamine, formaldehyde, and chloroform to more than 40 hours for methyl bromide. Small quantities of ^{14}C associated with the inhaled formaldehyde exhibited body retention lasting several weeks after exposure. These difference were caused by differences in metabolic pathways and rates among these chemicals.

The uptake fractions found in this study for beagles can be used directly for estimation of the uptake in people of these six xenobiotic chemical vapors in environmental exposures at trace levels for risk assessment. These values can also be used for related non-reactive chemicals. In the case of a xenobiotic chemical vapor of unknown relationship to those studied, the first approximation of the uptake fraction would be 50% of the inhaled dosage, but a much higher uptake may result for reactive vapors or gases such as ethylene oxide.

Future work using the methods developed in this project can be done with human volunteers since it is possible to work at very low vapor concentrations and calculate accurately the predicted radiation dose from the ^{14}C exposure. It might be possible to study ethylene oxide with these methods if a non-reactive pressure vessel were used. A teflon-lined compressed air tank might prevent the degradation of the ethylene oxide that precluded measurements of uptake in this project.

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 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 (Roach, 1966; 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-air and tissue-blood partition coefficients, effective alveolar concentration, distribution of the dissolved chemicals in the body, and alternative fates of elimination or enzymatic metabolic chemical alteration (Leibman, 1983; Fiserova-Bergerova, 1983a; Fiserova-Bergerova, 1983b). Experimental measurements are needed 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 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 do not provide information on the fraction of inhaled vapors that enter the blood, however. Rather they help in describing clearance after uptake.

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 all of the 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.

Organic vapors of the types to be studied are found in California air as reported for 1985 in the 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. methylchloroform had an average of 1.9 ppb and a maximum of 47 ppb. Other vapor

This project was initiated on July 27, 1984, to obtain needed information on the uptake of trace levels in air of several types of pollutant organic vapors utilizing an experimental animal model. Quantitative measurements were made of the systemic uptake during nasal breathing of low concentrations in air of six

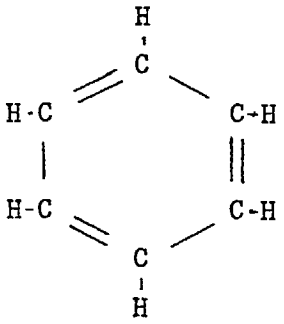
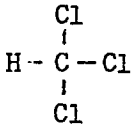
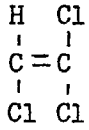
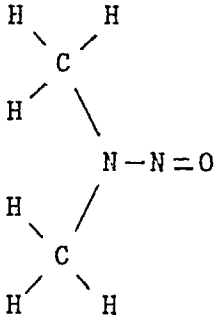
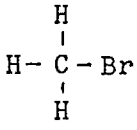
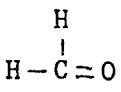
selected chemical vapors: benzene, dimethylnitrosamine, chloroform, methyl bromide, trichloroethylene, and formaldehyde (Table 1). Measurements of ethylene oxide were also attempted but were not successful. The experimental subjects were three purebred adult female beagles obtained from the dog colony at UC Davis.

The project was designed to be conducted in three phases: (1) construction of the exposure system, (2) testing of the exposure system, and (3) measurement of the uptake and metabolism of seven organic chemical vapors.

A special apparatus for the controlled inhalation exposure of individual beagles was designed, built, and tested. It consisted of a demand valve-based inhalation exposure system that separated inhaled and exhaled gases. The special method of concurrent flow spirometry (Raabe and Yeh, 1976) was adapted for use with a mass flow meter to measure the volumes of air inhaled and exhaled during the exposures. Each individual unanesthetized dog was immobilized with foam rubber padding in an upright lying position and fitted with a latex mask to prevent oral breathing. The organic vapor was produced from high specific activity carbon-14 labeled chemicals at concentrations in the range from about 1 to 600 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 three hours long, and the metabolic behavior of the chemicals was followed for up to 117 hours after exposure.

This work was performed in the new Toxic Pollutant Health Research Laboratory (TPHRL) on the campus of the University of California in Davis, a well equipped total-containment, inhalation-toxicology laboratory that is uniquely suited to this study involving inhalation of radioactively labeled vapors at very low chemical concentrations. The project began 27 July 1984 and was completed on 27 January 1986.

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

CHEMICAL	STRUCTURE	MOLECULAR WEIGHT (g/mole)	DIFFUSIVITY (cm^2/s)
BENZENE C_6H_6		78.11	0.13
CHLOROFORM $CHCl_3$		119.39	0.13
TRICHLOROETHYLENE C_2HCl_3		131.40	0.12
DIMETHYLNITROSAMINE $(CH_3)_2N_2O$		74.08	0.13
METHYL BROMIDE CH_3Br		94.95	0.15
FORMALDEHYDE CH_2O		30.03	0.23

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 consequent risk to the public associated with the inhalation of air containing low concentrations of certain xenobiotic and potentially toxic chemical vapors.

One of the objectives of this project was to develop a new methodology including the necessary experimental equipment for measuring the uptake, excretion, and metabolism of environmentally important xenobiotic organic vapors inhaled at very low concentrations utilizing radiolabeled chemicals and an experimental animal model (laboratory beagle). The biological behavior of seven representative chemicals, including benzene, dimethylnitrosamine, chloroform, methyl bromide, trichloroethylene, ethylene oxide, and formaldehyde, was to be measured during and after nasal inhalation by three individual beagles at rest. Measurements of uptake, excretion, and exhalation of vapors were to be made with three different beagles to provide appropriate estimates of biological variability for each of the characteristic parameters that was measured. The data were to be scaled with respect to species differences to predict the behavior of these vapors if inhaled by people, using relevant interspecies and biochemical information.

The principal results were to include: (a) fractional systemic uptake rate relationships for each of the vapors studied as a function of time from beginning of exposure, (b) the temporal retention and distribution in blood and excreta with respect to the uptake fraction, (c) the exhalation rate subsequent to up to three hours of exposure for up to 69 hours post-exposure, and (d) the rationale to be used to scale results to potential human exposures to these chemicals.

Another goal was to provide the methodology for the rapid evaluation of the uptake and biological behavior of other xenobiotic chemical vapors that may become of interest to the Air Resources Board.

TECHNICAL PLAN

The project was subdivided into three phases ending with the preparation of the final report and executive summary for the Air Resources Board. The first two phases were those associated with development of the methodology and equipment for making the vapor uptake measurements. The third phase consisted of the measurements themselves and included mathematical modeling activities.

Purebred beagles are an ideal experimental animal model for vapor inhalation uptake experiments, as well as for other studies intended for scaling to expected responses in people. Nine key reasons are summarized below:

(1) Health characteristics: Purebred beagles, born and raised at our lab, are very healthy and receive excellent veterinary care. They have documented health and genetic records, so that their health status is not in doubt.

(2) Serial samples: Serial samples of blood and urine were required over a 24-hour period and several samples are needed during the three hour exposure period; smaller animals would not be usable because serial samples of sufficient volume for measurements of the radiolabeled chemicals could not be obtained.

(3) Respiratory physiology: Breathing characteristics of the dog at rest are closer to those of people than smaller animals. Rodents typically inhale 100 very shallow breaths per minute while people and dogs at rest inhale about 10 to 20 deep breaths per minute.

(4) Repeatability of subjects: Biological variability between individuals is particularly great in experiments with small rodents, and rodents would have to be sacrificed to provide the necessary blood samples for a vapor deposition study; on the other hand the use of individual beagles allowed the very same dogs to be exposed to all of the vapors so that the effect of individual variability could be minimized and the uptake of the different vapors could be better compared.

(5) Ease of use: Research with laboratory beagles was facilitated because these dogs are docile, cooperative, and of convenient size; monkeys are incredibly

uncooperative and difficult to use so that experimental results with monkeys could be less reliable.

(6) Ease of care: We have an ongoing health program for over 200 beagles with a full-time veterinarian on duty at our laboratory.

(7) Appropriateness for scaling to people: With respect to anatomical size and physiological features, scaling factors are well documented and allow meaningful predictions of the expected response in people based upon beagle results. Biological characteristics of purebred beagles are well known and well-documented. UC Davis LEHR has published two books on the use of beagles in biomedical research (Andersen, 1970; and Shifrine & Wilson, 1980).

(8) Reduced biological variability: Only three animals were needed to obtain statistically useful data since biological variability among individual dogs in controlled experiments is much less than among rodents.

(9) Ease of exposure and respiratory monitoring: Each dog could be studied carefully as an individual (much as a human would be studied) and exposure conditions and respiratory behavior could be carefully measured and monitored.

FACILITIES

Unique and specialized new facilities at UC Davis were used to perform these studies. The new Toxic Pollutant Health Research Laboratory (TPHRL) is a total containment and safety-oriented toxicology laboratory where inhalation studies with radioactive and toxic materials can be safely performed and where the necessary equipment, radiochemical laboratories with Packard liquid scintillation counter, exposure rooms, and animal holding rooms are located. The TPHRL is a component of the Laboratory for Energy-related Health Research (LEHR), an Organized Research Unit of the University of California, Davis, administered by the School of Veterinary Medicine.

The laboratories in the Toxic Pollutant Health Research Laboratory (TPHRL) have a specially designed ventilation system that incorporates four levels of filtration that includes absolute filters and activated charcoal filters. The activated charcoal filtration system prevented releases of the radiolabeled vapors to the environment during these experiments. Measurements were made of the background concentrations in the exposure room of TPHRL by the Laboratory Services Section, Aerometric Data Division, California Air Resources Board (Robert Kuhlman, Manager; Debbie Okamoto, Kevin Mongar, and Bruce Oulrey). The range of two samples was 1.4 to 1.6 ppb benzene, 0.06 to 0.08 trichloroethylene, and 0.02 ppm chloroform. These concentrations are below the average concentrations of these vapors normally found in air in California.

The TPHRL has a Packard Tri-Carb 300C Liquid Scintillation Counter that was used in this study for ^{14}C counting with automatic quench corrections. It is located in the Sample Chemistry Laboratory. This new instrument is programmable and featured automatic quench and efficiency corrections.

Data collected in this project were processed and evaluated utilizing a Data General MV/8000 3 megabyte computer system with 178 megabyte disk. This system has 32 asynchronous communication ports, 20 terminals, 1800 L/M Printer, four 200 cps printers, Cal-Comp 563 Plotter, 2/75 ips Vacuum Column, 1600/800 bpi 9 track Mag Tape Drives, two 300 megabyte Ampex D9300 Disk Drives, 600 card/min reader, Tektronix 4014 Graphics Terminal, and Univac 1710 card punch.

METHODS

Exposure System

The exposure system was designed and built utilizing a two-stage demand regulator-based inhalation exposure system that separated inhaled and exhaled air (Figure 1). Each individual awake female beagle was comfortably immobilized in an upright lying position using foam rubber restraint and fitted with a latex mask to prevent oral breathing. All exposures were via a nose exposure connection to a second-stage demand regulator valve (Figure 2). This valve is designed to preclude rebreathing of inhaled and exhaled air and to minimize the external dead space (rebreathed air space). Since the mask placed on the dog prevented oral breathing and situated the nares of the dog directly up to the valve body, the dead space in this system cannot exceed the breathing zone portion of the valve whose physical volume was 7 mL or about 6% of the normal tidal volume during breathing. 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 dog to maintain normal breathing. A pressure differential of only about 0.5 cm water column was required to open the breathing valve, while the exhaust line was maintained near ambient pressure by the spirometer. No anesthetics were used and each dog received careful attention to insure a state of normal awake breathing during the exposure period.

Small quantities of high specific activity ^{14}C-labeled chemicals of each of the seven chosen for study were purchased from commercial suppliers (New England Nuclear, Boston, Massachusetts, and Pathfinder Laboratories Inc., St. Louis, Missouri). For each compound all carbon positions were labeled, although the the overall compounds were not completely free of non-radioactive ^{12}C. The ^{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 pressure vessel described below) and pressurized utilizing argon gas as an inert blanket. This provided a stable inert source of the vapor prior to each exposure and minimized the possibility of degradation between exposures. (Formaldehyde proved to be unstable at room temperature even in an argon atmosphere.) Just prior to use,

FIGURE 1

Schematic illustration of the inhalation exposure system designed and built in Phase I of this project to study the uptake of trace levels of organic vapors inhaled by individual beagles over a three hour period.

VAPOR UPTAKE EXPOSURE SYSTEM

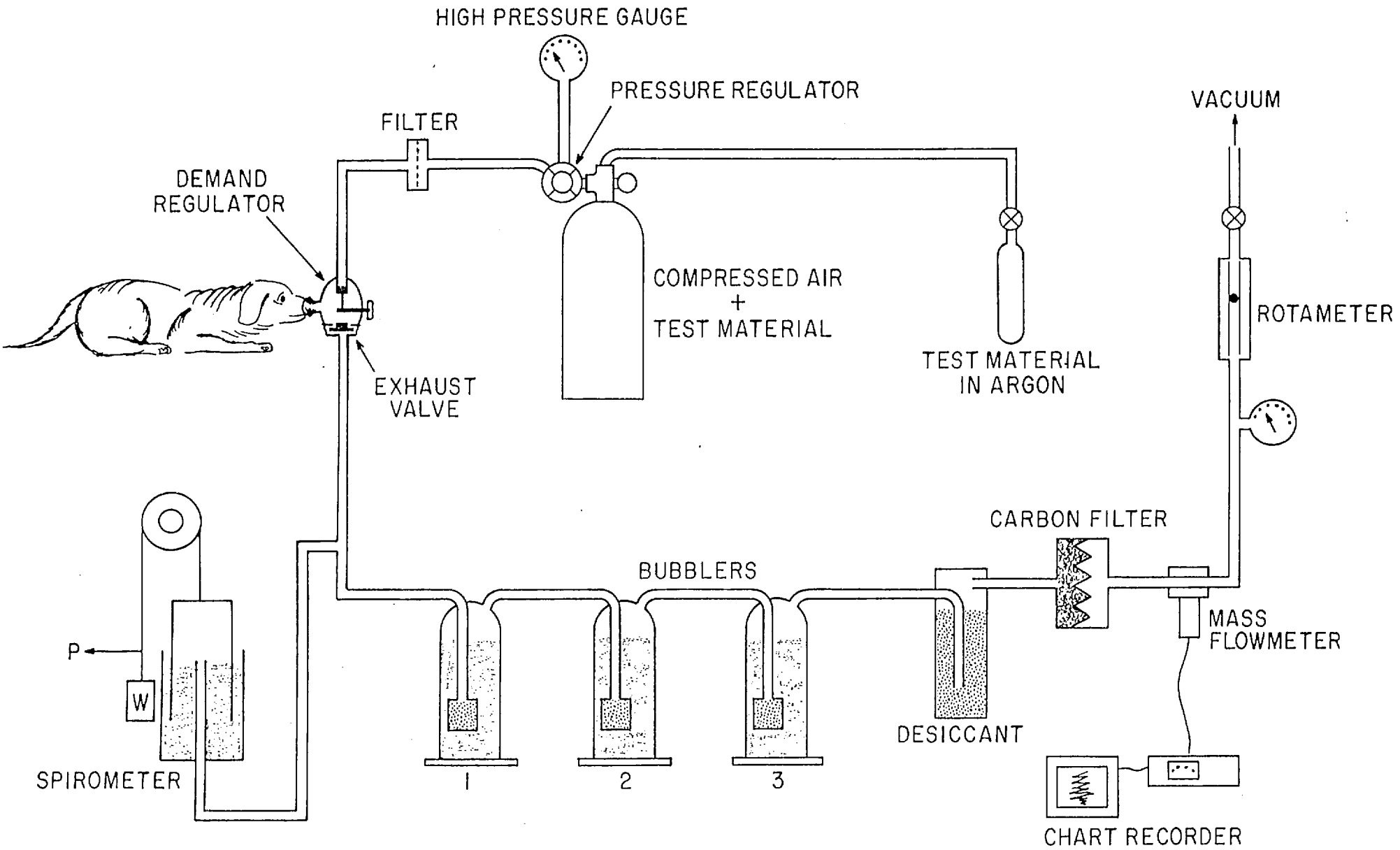
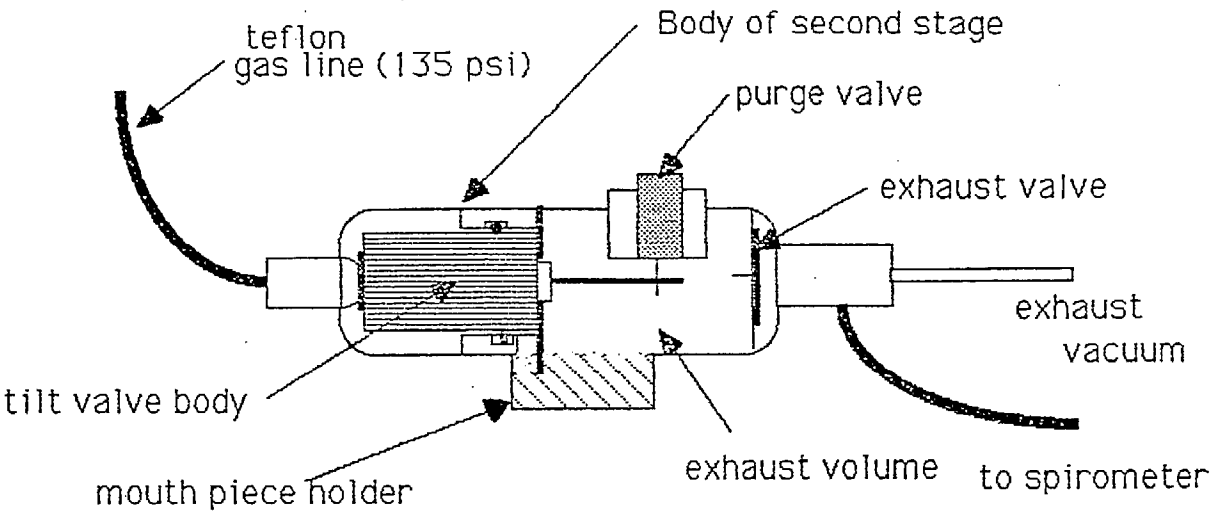


FIGURE 2

Schematic illustration of the demand-regulator breathing valve used in this study to exposure individual beagles to selected chemical vapors.



(striped part shows dead space volume)

Tekna T-2100 B/t-2100 BX second stage regulator.

Tilt valve secton = 5 ml
Mouth piece holder = 7 ml
Exhaust space = 36 ml

small quantities of the chemicals were transferred to a large compressed air cylinder (SCUBA tank) and mixed with very clean compressed air (zero air) at high enough pressure to operate the breathing valve for three hours and at the chosen concentration. The relative humidity was less than 5% at the valve.

The concentrations that were chosen for study depended primarily on the availability of high specific activity ^{14}C-labeled chemicals. The general goal was to use concentrations that were smaller than 500 ppb and as low as 0.1 ppb, if possible, to approximate environmental levels without sacrificing accuracy of radioassay. Since each chemical vapor was stored in a separate lecture bottle 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 sampling 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 conc. HCl/gallon) was usually used in the first two bubblers. 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 the three-hour exposure period the apparatus was switched to allow the dog to inhale only clean air, while the exhaled air is then monitored for 30 minutes longer.

The exposure apparatus delivered the gas or vapor of interest to the dog using a demand regulator valve and provided for measurement of the respiratory minute volume of air and breathing frequency of the animal. All parts of the exposure unit were clean metallic, glass, high-density plastic, silcone 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 air (zero air). A second compressed air tank with regulator (not shown in Figure 1) containing clean air (zero air) was connected with a switching valve (not shown) 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 2 (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 which was fitted with two chrome plated brass Imperial-Eastman polyflow quick-disconnect fittings (Imperial Clevite Inc., Chicago, Illinois) to accommodate two teflon exhaust lines. One line was 0.95 cm O.D. teflon 2 meters long with volume of 63 mL and was connected to a one liter spirometer (Warren Collins Inc., Braintree, Mass.) having an inlet tube with volume of 65 mL. The total buffer volume between the exhaust flow line and the spirometer chamber was therefore 128 mL. Because of the continuous exhaust flow, only about half of the dog's tidal volume passed into the spirometer buffer volume, so that this system could accommodate tidal volumes as large as 256 mL without losses occurring in the spirometer water bath. The other teflon line was connected from the valve exhaust to a three-way valve (not shown) that was used for changing the bubblers. Pressure in this section of line was measured 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°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.

Flow 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). After the exposure the strip chart was evaluated with a Video Plan image analyzer that integrated the area under the recording to give the total volume of air breathed by the dog. Later exposures used a similar analysis method that employed a program written for the HP-41C calculator that enabled real-time integration of the signal from the mass flow meter during each half hour exposure period and provided a printed output. 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 dog was also obtained from the pressure drop of the SCUBA tank over each half hour period.

Animal Care and Biological Sample Collection

Three healthy adult female dogs, ages 8-10 years, were used in this study. These dogs were obtained from the U.C. Davis beagle colony. Prior to their use their health status was verified by physical examination, blood, urine, and fecal analysis, and by chest x-ray. During the study period, these animals were overseen by a veterinarian and trained animal technicians in facilities

accredited by the American Association for Accreditation of Laboratory Animal Care. These animals also had physical examinations and blood, urine, and fecal analyses every four months during the study period.

Each dog was exposed for three hours to each of the six chemicals and lung clearance was measured at 0.5 and 21 hours post-inhalation (also at two hours in some cases). Prior to each exposure, a sterile indwelling catheter was inserted into the cephalic vein to provide blood samples. During the exposure period, each unanesthetized trained dog was lying comfortably on a foam mattress padding in a specially designed Plexiglas restrainer, immobilized and fitted with a nasal exposure latex mask that prevented oral breathing. The vapor-containing atmosphere was breathed via specially fitted nose-tubes. Blood samples (2 to 3 mL) were collected at 0.5, 1, 1.5, 2, 2.5, and 3 hours during the exposure period and at 0.5, 1.5, 2.5, 21, 45, 69, 93, and 117 hours post-inhalation. The blood samples were placed into pre-weighed and labeled heparinized container; plasma was separated from red blood cells by centrifugation at 1000 g for 15 minutes. These samples were processed for liquid-scintillation radioanalysis.

At the end of the three-hour exposure, each dog was housed in a stainless steel metabolism cage in a temperature and humidity controlled room (temperature 23°C, humidity 64%). The daily urine and fecal samples were collected at 21, 43, and 69 hours post-inhalation in pre-weighed and labeled containers and then the cage was decontaminated with 2% isoclean and water solution after each collection period. At the end of the third day post-inhalation, the dogs were housed outdoors in the dog kennel until the next exposure. Blood levels of ^{14}C-labeled compounds were checked periodically prior to the next exposure scheduled for the animal. At the end of the study, all the dogs were returned to the colony and their health condition was normal as verified by their physical examination, blood, urine, and fecal analysis, and by chest x-ray.

Exposure Sequence

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 dog was placed in the restrainer. The special dog mask was then placed on the dog and the fit was examined to preclude leaks. The mask was then connected to the second stage of the regulator.

The vapor was provided via the demand valve to the dog 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 dog 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 dog breathing variations and recording changes and breathing pattern by the spirometer was continued for a total time of three hours and for subsequent clearance measurements.

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 three-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 dog inhaled clean zero 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 dog 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 dog exposure.

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 1). 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 all three bubblers were each filled with 120 mL of the CO_2 absorber because that cocktail is an efficient collector of methyl bromide vapor while the alcohol was not a good collector. For all exposures the bubblers were placed in plastic containers and filled 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 130 mL plastic bottles and two 1.0 mL samples were taken for separate liquid scintillation counting utilizing 20 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.

The efficiencies of collection of the various ^{14}C-labeled vapors and CO_2 in this study are summarized in Table 2.

TABLE 2: Bubbler Collection Efficiencies (Percent)

Vapor/gas:	C_2HCl_3[a]	C_6H_6[a]	CH_3Br[b]	$CHCl_3$[a]	CH_2O[a]	$(CH_3)_2N_2O$[a]	CO_2[c]
Mean	89.09	82.18	55.33	93.07	97.80	99.48	99.90
SE	0.20	1.15	3.08	1.20	0.12	0.12	0.09

[a] First bubbler efficiency average for three exposures using acidified alcohol.
[b] Second bubbler efficiency average for three exposures using $^{14}CO_2$-absorbing cocktail.
[c] First bubbler efficiency average for five exposures from 0.5 to 4.0 L/min using $^{14}CO_2$-absorbing cocktail.

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 was found to be >99% efficient at flow rates measured up to 4.0 L/min. Acidified alcohol had only 39 nCi in the first bubbler and 16 nCi in the second bubbler

when 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 $^{14}CO_2$. The data indicate that the exhaled $^{14}CO_2$ was essentially all collected by the third bubbler exclusively.

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 beagle exposures by drawing the respective vapors through the bubbler train at average flow rates similar to the minute volume of the beagle. 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 a beagle 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 beagle'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 beagle was exposed (determined as the average concentration in the test runs before and after the beagle 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 was subtracted from the collected activity in bubbler #3 (B_3) to determine the $^{14}CO_2$ activity:

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

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.

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

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%. 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. Diethylamine has been shown to be an adequate absorber for methyl bromide (Viel, de Lavaur and Bourdin, 1969). 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). Due to their similar chemical nature, the $^{14}CO_2$-absorbing cocktail was used as an absorber for methyl bromide and was found to be about 60% efficient. For three bubblers in series about 94% of the exhaled activity was captured, so it proved to be a satisfactory absorber.

A single bubbler filled with 120 mL of $^{14}CO_2$-absorbing cocktail is a quantitative scavenger for CO_2. If $^{14}CO_2$ was exhaled from metabolized $^{14}CH_3Br$ then the efficiency of the first bubbler in each 0.5 hour period would be higher than the efficiency in the second bubbler in each series of three bubblers. This would occur because the first bubbler would contain $^{14}CH_3Br$ and all the exhaled $^{14}CO_2$ while the second and third bubblers would contain only a proportional amount of $^{14}CH_3Br$ and zero $^{14}CO_2$. For the three CH_3Br exposures, the efficiencies for the first bubbler for all but one of the eighteen possible 0.5 hour exposure periods (one abbreviated period due to foaming over of a bubbler) were lower than or equal to the efficiencies of the second bubbler, so little $^{14}CO_2$ was exhaled during the 30-minute exposure periods. Even if $^{14}CO_2$ was exhaled an estimate could have been made as long as the efficiency of the first bubbler was significantly higher than the second bubbler for that period. This would have been calculated based on the assumption that except for $^{14}CO_2$ the efficiencies of the first and second bubblers should be identical. The efficiency of the second bubbler can be used to predict the amount of activity of $^{14}CH_3Br$ to be expected in the first bubbler. The measured activity above that predicted for $^{14}CH_3Br$ would be assigned to $^{14}CO_2$. However, during the exposures the experimental variability between bubblers was too great to accurately estimate $^{14}CO_2$ levels below about 5% of the vapor concentration.

Exposures with beagles showed that only about 1% of the inhaled methyl bromide was exhaled as $^{14}CO_2$ during a single 30-minute exposure sub-period based upon the first 30-minute post-exposure samples. Although the system used for sample collection for the methyl bromide studies was not able to resolve precisely this small amount of exhaled $^{14}CO_2$ during exposures, this amount was readily measured during post-exposure clearance measurements because radioactive methyl bromide was present then only at very low concentrations. It was therefore assumed that negligible $^{14}CO_2$ was exhaled during the exposures to methyl bromide.

The efficiency, E, of collection of the respective vapors in the CO_2 cocktail in each of the three bubblers was determined during test runs before and after beagle exposures by drawing the respective vapors through the bubbler train at average flow rates similar to the minute volume of the beagle. This was calculated from the activities in bubbler #2 (B_2) and bubbler #3 (B_3) by:

$$E=(B_2-B_3)/B_2 \qquad (5)$$

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 a beagle during a single 30 minute exposure period was calculated from the activity in bubbler #2 (B_2) during the period by:

$$A=B_2/[(1-E)E] \qquad (6)$$

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 beagle'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 beagle was exposed (determined as the average concentration in the test runs before and after the beagle exposure), provides the fraction of the inhaled vapor that was exhaled. The observed uptake fraction is this exhaled fraction subtracted from unity:

$$\text{Uptake Fraction} = 1.0 - A/tV_mC \qquad (7)$$

The activity collected in the first bubbler includes about half of the exhaled vapor and essentially all of the exhaled $^{14}CO_2$. Since the total exhaled activity was calculated from B_2, it was possible to calculate the amount of ^{14}C-vapor collected in the first bubbler by assuming the same collection efficiency for vapor collection in the first bubbler as for the other bubblers. This was subtracted from the collected activity in bubbler #1 (B_1) to determine the $^{14}CO_2$ activity:

$$^{14}CO_2 = B_1 - B_2/(1-E) \qquad (8)$$

Also, trace degradation products or impurities if present may also be collected in the first bubbler. 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. Because the exhalation of $^{14}CO_2$ was

slight during the exposure period, calculated $^{14}CO_2$ activities were associated with small experimental errors; these were corrected by adding the observed activity of $^{14}CO_2$ (either positive of negative with corresponding sign) to the observed exhaled activity A to yield the corrected value of the A.

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

Dead-space Correction

Although the demand breathing valve used in this study was designed to minimize dead space, a volume, v_d, of about 7 mL was in effect an extension of the noses of the beagles 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 pure vapor-containing air at the end of inhalation that is the first portion of the exhaled air volume leaving the valve during the 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 beagles was about 120 mL, the systematic error in observed uptake fractions would be about 6%. Hence, the observed uptake fractions and calculated inhaled activity were corrected for dead space using a dead space correction factor given by:

$$f=1.0/(1.0 - v_d/V_T) \qquad (9)$$

where f is the dead space correction factor (always larger than unity), v_d is the 7 mL dead space, and V_T is the average tidal volume measured for the individual beagles during each separate three-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. All the biological data were corrected for the dead space

Biological Samples

Triplicate samples of feces and duplicate samples of RBC's were combusted using a biological-material oxidizer (Model OX-300, R. J. Harvey, Hillsdale, N. J.) utilizing oxygen gas at 900°C. Any $^{14}CO_2$ generated was quantitatively trapped in 15 mL of $^{14}CO_2$-absorbing liquid-scintillation cocktail and counted with a Packard Tri-Carb 300C liquid scintillation system (Packard Instrument Co., Downers Grove, Illinois.). The samples were each counted for 10 minutes or to achieve coefficient of variation of 0.5% over a beta particle energy region of 0 to 156 KeV. Oxidizer collection efficiencies were determined to be about 100% using separate test standards spiked with the ^{14}C-labeled chemicals. Duplicate 0.2 mL urine samples were also analyzed for ^{14}C but without oxidation with the 3a70B scintillation cocktail. Most samples were greater than 2 times pre-exposure sample levels (which were subtracted as background) to yield net post exposure activity values).

The ^{14}C activities measured in the various biological samples were normalized by dividing in each case by the total inhaled activity during the separate three-hour beagle exposures. This allows the results to be readily applied to other exposure levels. Clearance during the first 21 hours post-exposure was monitored with two 30-minute exhaled air measurements. If possible, a simple single phase exponential clearance model was used to integrate the observed exhaled ^{14}C-vapor and $^{14}CO_2$ over the full 21 hour post-exposure period. This was successful with benzene, methyl bromide, and trichloro- ethylene. A two phase clearance model based on some ancillary measurements was necessary for the chloroform. Formaldehyde and dimethylnitrosamine clearance was multiphasic and would have required a much more extensive clearance study to fully evaluate. However, for these two chemicals the exhaled activity was high in the first 21 hours, demonstrating clearance half-times of less than about 10 hours.

The details associated with the processing of the biological data are discussed in Appendix B along with example data sheets.

RESULTS

Early tests with formaldehyde and benzene revealed technical problems with water condensation, vapor collection, beagle behavior, and breathing patterns which were all corrected for those studies utilized in the final data analyses. It was not possible to obtain meaningful exposures with ethylene oxide because of the inherent instability of this chemical. Soon after introduction of radiolabeled ethylene oxide, the concentration in the vapor state decreased to exceedingly low levels. The radioactivity was found to be coating the walls of the clean metal gas cylinders. It is probable that the ethylene oxide quickly polymerized or degraded to a non-volatile form. Successful results were obtained with the other six chemicals.

Quantitative measurements were made of the systemic uptake during nasal breathing of very low concentrations in air of six selected chemical vapors including benzene, dimethylnitrosamine, chloroform, methyl bromide, trichloroethylene, and formaldehyde. Tables 3 through 20 provide the uptake results, the blood concentration data, and the early clearance data for each chemical in groups of three tables. Table 21 provides the exposure conditions, schedule, and results of individual uptake measurements both as observed and after correction for dead space. The beagles suffered no harm or pain, and they were returned to the dog colony in good health at the end of the study.

The results 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. All but formaldehyde and dimethylnitrosamine reached steady state in less than 30 minutes. The steady state fractional systemic uptake of the total vapor (corrected for dead space), based upon the last four 30-minute exposure sub-periods in each case, was 39.5%$\pm$1.0% SE for methyl bromide at concentrations from 174 to 361 ppb, and 39.8%$\pm$1.5% SE for chloroform at concentrations from 393 to 594 ppb, 42.1%$\pm$2.2% SE for benzene at three concentrations from 10 to 46 ppb, 48.0%$\pm$0.8% SE for trichloroethylene at concentrations from 85 to 250 ppb, 53.6%$\pm$2.1% SE for dimethylnitrosamine at concentrations from 22 to 72 ppb, 54.4%$\pm$0.9 %SE for formaldehyde at concentrations from 1.4 to 1.9 ppb.

TABLE 3. Pharmacokinetics of the Inhaled Trichloroethylene (TCE) in Adult Beagle Dog (Steady State Uptake % = 48.03 ± 0.80 SE)[1]

Exposure Intervals (Minutes)	µg Inhaled[2] TCE per Interval Exp. # 16	Exp. # 15	Exp. # 17	$\bar{x}$ ± S.E., N=3 % Uptake of Inhaled	CO_2[3] Exhaled as % of Inhaled Per Interval	Blood Burden as % of Accumulative Inhaled
0-30	25.73	34.11	65.40	55.22±8.71	N.D.	2.26±0.30
31-60	18.34	34.03	60.86	49.64±1.31	0.06±0.06	2.29±0.43
61-90	18.43	34.62	62.63	49.19±0.74	0.20±0.13	2.78±0.25
91-120	19.59	30.03	58.33	50.18±2.00	0.46±0.19	2.75±0.29
121-150	20.10	33.38	64.90	48.25±0.95	0.68±0.15	2.91±0.12
151-180	17.48	29.09	53.16	44.57±0.37	1.17±0.14	2.50±0.40
Accumulative Total	119.7	195.3	365.3		0.43±0.11[4]	

1 Based on 12 measurements during last 2 hours of exposures of 3 beagles.

2 TCE air concentration (ppb) = Exp. # 16 = 85, Exp.# 15 = 143, Exp.# 17 = 250
(nCi/L) = Exp. # 16 = 53, Exp.# 15 = 89, Exp. # 17 = 156

3 N.D. = Not detectable

4 Accumulative total CO_2 exhaled during the exposure period as % of total inhaled.

Table 4. Blood Clearance of ^{14}C From the Inhaled Trichloroethylene at Different Times Post-Inhalation in Adult Beagle Dogs. ($\bar{x}$ ± S.E., n = 3)

Time Post Inhalation (Hours)	As % of Total Inhaled		
	Plasma Total	RBC Total	Blood Total
0	1.38±0.37	1.12±0.08	2.50±0.40
0.5	1.38±0.39	0.97±0.13	2.36±0.46
1.5	1.60±0.50	0.92±0.07	2.51±0.53
2.5	2.19±0.34	1.04±0.10	3.23±0.44
21	1.77±0.40	0.48±0.02	2.25±0.42
45	0.98±0.19	0.29±0.03	1.27±0.21
69	0.60±0.15	0.16±0.03	0.76±0.12
93	0.47±0.12	0.57±0.52	1.03±0.48
117	0.34±0.06	0.57±0.53	0.91±0.49

TABLE 5. Excretion and Retention of ^{14}C From the Inhaled Trichloroethylene at Different Times Post-Inhalation in Adult Beagle Dog. Values as % of Total Inhaled ($\bar{x}$ ± S.E., n = 3)

A. Total body retention at zero time post-inhalation = 47.51 ± 2.19

B. 0 - 21 hours

1. Urine = 16.61 ± 1.04
2. Fecal = 1.02 ± 0.90
3. Exhaled as CO_2 = 4.34 ± 0.18
4. Exhaled as trichloroethylene (and/or metabolites) = 12.38 ± 0.87
5. Total clearance (1-4) = 34.34 ± 2.12
6. Total body retention at 21 hours post-inhalation = 13.17 ± 3.22

C. 21 - 45 hours

1. Urine = 6.37 ± 2.43
2. Fecal = 0.71 ± 0.18

D. 45 - 69 hours

1. Urine = 2.21 ± 0.64
2. Fecal = 0.82 ± 0.33

E. Accumulated excreta (0 - 69 hours)

1. Urine = 25.19 ± 2.03
2. Fecal = 2.54 ± 0.62
3. Total = 27.73 ± 1.80

F. Estimated clearance half-time (hours) = 11.07

G. Unaccounted ^{14}C exhaled after 21 hours and/or excreted after 69 hours = 3.07 ± 2.41

TABLE 6. Pharmacokinetics of the Inhaled Benzene in Adult Beagle Dog (Steady State Uptake % = 42.07 ± 2.18 SE)[1]

Exposure Intervals (Minutes)	µg Inhaled[2] Benzene per Interval Exp. # 14	Exp. # 13	Exp. # 4	$\bar{x}$ ± S.E., N=3 % Uptake of Inhaled	CO_2 Exhaled as % of Inhaled Per Interval	Blood Burden as % of Accumulative Inhaled
0-30	2.38	2.70	10.99	46.01±3.17	0.21±0.12	8.09±4.11
31-60	2.57	2.97	10.40	42.32±2.49	0.57±0.07	8.49±3.74
61-90	3.15	1.47	9.81	42.05±5.53	0.85±0.23	9.37±4.56
91-120	3.70	4.37	9.89	42.04±6.67	1.10±0.35	7.73±3.14
121-150	2.35	2.90	9.53	42.51±3.86	1.10±0.33	7.72±3.12
151-180	2.30	2.93	9.12	41.72±3.41	1.39±0.49	9.15±5.40
Accumulative Total	16.45	17.37	59.74		0.89±0.23[3]	

1 Based on 12 measurements during last 2 hours of exposure of 3 beagles.

2 Benzene air concentration (ppb) = Exp.# 14 = 10, Exp.# 13 = 19, Exp.# 4 = 46.0
(nCi/L) = Exp.# 14 = 24, Exp.# 13 = 45, Exp.# 4 = 108

3 Accumulative total CO_2 exhaled during the exposure period as % of total inhaled.

Table 7. Blood Clearance of ^{14}C From the Inhaled Benzene at Different Times Post-Inhalation in Adult Beagle Dogs. ($\bar{x}$ ± S.E., n = 3)

Time Post Inhalation (Hours)	As % of Total Inhaled		
	Plasma Total	RBC Total	Blood Total
0	7.98±5.46	1.16±0.07	9.15±5.40
0.5	7.24±5.00	1.31±0.16	8.56±5.01
1.5	6.58±4.15	1.20±0.05	7.78±4.14
2.5	7.35±5.12	1.33±0.15	8.68±5.07
21	2.56±1.86	0.50±0.08	3.07±1.93
45	0.34±0.10	0.24±0.16	0.59±0.26
69	0.47±0.35	0.25±0.02	0.71±0.34
93	0.38±0.18	0.11±0.10	0.49±0.26
117	0.16±0.10	0.16±0.07	0.32±0.10

TABLE 8. Excretion and Retention of ^{14}C From the Inhaled Benzene at Different Times Post-Inhalation in Adult Beagle Dog. Values as % of Total Inhaled ($\bar{x}$ ± S.E., n = 3)

A. Total body retention at zero time post-inhalation = 39.49 ± 4.31

B. 0 - 21 hours

1. Urine = 16.80 ± 2.99
2. Fecal = 0.54 ± 0.38
3. Exhaled as CO_2 = 2.69 ± 1.11
4. Exhaled as benzene (and/or metabolites) = 6.75 ± 0.43
5. Total clearance (1-4) = 26.79 ± 4.19
6. Total body retention at 21 hours post-inhalation = 12.70 ± 6.17

C. 21 - 45 hours

1. Urine = 4.13 ± 1.84
2. Fecal = 0.99 ± 0.55

D. 45 - 69 hours

1. Urine = 1.21 ± 0.39
2. Fecal = 0.97 ± 0.45

E. Accumulated excreta (0 - 69 hours)

1. Urine = 22.14 ± 2.23
2. Fecal = 2.49 ± 0.62
3. Total = 24.64 ± 1.80

F. Estimated clearance half-time (hours) = 12.53

G. Unaccounted ^{14}C exhaled after 21 hours and/or excreted after 69 hours = 5.41 ± 4.80

TABLE 9. Pharmacokinetics of the Inhaled Methylbromide (MB) in Adult Beagle Dog (Steady State Uptake % = 39.5 ± 1.02 SE)[1]

Exposure Intervals (Minutes)	µg Inhaled[1] M.B. per Interval Exp. # 21	Exp. # 19	Exp. # 20	$\bar{x}$ ± S.E., N=3 % Uptake of Inhaled	CO_2[2] Exhaled as % of Inhaled Per Interval	Blood Burden as % of Accumulative Inhaled
0-30	27.67	42.17	54.54	42.87±2.07	N.D.	1.02±0.15
31-60	26.37	41.20	49.17	40.26±1.71	N.D.	1.01±0.13
61-90	27.80	45.11	56.24	40.35±2.39	N.D.	1.22±0.13
91-120	27.27	45.43	52.45	40.67±0.88	N.D.	1.33±0.03
121-150	26.76	7.5	79.72	38.42±1.66	N.D.	1.55±0.15
151-180	24.57	77.83	79.85	38.57±3.46	N.D.	1.56±0.05
Accumulative Total	160.44	259.24	371.98		N.D.	

1 Based upon 12 measurements during last 2 hours of exposure of 3 beagles.

2 MB air concentration (ppb) = Exp. # 21 = 174, Exp. # 19 = 302, Exp. # 20 = 361
(nCi/L) = Exp. # 21 = 93, Exp. # 19 = 161, Exp. # 20 = 192

3 N.D. = not detectable.

Table 10. Blood Clearance of the ^{14}C From Inhaled Methylbromide at Different Times Post-Inhalation in Adult Beagle Dogs. ($\bar{x}$ ± S.E., n = 3)

Time Post Inhalation (Hours)	As % of Total Inhaled		
	Plasma Total	RBC Total	Blood Total
0	0.93±0.06	0.63±0.05	1.56±0.05
0.5	1.02±0.06	0.68±0.07	1.70±0.14
1.5	1.21±0.07	0.70±0.03	1.91±0.04
2.5	1.40±0.08	1.04±0.10	2.44±0.16
21	2.22±0.11	1.10±0.07	3.32±0.15
45	1.24±0.02	0.45±0.02	1.69±0.02
69	0.91±0.04	0.37±0.03	1.29±0.07
93	0.91±0.06	0.45±0.05	1.36±0.11
117	0.73±0.03	0.49±0.05	1.22±0.08

TABLE 11. Excretion and Retention of ^{14}C From the Inhaled Methylbromide at Different Times Post-Inhalation in Adult Beagle Dog. Values as % of Total Inhaled ($\bar{x}$ ± S.E., n = 3)

A. Total body retention at zero time post-inhalation = 37.69 ± 1.14

B. 0 - 21 hours

1. Urine = 1.08 ± 0.52
2. Fecal = 0.04 ± 0.02
3. Exhaled as CO_2 = 4.23 ± 0.80
4. Exhaled as methylbromide (and/or metabolites) = 5.63 ± 0.73
5. Total clearance (1-4) = 10.98 ± 1.34
6. Total body retention at 21 hours post-inhalation = 26.71 ± 1.12

C. 21 - 45 hours

1. Urine = 3.43 ± 0.68
2. Fecal = 0.22 ± 0.02

D. 45 - 69 hours

1. Urine = 1.20 ± 0.12
2. Fecal = 0.45 ± 0.12

E. Accumulated excreta (0 - 69 hours)

1. Urine = 5.72 ± 0.31
2. Fecal = 0.71 ± 0.14
3. Total = 6.42 ± 0.29

F. Estimated clearance half-time (hours) = 41.26

G. Unaccounted ^{14}C exhaled after 21 hours and/or excreted after 69 hours = 21.41 ± 1.57

TABLE 12. Pharmacokinetics of the Inhaled Chloroform in Adult Beagle Dog (Steady State % Uptake = 39.82 ± 1.52 SE)[1]

Exposure Intervals (Minutes)	µg Inhaled[2] Chloroform per Interval Exp.# 18	Exp.# 30	Exp.# 31	$\bar{x}$ ± S.E., N=3 % Uptake of Inhaled	CO_2[3] Exhaled as % of Inhaled Per Interval	Blood Burden as % of Accumulative Inhaled
0-30	90.73	134.45	157.72	42.91±0.76	N.D.	4.55±1.14
31-60	82.86	129.97	186.52	42.60±0.86	4.63±2.06	4.28±1.04
61-90	83.41	152.05	221.06	40.86±2.67	7.91±1.88	3.71±0.96
91-120	86.34	128.03	253.11	38.56±3.26	11.22±1.88	3.42±0.65
121-150	91.46	124.63	236.55	41.66±3.50	13.23±2.45	3.28±0.62
151-180	81.95	116.92	237.13	38.58±2.76	18.34±1.98	3.34±0.56
Accumulative Total	516.74	789.05	1292.1		9.42±2.08[4]	

[1] Based on 12 measurements for last 2 hours of exposure of 3 beagles.

[2] Chloroform air concentration (ppb) = Exp.# 18 = 393, Exp.# 30 = 594, Exp.# 31 = 555
(nCi/L) = Exp.# 18 = 224, Exp.# 30 = 338, Exp.# 31 = 316

[3] Not detectable

[4] Accumulative total CO_2 exhaled during the exposure period as % of total inhaled.

Table 13. Blood Clearance of ^{14}C From the Inhaled Chloroform at Different Times Post-Inhalation in Adult Beagle Dogs. ($\bar{x}$ ± S.E., n = 3)

Time Post Inhalation (Hours)	As % of Total Inhaled		
	Plasma Total	RBC Total	Blood Total
0	0.81±0.15	2.53±0.46	3.34±0.58
0.5	0.55±0.10	2.31±0.41	2.86±0.46
1.5	0.35±0.05	2.06±0.39	2.41±0.41
2.5	0.28±0.04	1.85±0.32	2.13±0.33
21	0.13±0.03	0.35±0.12	0.48±0.15
45	0.08±0.01	0.07±0.04	0.16±0.06
69	0.07±0.01	0.06±0.03	0.12±0.04
93	0.05±0.01	0.03±0.03	0.08±0.06
117	0.05±0.004	0.05±0.03	0.09±0.05

TABLE 14. Excretion and Retention of ^{14}C From the Inhaled Chloroform at Different Times Post-Inhalation in Adult Beagle Dog. Values as % of Total Inhaled ($\bar{x}$ ± S.E., n = 3)

A. Total body retention at zero time post-inhalation = 28.99 ± 3.82

B. 0 - 21 hours

1. Urine = 1.72 ± 0.94
2. Fecal = 0.06 ± 0.05
3. Exhaled as CO_2 = 14.90 ± 2.24*
4. Exhaled as chloroform (and/or metabolites) = 5.34 ± 1.57*
5. Total clearance (1-4) = 22.02 ± 3.24
6. Total body retention at 21 hours post-inhalation = 6.97 ± 2.70

C. 21 - 45 hours

1. Urine = 0.64 ± 0.22
2. Fecal = 0.37 ± 0.22

D. 45 - 69 hours

1. Urine = 0.19 ± 0.02
2. Fecal = 0.07 ± 0.04

E. Accumulated excreta (0 - 69 hours)

1. Urine = 2.55 ± 0.72
2. Fecal = 0.50 ± 0.18
3. Total = 3.04 ± 0.64

F. Estimated clearance half-time (hours) = 9.97

G. Unaccounted ^{14}C exhaled after 21 hours and/or excreted after 69 hours = 5.70 ± 2.68

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* Modeled using two exponential clearance based upon two ancillary clearance measurements.

TABLE 15. Pharmacokinetics of the Inhaled Formaldehyde in Adult Beagle Dog (Steady State % Uptake = 54.35 ± 0.92 SE)[1]

Exposure Intervals (Minutes)	µg Inhaled[2] Formaldehyde per Interval			$\bar{x}$ ± S.E., N=3		
	Exp. # 28	Exp. # 29	Exp. # 27	% Uptake of Inhaled	CO_2 Exhaled as % of Inhaled Per Interval	Blood Burden as % of Accumulative Inhaled
0-30	0.09	0.10	0.12	36.44±5.66	0.79±0.79	25.06±6.09
31-60	0.10	0.11	0.10	51.29±2.12	6.15±3.10	20.22±7.48
61-90	0.10	0.11	0.09	55.58±1.44	9.73±3.84	27.48±7.30
91-120	0.12	0.10	0.11	56.46±1.05	14.83±3.43	9.67±2.15
121-150	0.10	0.10	0.12	55.03±1.35	16.34±3.56	10.76±4.33
151-180	0.09	0.10	0.11	50.30±0.63	26.10±3.90	12.36±4.72
Accumulative Total	0.61	0.62	0.65		12.32±3.16[3]	

1 Based upon 12 measurements during last 2 hours of exposure of 3 beagles.

2 Formaldehyde air concentration (ppb) = Exp. # 28 = 1.94, Exp. # 29 = 1.85, Exp.# 27 = 1.43; (nCi/L) = Exp.# 28 = 4.18, Exp.# 29 = 3.97, Exp.# 27 = 3.07

3 Accumulative total CO_2 exhaled during the exposure period as % of total inhaled.

Table 16. Blood Clearance of ^{14}C From the Inhaled Formaldehyde at Different Times Post-Inhalation in Adult Beagle Dogs. ($\bar{x}$ ± S.E., n = 3)

Time Post Inhalation (Hours)	As % of Total Inhaled		
	Plasma Total	RBC Total	Blood Total
0	2.73±0.31	9.63±5.01	12.36±4.72
0.5	2.64±0.36	4.98±2.45	7.50±2.84
1.5	3.97±1.55	11.37±4.90	15.33±6.42
2.5	4.12±0.95	8.06±4.43	12.18±4.47
21	2.74±0.93	10.88±3.01	13.62±3.52
45	1.21±0.14	5.17±1.84	6.38±1.74
69	0.63±0.19	0.81±0.74	1.44±0.56
93	0.23±0.05	5.77±2.70	5.99±2.74
117	0.01±0.004	19.52±7.34	19.52±7.33

TABLE 17. Excretion and Retention of ^{14}C From the Inhaled Formaldehyde at Different Times Post-Inhalation in Adult Beagle Dog.

Values as % of Total Inhaled ($\bar{x}$ ± S.E., n = 3)

A. Total body retention at zero time post-inhalation = 35.75 ± 3.69

B. 0 - 21 hours

1. Urine = 4.27 ± 0.77
2. Fecal = 0.15 ± 0.15
3. Exhaled as CO_2 = Not Determined
4. Exhaled as formaldehyde (and/or metabolites) = Not Determined
5. Total clearance (1-4) = Not Determined
6. Total body retention at 21 hours post-inhalation = Not Determined

C. 21 - 45 hours

1. Urine = 1.87 ± 0.96
2. Fecal = 2.30 ± 1.64

D. 45 - 69 hours

1. Urine = 0.73 ± 0.45
2. Fecal = 0.83 ± 0.58

E. Accumulated excreta (0 - 69 hours)

1. Urine = 6.87 ± 0.73
2. Fecal = 3.29 ± 1.56
3. Total = 10.16 ± 1.39

F. Estimated clearance half-time (hours) = Multiphase Not Determined, but less than 10 hours.

TABLE 18. Pharmacokinetics of the Inhaled Dimethylnitrosamine (DMNA) in Adult Beagle Dog (Steady State % Uptake = 53.64 ± 2.08 SE)[1]

Exposure Intervals (Minutes)	µg Inhaled[2] DMNA per Interval Exp.# 24	Exp.# 23	Exp.# 25	$\bar{x}$ ± S.E., N=3 % Uptake of Inhaled	CO_2 Exhaled as % of Inhaled Per Interval	Blood Burden as % of Accumulative Inhaled
0-30	2.91	6.69	10.62	C.N.D.[3]	1.75±0.36	5.37±0.51
31-60	2.84	6.85	9.59	43.28±3.99	8.02±0.78	5.52±0.13
61-90	2.89	7.03	10.19	52.85±3.14	13.02±0.78	5.49±0.28
91-120	2.80	6.51	10.99	49.87±2.33	18.43±0.22	5.32±0.26
121-150	3.02	9.90	9.64	59.03±6.90	20.23±3.21	5.18±0.55
151-180	2.85	6.31	7.87	52.95±3.66	27.30±1.24	5.59±0.41
Accumulative Total	17.32	43.30	58.90		14.59±0.43[4]	

1 Based upon 12 measurements during last 2 hours of exposure for 3 beagles.

2 DMNA air concentration (ppb) = Exp.# 24 = 22, Exp.# 23 = 68, and Exp.# 25 = 72
(nCi/L) = Exp.# 24 = 49, Exp.# 23 = 143, Exp.# 25 = 159

3 C.N.D. It cannot be determined accurately due to the residual contamination in the system from the pretest concentration measurement of DMNA.

4 Accumulative total CO_2 exhaled during the exposure period as % of total inhaled.

Table 19. Blood Clearance of ^{14}C From the Inhaled Dimethylnitrosamine at Different Times Post-Inhalation in Adult Beagle Dogs. ($\bar{x}$ ± S.E., n = 3)

Time Post Inhalation (Hours)	As % of Total Inhaled		
	Plasma Total	RBC Total	Blood Total
0	4.33±0.44	1.25±0.04	5.59±0.41
0.5	4.43±0.53	1.20±0.02	5.64±0.54
1.5	4.52±0.55	1.17±0.12	5.68±0.67
2.5	4.60±0.63	1.23±0.19	5.84±0.82
21	3.61±0.53	0.87±0.10	4.48±0.55
45	2.69±0.35	0.72±0.13	3.41±0.47
69	2.03±0.20	0.81±0.14	2.84±0.33
93	1.71±0.09	1.05±0.12	2.76±0.21
117	1.48±0.13	0.84±0.13	2.32±0.56

TABLE 20. Excretion and Retention of ^{14}C From the Inhaled Dimethylnitrosamine at Different Times Post-Inhalation in Adult Beagle Dog. Values as % of Total Inhaled ($\bar{x} \pm$ S.E., n = 3)

A. Total body retention at zero time post-inhalation = 26.33 ± 3.76

B. 0 - 21 hours

1. Urine = 2.98 ± 0.65
2. Fecal = 0.46 ± 0.19
3. Exhaled as CO_2 = Not Determined
4. Exhaled as dimethylnitrosamine (and/or metabolites) = Not Determined
5. Total clearance (1-4) = Not Determined
6. Total body retention at 21 hours post-inhalation = Not Determined

C. 21 - 45 hours

1. Urine = 1.48 ± 0.40
2. Fecal = 0.42 ± 0.08

D. 45 - 69 hours

1. Urine = 0.62 ± 0.06
2. Fecal = 0.45 ± 0.11

E. Accumulated excreta (0 - 69 hours)

1. Urine = 5.07 ± 0.21
2. Fecal = 1.32 ± 0.15
3. Total = 0.40 ± 0.36

F. Estimated clearance half-time (hours) = Not determined but less than 10 hours.

TABLE 21

Exposures of Individual Beagles to Vapors With Observed and Corrected Uptake

(*Indicates satisfactory experiments used in the data summaries.)

No.	DATE (1985)	CHEMICAL	CONCENTRATION (nCi/L)	CONCENTRATION (ppb)	DOG	WEIGHT (kg)	MIN.VOL. (LPM±SE)	BPM (SE)	UPTAKE(%±SE) OBS.	UPTAKE(%±SE) CORR.
1	1/22	CH_2O	---	---	75H02C	11.4	---	---	---	---
2	2/21	C_6H_6	---	---	76K01B	11.4	2.5±0.1	19+1	---	---
3	3/5	C_6H_6	108	45.9	77H20F	9.4	1.7±0.2	22+1	---	---
4*	3/19	C_6H_6	108	46.1	76K01B	11.4	2.6±0.2	20+1	46.1±0.6	47.6±0.6
5	3/27	C_6H_6	110	46.6	75H02C	11.4	3.9±0.1	27+1	---	---
6	4/2	$CHCl_3$	259	454	77H20F	9.4	4.5±0.2	44+2	---	---
7	4/9	$CHCl_3$	81.7	160	76K01B	11.4	2.8±0.3	22+2	---	---
8	4/23	$CHCl_3$	187	328	75H02C	11.4	2.0±0.1	14+1	---	---
9	5/7	CH_2O	63.2	29.4	77H20F	9.4	---	---	---	---
10	6/4	CH_2O	17.3	8.0	76K01B	11.4	1.8±0.1	14+1	---	---
11	6/11	CH_2O	7.1	3.3	77H20F	9.4	1.7±0.1	14+1	---	---
12	6/18	CH_2O	15.6	7.2	75H02C	11.4	2.1±0.2	19+2	---	---
13*	6/25	C_6H_6	45.4	19.3	77H20F	9.4	1.6±0.1	13+1	42.2±1.5	43.6±1.6
14*	7/2	C_6H_6	24.3	10.3	75H02C	11.4	3.0±0.3	21+3	31.1±1.6	32.0±1.6
15*	7/16	C_2HCl_3	89.1	143	76K01B	11.4	1.5±0.1	12+1	45.5±1.3	47.0±1.3
16*	7/23	C_2HCl_3	52.7	84.7	77H20F	9.4	1.7±0.3	14+1	46.2±1.9	47.8±2.0
17*	7/30	C_2HCl_3	156	250	75H02C	11.5	1.6±0.1	14+1	44.0±0.5	45.6±0.5
18*	8/6	$CHCl_3$	224	393	76K01B	10.0	1.6±0.1	11+1	37.0±1.1	38.0±1.1
19*	8/13	CH_3Br	161	302	77H20F	10.3	1.3±0.1	14+1	36.8±1.8	38.5±1.9
20*	8/20	CH_3Br	192	361	75H02C	10.3	1.6±0.1	15+1	35.4±1.8	36.8±1.9
21*	8/27	CH_3Br	92.6	174	76K01B	10.8	1.4±0.1	12+1	38.4±1.4	39.8±1.5
22	9/10	$(CH_3)_2N_2O$	58.8	26.6	75H02C	10.3	2.1±0.1	16+1	---	---
23*	9/17	$(CH_3)_2N_2O$	143	67.7	77H20F	8.8	1.3±0.1	10+1	56.4±4.1	58.2±4.2
24*	9/24	$(CH_3)_2N_2O$	49.4	22.3	76K01B	10.0	1.4±0.1	12+1	44.1±0.8	45.7±0.8
25*	10/1	$(CH_3)_2N_2O$	159	72.0	75H02C	10.3	1.6±0.1	12+1	51.6±0.8	53.2±0.8
26	10/8	$(CH_3)_2N_2O$	74.1	33.5	76K01B	10.8	1.5±0.1	11+1	---	---
27*	10/22	CH_2O	3.1	1.4	77H20F	8.7	2.2±0.1	20+1	52.6±1.7	54.6±1.8
28*	10/29	CH_2O	4.2	1.9	75H02C	10.3	1.5±0.1	10+1	50.6±0.9	52.0±0.9
29*	11/5	CH_2O	4.0	1.9	76K01B	10.8	1.6±0.1	13+1	50.7±1.7	52.4±1.8
30*	11/12	$CHCl_3$	338	594	75H02C	10.3	1.6±0.1	11+1	42.9±0.9	44.1±0.9
31*	11/19	$CHCl_3$	316	555	77H20F	8.7	2.8±0.1	26+2	33.3±0.8	34.6±0.8

Although the uptake fractions were similar for the six chemicals that were studied, the temporal retention and distribution in blood and excreta relative to the uptake fraction varied considerably depending upon the metabolic characteristics of the chemicals. The blood concentrations rose sharply during the exposures, but was generally a fixed fraction of the cumulative total amount of vapor inhaled. After the 3 hour exposure the blood concentrations as percentage of total inhaled vapor were 1.6%±0.1% SE for methyl bromide 3.3%±0.6% SE for chloroform, 5.6%±0.4% SE for dimethylnitrosamine 2.5%±0.4% SE for trichloroethylene, 9.2%±5.4% SE for benzene, and 12.4%±4.7% SE for formaldehyde. Clearance half-times after exposure based upon the radiocarbon label ranged from about 10 hours or less for dimethylnitrosamine, chloroform, and formaldehyde to about 40 hours for methyl bromide.

The biological and post-exposure clearance data provided a basis for mass-balance analysis of the results. Essentially all of the ^{14}C from trichloroethylene, chloroform, and benzene was accounted for in the clearance analysis. This result independently corroborates the uptake measurements. Although it was not possible to ascertain the exact clearance half-times for formaldehyde and dimethylnitrosamine, it was seen that the clearance half-times were less than 10 hours for both of these chemicals. In just the first 30 minutes post-exposure, 15.7% of the uptaken ^{14}C from formaldehyde was exhaled (11.8% as CO_2 and 3.9% as formaldehyde or other products). Likewise, in the first 30 minutes post-exposure, 23.3% of the uptaken ^{14}C from dimethylnitrosamine was exhaled (16.8% as CO_2 and 6.5% as nitrosamine or other products). In contrast, there was still about 70% of the uptaken methyl bromide retained by the beagles 21 hours post-exposure; most of the cleared ^{14}C was exhaled as CO_2, methyl bromide, or other metabolic products but with a clearance half-time of about 40 hours.

DISCUSSION

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 42.1%±2.2%SE. These results spanning from man to dog for concentrations that vary up to a factor of about 20,000 are remarkably similar (Figure 3). The short exposure duration may explain the observed higher uptake associated with the Astrand (1975) measurements (Figure 4).

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 48.0%±0.8%SE. Bergman (1979) had similar results for mice. These results show about the same uptake over a wide range of concentrations (Figure 5) and exposure times (Figure 6).

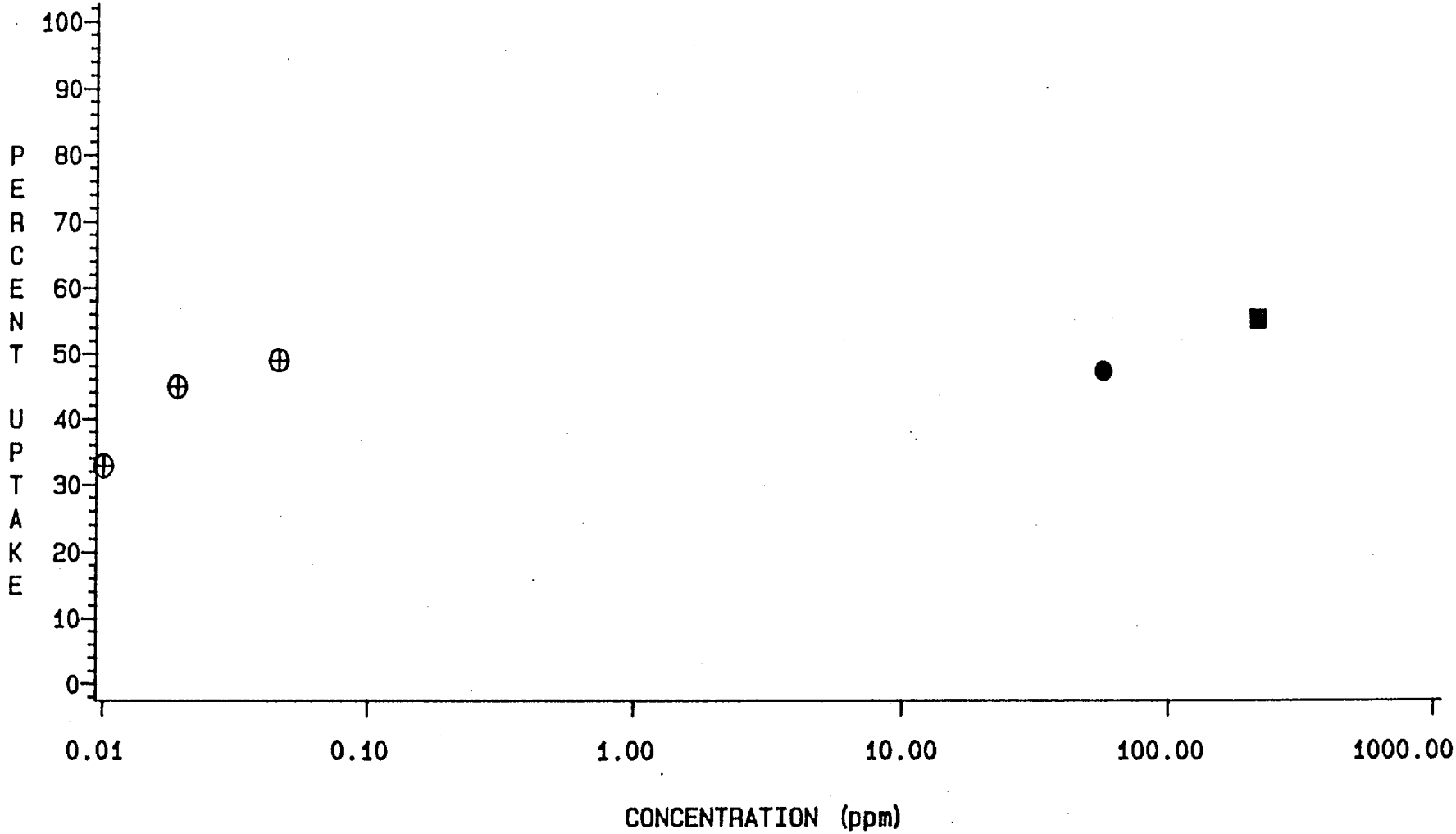
Medinsky et al. (1985) measured the uptake of ^{14}C-labeled methyl bromide by Fischer-344 rats for six hours at concentrations from 1.6 to 310 ppm. They found that in their apparatus the fractional uptake of methyl bromide vapor ranged from 37% to 27% at the highest concentrations to about 48% at the lower concentrations. Their result at 1.6 ppm of about 48% uptake is compared to the beagle results in Figures 7 and 8. Their results at the lowest concentration are only slightly higher than observed for beagles. They 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.

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

FIGURE 3

Comparison of observed uptake fractions of benzene vapor by beagles in this project and in reported studies with human volunteers by Astrand (1975) and Nomiyama and Nomiyama (1974) with respect to exposure concentration.

BENZENE % UPTAKE



⊕ – RAABE/BEAGLES ● – NOMIYAMA/HUMAN ■ – ASTRAND/HUMAN

FIGURE 4

Comparison of observed uptake fractions of benzene vapor by beagles in this project and in reported studies with human volunteers by Astrand (1975) and Nomiyama and Nomiyama (1974) with respect to duration of exposure.

BENZENE % UPTAKE

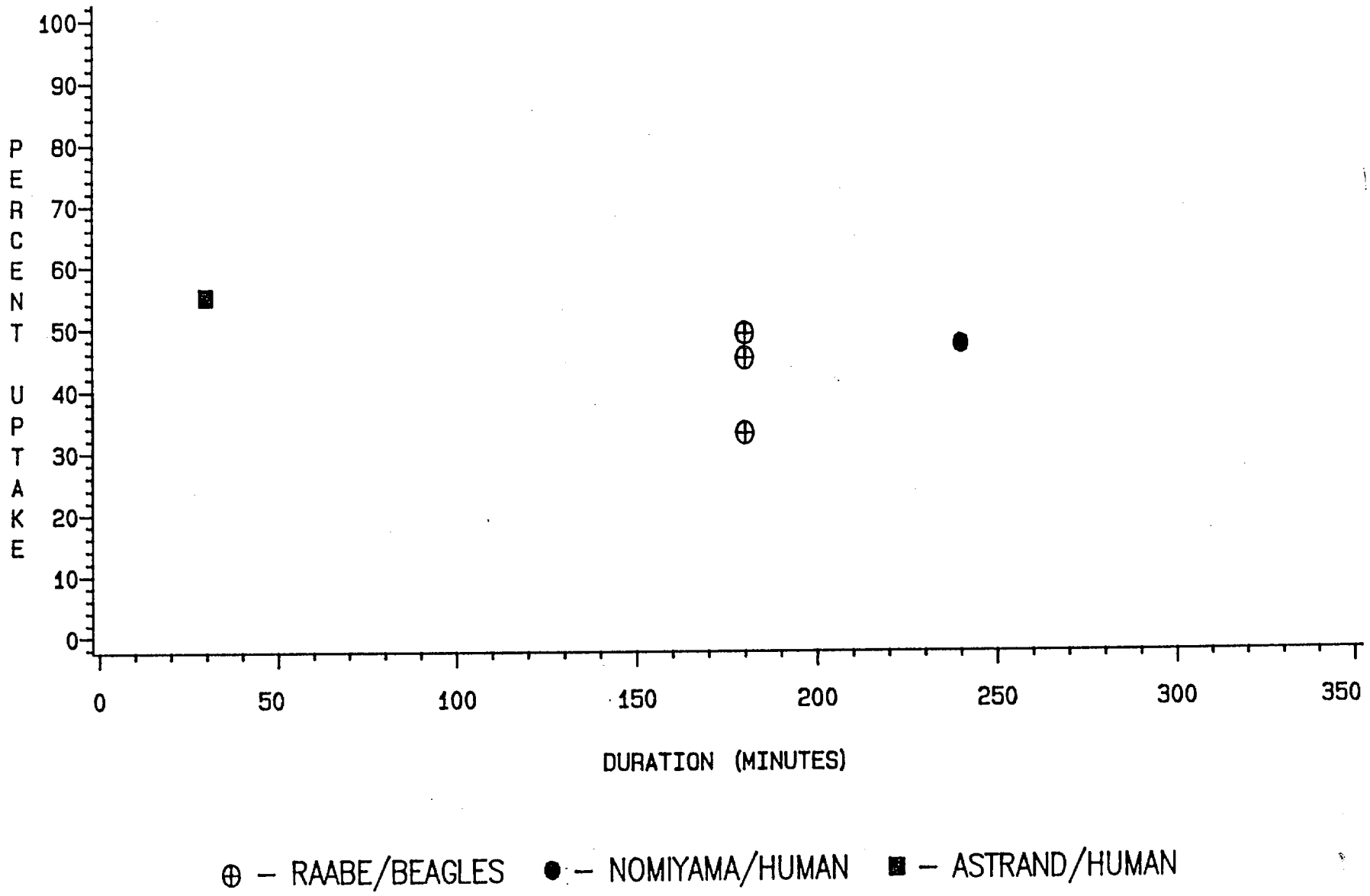


FIGURE 5

Comparison of observed uptake fractions of trichloroethylene vapor by beagles in this project and in reported studies with 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.

TRICHLOROETHYLENE PERCENT UPTAKE

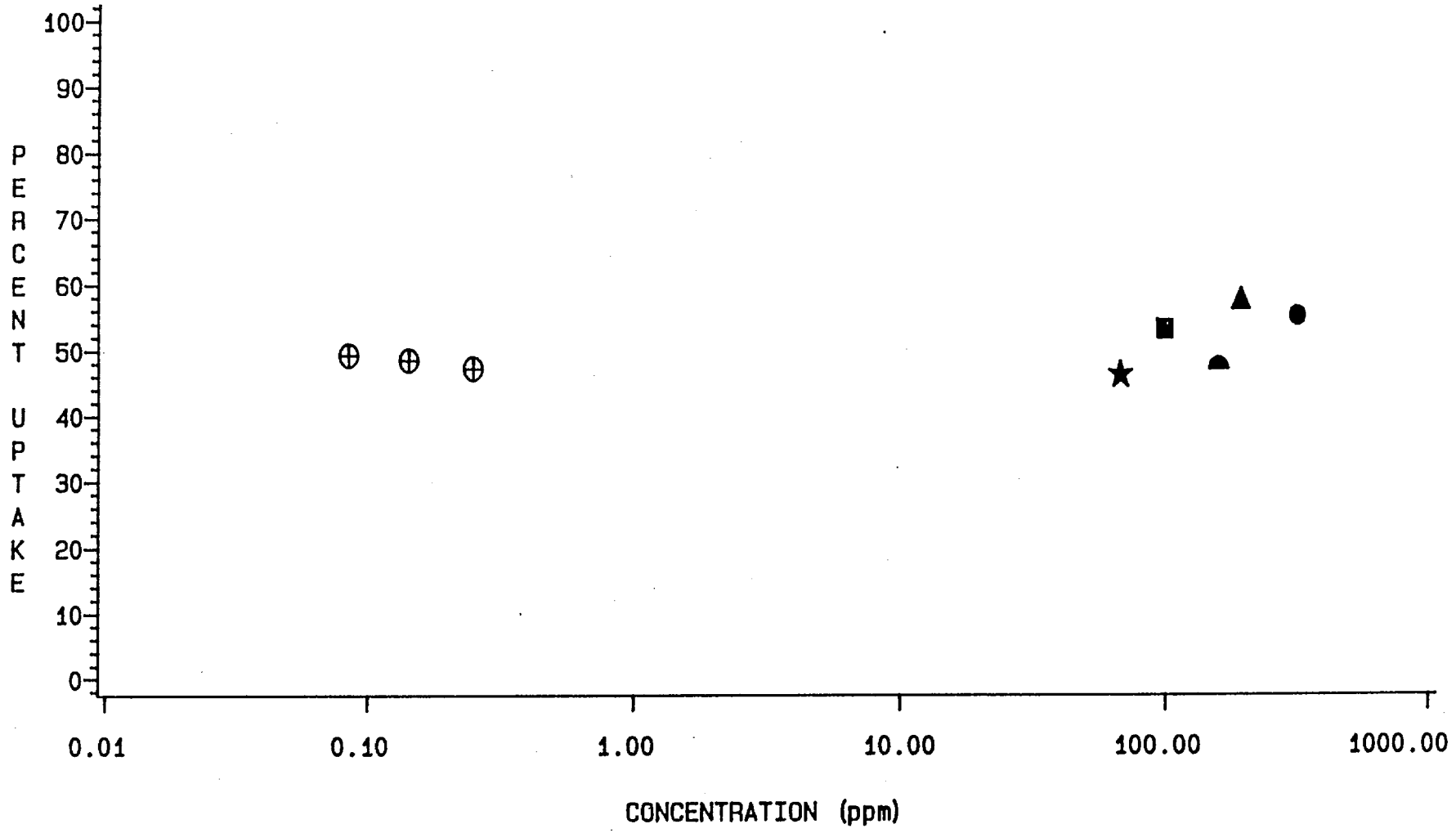


FIGURE 6

Comparison of observed uptake fractions of trichloroethylene vapor by beagles in this project and in reported studies with 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.

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 uptake of the water soluble formaldehyde was expected to be near 100%. The observed uptake was only about 55%. 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 (on a weight basis). The beagles were exposed to only 1.4 to 1.9 ppb. This gradient between body tissue levels and the inhaled air may have influenced the result, although the radioactively labeled formaldehyde would be expected to exhibit an independent behavior.

If these vapors 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 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 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 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 accommodation coefficient for diffusive adsorption must be much less than unity for these vapor molecules contacting the moist epithelium of the respiratory airways.

TRICHLOROETHYLENE PERCENT UPTAKE

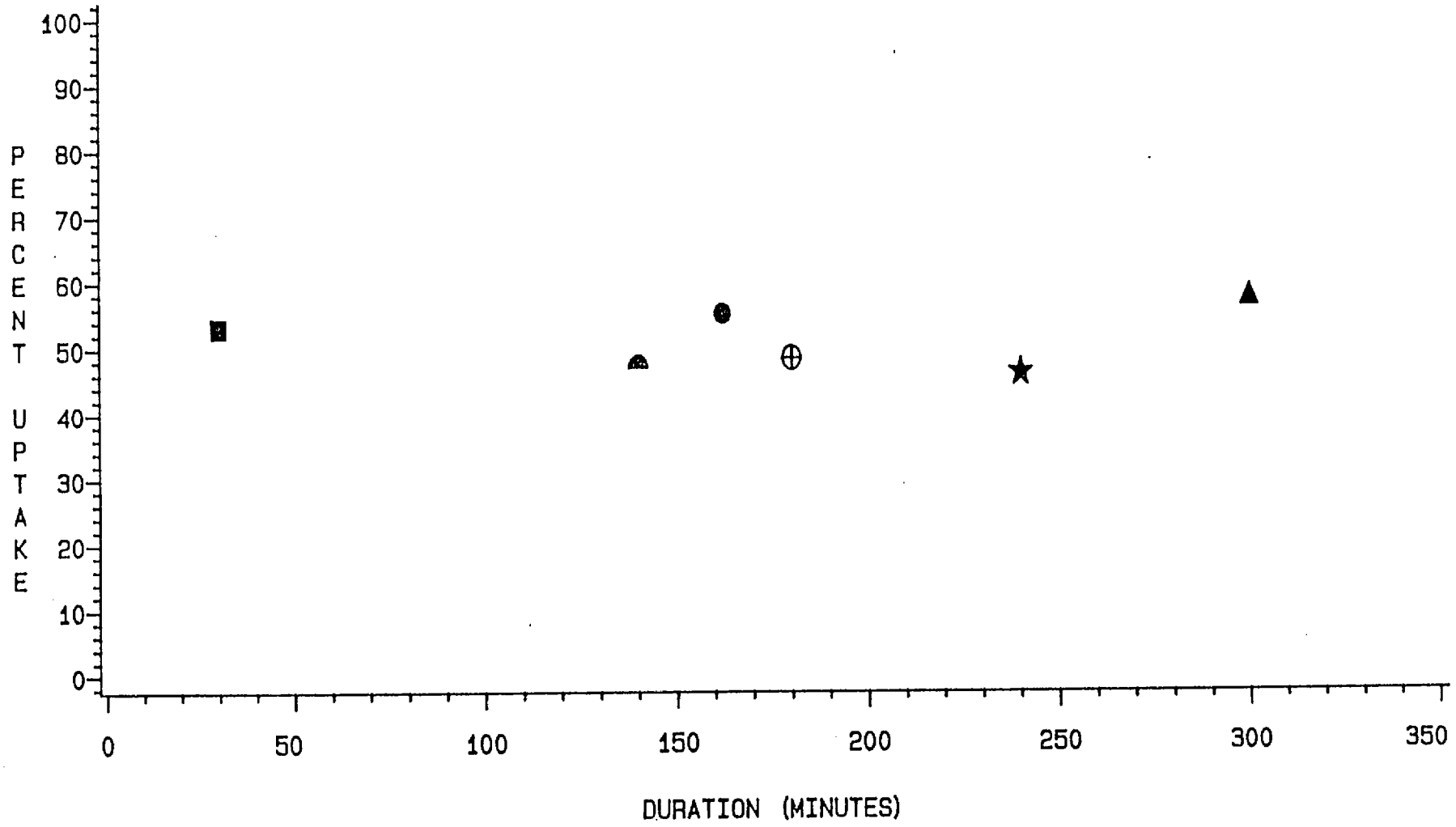
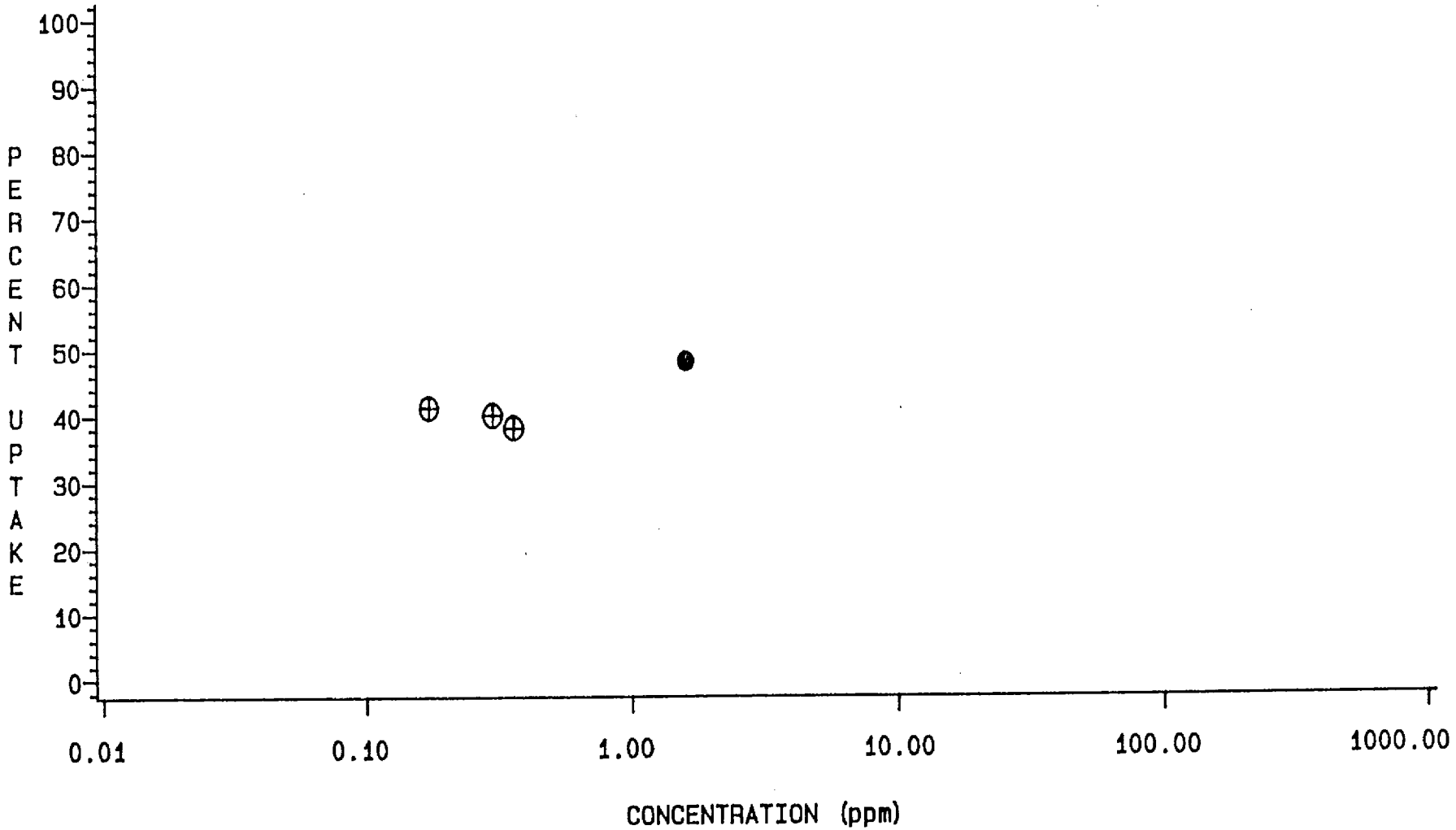


FIGURE 7

Comparison of observed uptake fractions of methyl bromide vapor by beagles in this project and in reported studies with Fischer-344 rats by Medinsky et al. (1985) with respect to exposure concentration.

METHYLBROMIDE % UPTAKE

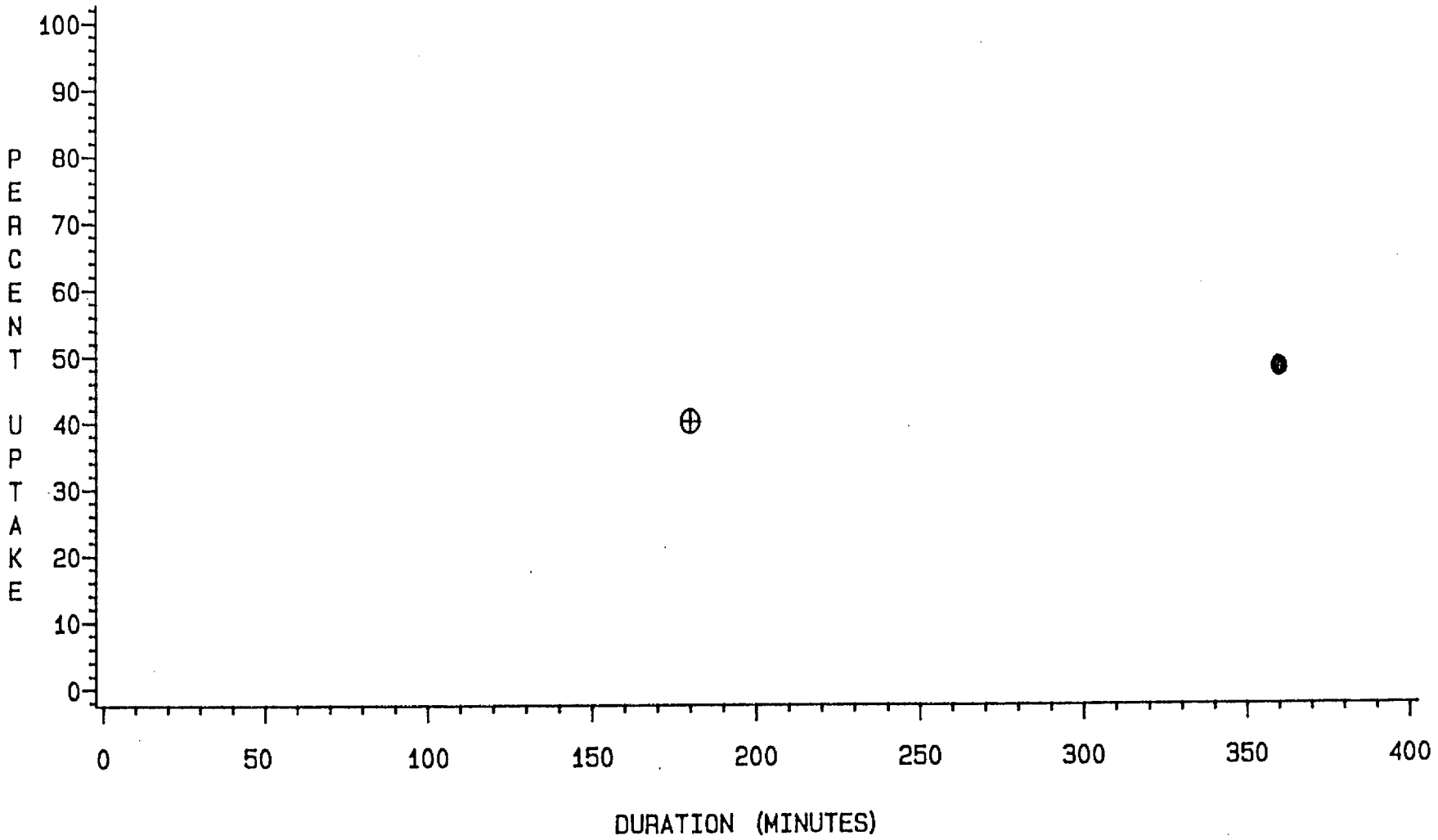


⊕ – RAABE/BEAGLES ● – MEDINSKY/RAT

FIGURE 8

Comparison of observed uptake fractions of methyl bromide vapor by beagles in this project and in reported studies with Fischer-344 rats by Medinsky et al. (1985) with respect to duration of exposure.

METHYLBROMIDE % UPTAKE



⊕ – RAABE/BEAGLES ● – MEDINSKY/RAT

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. Since mammalian ventilation is quantitatively similar among species depending on metabolic oxygen needs, the scaling to other species in the first approximation implies similar uptake fractions under similar metabolic conditions. This is true even though the other data were collected at concentrations up to 1,000 times higher.

Astrand (1983) provided data that show the effect of increased ventilation associated with higher levels of activity. With strenuous exertion the increased breathing rate and volumes led to about a one-fifth reduction in the observed uptake fractions for several chemical vapors as compared to measurements made during restful breathing.

The clearance data provided a check on the experiments since they represented the mass balance calculations. Essentially all ^{14}C was accounted in these clearance studies for trichloroethylene, benzene, and chloroform. Methyl bromide remained in the dogs for extended periods so that much of it was not accounted for in the brief clearance studies; this results agrees with other studies (Medinsky et al., 1985). It was not possible to precisely determine the clearance half-times for dimethylnitrosamine or formaldehye. This was because of the rapid clearance that indicated more than enough ^{14}C being exhaled to account for the measured uptake. The appearance of $^{14}CO_2$ as a metabolic product was dependent on the specific metabolic pathways of elimination of the chemicals. For example, benzene had very little conversion to carbon dioxide, while carbon dioxide was a major metabolic product of chloroform.

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APPENDIX A: Sample Worksheets for Uptake Measurement

The sample worksheets presented are for trichloroethylene (C_2HCl_3) exposure #15 identified as C_2HCl_3#15ABS and for methyl bromide (CH_3Br) exposure #21 identified as CH_3Br#21ABS. 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 16 titled columns; columns A to P. The area bounded by rows 5 and 6 and columns A and B identify the beagle used and the exposure date. Row 9 column A was labeled "BLANK DPM". The data for control blanks in DPM for duplicate samples of 1.0 mL ethyl alcohol + 20.0 mL 3a70B liquid scintillation cocktail appear in columns E and F with the average in row 9 column H. Data for 1.0 mL of $^{14}CO_2$-absorbing cocktail + 20.0 mL 3a70B cocktail were virtually identical so only the alcohol blank was used except for the methyl bromide exposures where only $^{14}CO_2$ cocktail blank was used. The C_2HCl_3#15ABS worksheet represented the way in which trichloroethylene, benzene, formaldehyde, dimethylnitrosamine, and chloroform vapors were studied; the first two bubblers had acidified ethyl alcohol and the third bubbler had ^{14}C cocktail in each case. The methyl bromide studies illustrated by CH_3Br#21ABS utilized $^{14}CO_2$-absorbing cocktail in each of the three absorber bubblers.

Description of C_2HCl_3#15ABS

Column A was labeled "BUBBLER #" and runs from row 11 to row 40 or 43 depending on whether 30 or 33 bubblers were used during that exposure. The bubbler data were grouped into sets of three and were separated by an underline after every third bubbler. The tare weight in grams for each bubbler was recorded in column B. Column C labeled "FINAL WEIGHT" was the weight in grams of each bubbler after the exposure. Column D labeled "TOTAL VOL(ML)" was obtained by subtracting the tare weight from the final weight for each bubbler and dividing by 0.8065 or 0.9256. The values of 0.8065 and 0.9256 were the measured specific gravities of ethyl alcohol and $^{14}CO_2$-absorbing cocktail, respectively. The net weight of the first and second alcohol bubblers of each set of three were divided by 0.8065. For example, bubbler #1 = 494.06 - 394.85/0.8065 = 123.01 mL and bubbler #3 = 497.92 - 384.97/0.9256 = 122.03 mL.

Column E labeled "LITERS", contain the total liters used during each 0.5 hour period. Columns F ("SAMPLE#1 DPM/ML") and G ("SAMPLE#2 DPM/ML") contain the data for 1.0 mL of each bubbler + 20 mL of 3a70B liquid-scintillation cocktail in duplicate. Column H labeled "AVE NET DPM/ML" contains the average counts in disintegrations per minute (DPM) for each set of duplicate bubbler samples minus the average blank in DPM found in row 9 column H. For example, in C_2HCl_3#15ABS bubbler #1 = [(128081 + 131144)/2]-31.45 = 129581.04. Column I labeled "nCi/ML" was calculated by dividing the average net DPM/mL for each bubbler in column H by 2220 which is the number of radioactive disintegrations per minute per nanocurie. For bubbler #1 = 129581.04/2220 = 58.37. Column J labeled "nCi/BUBBLER" was calculated by multiplying the nCi/mL in column I by the volume for that bubbler in column D. For example, bubbler #1 = 58.37 nCi/mL * 123.01 mL = 7180.25 nCi/BUBBLER.

Column K labeled "EFF" lists the efficiency of the first and second bubblers of each set of three bubblers for the exposure vapor. The efficiency of bubbler #1 was calculated by subtracting the nCi/BUBBLER of bubbler #2 from the nCi/BUBBLER #1 divided by the nCi/BUBBLER #1 and multiplied by 100. For example, in C_2HCl_3#15ABS the efficiency of bubbler #1 = [(7180.25 - 783.07)/7180.25 * 100] = 89.09%. The average test efficiency for the pre-test and post-test is also in column K at row 42 or 45 depending on whether 30 or 33 bubblers were used. It was calculated by averaging the efficiency of bubbler #1 and bubbler #25 since they are always the first bubblers in the pre-test and post-test. For example, the average test efficiency = [(89.09 + 89.56)/2] = 89.32. The average test efficiency was used in the calculations as the bubbler efficiency for vapor collection. Two other values were calculated and given but not used; they were the average run efficiency (the average efficiency of the first bubbler in each of the six 0.5 hour exposure periods) and the average efficiency (the average of both the test and run averages).

Column L labeled "TOTAL nCi" is the sum of the nCi/BUBBLER for each set of three bubblers. For example, in C_2HCl_3#15ABS the total nCi for the pre-test was the sum of first three bubblers = [7180.25 + 783.07 + 145.93] = 8109.26.

Column M labeled "ESTIMATED TOTAL nCi" is composed of two values for each set of three bubblers. The top value is the estimated total nCi of ^{14}C labeled vapor that entered the bubbler train. This was calculated by adding the nCi in the second bubbler divided by the average test efficiency plus the nCi in the first bubbler for each 0.5 hour period. For example, in C_2HCl_3 #15ABS the estimated total nCi for the pre-test = 7180.25 + 783.07/.8932 = 8056.91. The second value represents the estimated total nCi of $^{14}CO_2$ that was collected by the third bubbler after subtracting the predicted activity of vapor activity collected in the third bubbler. For example, estimated total nCi of $^{14}CO_2$ (or ^{14}C impurities) in the pre-test = 145.93 - 783.07 * (1 - 0.8932) = 62.34.

Column N labeled "nCi/L" is composed of two values for each set of three bubblers. The top value is the nCi/LITER of ^{14}C labeled exposure vapor and was calculated by dividing the estimated total nCi of ^{14}C exposure vapor by the measured liters of vapor used in each 0.5 hour period. For example, the nCi/LITER or concentration of the exposure vapor in the pre-test = 8056.91/88.90 = 90.63. The second value is the nCi/LITER of $^{14}CO_2$ in the exposure vapor and was calculated by dividing the estimated total nCi of $^{14}CO_2$ in every third bubbler by the measured liters of vapor used in each 0.5 hour period. For example, the nCi/LITER or concentration of $^{14}CO_2$ (or trace ^{14}C impurities) in the pre-test = 62.34/ 88.90 = 0.70. The next to last value in column N is the average nCi/LITER of $^{14}CO_2$ (or ^{14}C-labeled impurities) in the exposure vapor as measured in bubblers #3 and #27 of the pre-test and post-test. For example, the average nCi/LITER or concentration of $^{14}CO_2$ or ^{14}C impurities = (0.70 + 0.75)/2 = 0.73. The last value in column N is the average nCi/LITER of ^{14}C labeled exposure vapor and was calculated by averaging the pre-test and post-test. For example, the the average nCi/LITER or concentration of ^{14}C labeled vapor for the exposure = (90.63 + 87.61)/2 = 89.12.

Column O labeled "%C_2HCl_3 UPTAKE" is the amount of ^{14}C labeled exposure vapor that was taken up by the dog and was calculated by subtracting from 100% the ratio (in percent) of the concentration in nCi/LITER for each of the six 0.5 hour exposure sub-periods divided by the average concentration of ^{14}C labeled vapor in nCi/LITER. For example, the %C_2HCl_3 uptake for the first 0.5 hour period= 100% - (49.23/89.12) * 100 = 44.75%.

Column P labeled "% CO_2 EXHALED" was the amount of $^{14}CO_2$ exhaled as a percentage of the average concentration of ^{14}C labeled vapor and consisted of two values for each of the six 0.5 hour exposure periods. The top value was calculated as the percentage of $^{14}CO_2$ in every third bubbler by the average concentration of ^{14}C labeled vapor. For example, in the first 0.5 hour exposure period the % CO_2 exhaled = 0.50/89.12 * 100 = 0.57%. Since it was shown that the exposure vapor had an average of 0.73 nCi/L of $^{14}CO_2$ or ^{14}C impurities this was subtracted from the excess nCi in every third bubbler to give the second or corrected % CO_2 exhaled value. For example, in the first 0.5 hour period the % CO_2 exhaled = (0.50 - 0.73)/89.12 * 100 = -0.25%. This negative value indicates that within experimental error no $^{14}CO_2$ was exhaled in the first 0.5 hour period. For the sixth 0.5 hour exposure period the corrected % CO_2 exhaled = (1.54 - 0.73)/89.12 * 100 = 1.37%. For the clearance studies (immediately after exposure, 2 hour post-exposure and 21 hours post-exposure) only one uncorrected value for % CO_2 exhaled was calculated because there was no need to correct for the $^{14}CO_2$ or traces of ^{14}C labeled impurities in the exposure vapor since the exposure was over and the dog was the sole source of exhaled $^{14}CO_2$.

Description of CH_3Br#21ABS

Column A was labeled "BUBBLER #" and runs from row 11 to row 40 or 43 depending on whether 30 or 33 bubblers were used during that exposure. The bubbler data were grouped into sets of three and were separated by an underline after every third bubbler. The tare weight in grams for each bubbler was recorded in column B. Column C labeled "FINAL WEIGHT" was the weight in grams of each bubbler after the exposure. Column D labeled "TOTAL VOL(ML)" was obtained by subtracting the tare weight from the final weight for each bubbler and dividing 0.9256. The value of 0.9256 was the measured specific gravity of the $^{14}CO_2$-absorbing cocktail that was in all three bubblers.

Column E labeled "LITERS", contain the total liters used during each 0.5 hour period. Columns F and G contain the DPM/mL of each of the first two bubblers based on counts of 1 mL aliquots in 20 mL of 3A70B scintillation cocktail in duplicate. Column H labeled "AVE NET DPM/ML" contains the average counts in DPM for each set of duplicate bubbler samples minus the average blank in DPM found in row 9 column H. Column I labeled "nCi/mL" was calculated by

dividing the average net DPM/mL for each bubbler in column H by 2220 which is the number of DPM/nanocurie. Column J labeled "nCi/BUBBLER" was calculated by multiplying the nCi/mL in column I by the volume for that bubbler in column D.

Column K labeled "EFF" lists the efficiency of the first and second bubblers of each set of three bubblers for the exposure vapor. For methyl bromide exposures the average test efficiency was the average of the efficiencies of the second bubblers in the pre-test and post-test (bubblers #2 and #26 on CH_3Br#21ABS) because the first bubblers will collect both some methyl bromide and all $^{14}CO_2$. The average test efficiency was used in the calculations as the bubbler efficiency for vapor collection. Two other values were calculated and given but not used; they were the average run efficiency (the average efficiency of the second bubbler in each of the six 0.5 hour exposure periods) and the average efficiency (the average of both the test and run averages).

Column L labeled "TOTAL nCi" is the sum of the nCi/BUBBLER for each set of three bubblers. Column M labeled "ESTIMATED TOTAL nCi" is composed of two values for each set of three bubblers. The top value is the estimated total nCi of ^{14}C labeled vapor that entered the bubbler train. For methyl bromide exposures the top value was calculated by dividing the nCi/BUBBLER for every second bubbler in each 0.5 hour period by [(1 - average test efficiency) * average test efficiency]. The second value in column M is the calculated excess activity in the first bubbler of each set that is considered to be $^{14}CO_2$. It is calculated by subtracting from the nCi/BUBBLER from the first bubbler of each set the nCi/Bubbler from the second bubbler divided by (1 - the average test efficiency).

Column N labeled "nCi/L" is composed of two values for each set of three bubblers. The top value is the nCi/LITER of ^{14}C labeled exposure vapor and was calculated by dividing the estimated total nCi of ^{14}C exposure vapor by the measured liters of vapor used in each 0.5 hour period. The second value is the nCi/L of $^{14}CO_2$ and was calculated by dividing the estimated total nCi of ^{14}C exposure vapor by the measured liters of vapor used in each 0.5 hour period. The next-to-last value in column N is the average nCi/L of $^{14}CO_2$ in the exposure vapor as measured in the test runs (bubblers #1 and #25). The last value in column N is the average nCi/LITER of ^{14}C labeled exposure vapor and was calculated by averaging the pre-test and post-test.

Column O labeled "%CH_3Br UPTAKE" is the amount of ^{14}C-labeled exposure vapor that was taken up by the dog and was calculated by subtracting from 100% the ratio (in percent) of the concentration in nCi/LITER for each of the six 0.5 hour exposure periods divided by the average concentration of ^{14}C-labeled vapor in nCi/LITER. For methyl bromide exposures column O contains two values. The top value is calculated the same as just described but the second value is corrected for the inappropriate estimation of $^{14}CO_2$ associated with the poor precision of this system for measurement of carbon dioxide during exposure. The post exposure measurements indicated little $^{14}CO_2$ is exhaled by the beagles that have inhaled methyl bromide. Other studies indicate that metabolism of methyl bromide to carbon dioxide is slow (Medinsky, et al., 1985). Hence small or negative values determined for $^{14}CO_2$ were added (with appropriate sign) to the exhaled vapor value and subtracted (with appropriate sign) from the uptake fraction to provide the corrected observed percent uptake.

Column P labeled "% CO_2 EXHALED" was the amount of $^{14}CO_2$ exhaled as a percentage of the average concentration of ^{14}C labeled vapor and consisted of two values for each of the six 0.5 hour exposure1 sub-periods. The top value was calculated as the percentage of excess nCi in the first bubbler. The bottom value is the corrected percentage of $^{14}CO_2$ nCi/L with respect to the average concentration of the ^{14}C-labeled methyl bromide. It was seen that in this case the exposure vapor had an average of 4.14 nCi/L of $^{14}CO_2$. This was subtracted from the calculated nCi/L of $^{14}CO_2$ for each of the six 0.5 hour exposure sub-periods and the result was divided by the average concentration of ^{14}C-labeled methyl bromide to give the second or corrected "% CO_2 EXHALED."

For the clearance studies (immediately after exposure, 2 hour post-exposure and 21 hours post-exposure) only one uncorrected value for % CO_2 exhaled was calculated because there was no need to correct for the $^{14}CO_2$ or traces of ^{14}C labeled impurities in the exposure vapor since the exposure was over and the dog was the sole source of exhaled $^{14}CO_2$.

BUBBLER #	TARE WEIGHT	FINAL WEIGHT	TOTAL VOL(ML)	LITERS	SAMPLE#1 DPM/ML	SAMPLE#2 DPM/ML	AVE NET DPM/ML	nCi/ML	nCi/ BUBBLER	EFF	ESTIMATED TOTAL nCi	TOTAL nCi	nCi/L	%C2HC13 UPTAKE	% CO2 EXHALED
ANIMAL ID	76K01B														
EXP. DATE	7/16/85														
BLANK DPM					31.03	31.88	31.45								
1	394.85	494.06	123.01	88.90	128081.00	131144.00	129581.04	58.37	7180.25	89.09	8109.26	8056.91	90.63		
2	394.35	496.50	126.66		13810.00	13703.50	13725.29	6.18	783.07	81.36					
3	384.97	497.92	122.03		2673.26	2699.35	2654.85	1.20	145.93			62.34	0.70		
4	392.32	493.39	125.32	46.90	39161.10	37911.70	38504.94	17.34	2173.61	94.43	2331.16	2309.05	49.23	44.75	0.57
5	392.79	495.42	127.25		2124.87	2159.07	2110.51	0.95	120.98	69.77					
6	375.98	490.78	124.03		683.02	689.10	654.60	0.29	36.57			23.66	0.50		-0.25
7	381.89	483.49	125.98	46.80	37328.50	37053.10	37159.34	16.74	2108.65	94.28	2283.05	2243.67	47.94	46.20	0.98
8	395.56	498.13	127.18		2171.44	2101.93	2105.23	0.95	120.60	55.39					
9	395.43	510.02	123.80		988.41	1003.91	964.70	0.43	53.80			40.92	0.87		0.16
10	379.58	478.43	122.57	47.60	37528.10	39312.60	38388.89	17.29	2119.46	94.20	2308.06	2256.97	47.42	46.79	1.24
11	382.37	485.52	127.90		2165.59	2161.55	2132.11	0.96	122.84	46.46					
12	402.29	516.35	123.23		1214.17	1218.27	1184.76	0.53	65.76			52.65	1.11		0.42
13	401.63	496.90	118.13	41.30	34742.70	35050.50	34865.14	15.71	1855.20	94.64	2023.08	1966.52	47.62	46.57	1.57
14	399.30	494.87	118.50		1849.72	1938.97	1862.89	0.84	99.44	31.17					
15	400.41	515.87	124.74		1232.62	1266.33	1218.02	0.55	68.44			57.82	1.40		0.75
16	396.76	491.85	117.90	45.90	38335.30	38172.50	38222.44	17.22	2030.00	94.13	2232.41	2163.33	47.13	47.11	1.73
17	401.08	498.32	120.57		2268.74	2179.99	2192.91	0.99	119.10	30.05					
18	399.46	515.41	125.27		1507.26	1508.63	1476.49	0.67	83.32			70.60	1.54		0.91
19	399.95	496.42	119.62	40.00	36233.60	35912.90	36041.79	16.24	1941.96	93.42	2161.36	2085.01	52.13	41.51	2.19
20	400.64	497.67	120.31		2394.62	2383.80	2357.75	1.06	127.78	28.30					
21	400.16	515.96	125.11		1659.72	1654.72	1625.76	0.73	91.62			77.98	1.95		1.37
22	400.46	497.23	119.99	39.60	2052.75	2042.31	2016.07	0.91	108.97	93.60	170.41	116.77	2.95		1.52
23	400.74	497.58	120.07		166.68	153.97	128.87	0.06	6.97	-681.58					
24	400.60	515.24	123.85		1002.47	1013.41	976.48	0.44	54.48			53.73	1.36		
25	399.31	494.84	118.45	89.60	133030.00	130462.00	131714.54	59.33	7027.75	89.56	7907.69	7849.52	87.61		
26	403.18	500.23	120.33		13634.90	13512.10	13542.04	6.10	734.04	80.12					
27	400.67	515.72	124.30		2638.41	2636.04	2605.77	1.17	145.90			67.53	0.75		
28	401.19	501.09	123.87	49.30	431.60	417.58	393.13	0.18	21.94	90.29	32.83	24.32	0.49		0.19
29	393.00	492.95	123.93		74.16	65.02	38.13	0.02	2.13	-311.60					
30	395.84	510.08	123.42		192.04	186.09	157.61	0.07	8.76			8.54	0.17		
AVE TEST										89.32					
AVE RUN										94.19			0.73		
AVE EFF										91.75			89.12		

BUBBLER #	TARE WEIGHT	FINAL WEIGHT	TOTAL VOL(ML)	LITERS	SAMPLE#1 DPM/ML	SAMPLE#2 DPM/ML	AVE NET DPM/ML	nCi/ML	nCi/ BUBBLER	EFF	ESTIMATED TOTAL nCi	TOTAL nCi	nCi/L	%CH3BR UPTAKE	% CO2 EXHALED
ANIMAL ID	76K01B														
EXP. DATE	8/27/85														
BLANK DPM					34.72	35.75	35.23								
1	394.85	506.74	120.88	59.62	64288.50	63927.20	64072.61	28.86	3488.89	59.88	5478.33	5709.11	95.76		
2	394.35	506.84	121.53		25522.60	25680.50	25566.31	11.52	1399.61	57.86					
3	384.97	496.91	120.94		10966.50	10758.70	10827.36	4.88	589.84			236.87	3.97		
4	392.32	507.59	124.54	43.53	27976.20	27937.60	27921.66	12.58	1566.32	62.34	2359.53	2406.43	55.28	40.34	4.85
5	392.79	506.58	122.94		10844.10	10532.90	10653.26	4.80	589.94	65.55					
6	375.98	487.97	120.99	4033.26	3827.56	3702.04	3729.56	1.68	203.26			195.57	4.49	39.95	0.38
7	381.89	496.03	123.31	41.49	28535.60	28782.10	28623.61	12.89	1589.96	60.77	2444.24	2544.07	61.32	33.82	3.66
8	395.56	508.43	121.94		11448.30	11331.00	11354.41	5.11	623.69	63.03					
9	395.43	507.99	121.61	3844.24	4269.43	4220.32	4209.64	1.90	230.60			140.81	3.39	34.62	-0.80
10	379.58	493.54	123.12	43.75	26838.80	27057.20	26912.76	12.12	1492.57	60.17	2312.01	2425.02	55.43	40.18	2.74
11	382.37	493.75	120.33		10988.60	11017.60	10967.86	4.94	594.50	62.16					
12	402.29	513.19	119.81	4053.64	4178.91	4227.35	4167.89	1.88	224.94			111.23	2.54	41.90	-1.72
13	401.63	516.03	123.60	42.90	28253.70	27942.50	28062.86	12.64	1562.36	60.15	2418.23	2539.95	59.21	36.10	2.91
14	399.30	511.93	121.68		11456.00	11334.80	11360.16	5.12	622.68	62.55					
15	400.41	512.20	120.78	3974.89	4276.01	4367.28	4286.41	1.93	233.20			115.56	2.69	37.66	-1.56
16	396.76	511.41	123.87	42.10	27092.20	27026.90	27024.31	12.17	1507.83	60.38	2328.48	2436.79	57.88	37.53	3.07
17	401.08	514.70	122.75		10940.20	10737.90	10803.81	4.87	597.39	62.63					
18	399.46	512.28	121.89	3900.76	4119.51	4083.59	4066.31	1.83	223.26			119.79	2.85	38.93	-1.39
19	399.95	516.12	125.51	38.65	25058.60	24482.40	24735.26	11.14	1398.41	55.67	2265.34	2528.59	65.42	29.39	-1.17
20	400.64	513.97	122.44		11374.90	11174.60	11239.51	5.06	619.89	60.15					
21	400.16	513.62	122.58	3581.10	4623.95	4394.45	4473.96	2.02	247.04			-41.93	-1.08	35.03	-5.64
22	400.46	518.97	128.04	43.06	1374.25	1319.87	1311.82	0.59	75.66	73.41	108.22	82.06	1.91		0.72
23	400.74	519.07	127.84		378.60	390.52	349.32	0.16	20.12	38.13					
24	400.60	520.14	129.15		256.23	242.14	213.95	0.10	12.45			28.92	0.67		
25	399.31	519.40	129.74	60.35	57787.30	56518.80	57117.81	25.73	3338.12	60.31	5245.10	5404.41	89.55		
26	403.18	514.01	119.74		24788.30	24410.80	24564.31	11.07	1324.91	56.07					
27	400.67	511.45	119.68		10705.40	10958.50	10796.71	4.86	582.07			259.66	4.30		
28	277.50	389.67	121.19	63.67	671.43	645.03	622.99	0.28	34.01	92.22	37.70	10.80	0.17		0.47
29	393.00	503.88	119.79		70.94	97.63	49.05	0.02	2.65	60.63					
30	395.84	505.92	118.93		54.06	55.31	19.45	0.01	1.04			27.86	0.44		
AVE TEST										56.96					
AVE RUN										62.68			4.14		
AVE EFF										59.82			92.65		

APPENDIX B : Sample Worksheet for Biological Data

The biological raw data for each exposure was recorded on a data form, reviewed, and keyed into a computer file using the office terminal. The data were calculated using the spread-sheet program C-CALC on the Data General MV8000 at LEHR. The sample worksheet presented is for trichloroethylene, exposure #15, and is identified by the heading that contains the exposure number (15), the dog I. D. (76K01B), compound name (C_2HCL_3), and the exposure date (7/16/85). The worksheet is divided into two sections that contain the data and the results for blood (section I), and excreta with cage wash (section II). Each section is divided into several columns (alphabetical order from left to right) as described below :

Section I : Blood, plasma, and RBC

COLUMN #	LABEL	DESCRIPTION
A	Sample Type	Blood
B	Sample Time	Includes exposure date and collection time
C	T.P.E. (hours)	Time post-exposure starting time
D	Blood Total (g)	Weight (g) of collected blood sample
E through I	RBC	Raw data and results for red blood cells
E	(g)	Weight (g) of collected RBC sample
F	c.s. (g)	Weight (g) of combusted RBC sample
G	c.s. (DPM)	DPM for combusted RBC
H	nCi/g	= (G) / [2220 x (F)]
I	Net nCi/g	= (nCi/g of exposed) - (nCi/g pre-exposed)

J through N	Plasma	Raw data and results for plasma
J	(g)	Weight (g) of collected plasma sample
K	c.s. (g)	Weight (g) of counted plasma aliquot
L	c.s. (DPM)	DPM per counted aliquot
M	nCi/g	= (L) / [(2000 x (K)]
N	Net nCi/g	= (nCi/g of exposed) - (nCi/g pre-exposed)
O	Blood Net nCi/g	= Net (M + N) / 2
P	Accum. Inhaled nCi	= Total inhaled (nCi) for the exposure duration, (the time from the beginning of the exposure to the sample time).
Q through S		Plasma, RBC, and blood burden as a percentage of total inhaled
Q	Plasma	= (N) x 40 x body weight (kg) x 100 / (P)
R	R.B.C.	= (I) x 40 x body weight (kg) x 100 / (P)
S	Blood	= (O) x 80 x body weight (kg) x 100 / (P)

Section II : Urine, Fecal, and Cage Wash

Column #	Label	Description
A	Sample	Urine, fecal, or cage wash
B	Sample date	Date of collection
C	T.P.E. (days)	Days post-exposure date
D	Tot. Vol. (mL)	Total volume of sample collected
E	mL or g	Volume (mL) or weight (g) of aliquot taken for counting
F	DPM c. sample	DPM per aliquot
G	nCi (g or mL)	= (DPM per aliquot) / (2220 x weight (g) or volume (mL)
H	Net nCi/mL or g	= Value in (G) - (nCi/g of counter aliquot at pre-exposure time)
I	Total nCi	= net nCi/g x total volume (mL) or weight (g)
J	Total % of inhaled	= Values in (I) x 100 / total inhaled

05-May-86 11:12
Worksheet: (77) ARB#15C2CHCL3-COPY Range: A1..V53

EXPOSURE#	15	DATE:	7/16/85	Start:	10:38	End:	1:38												
DOG I.D:	76K01B	Duration	(Min):	180	A.(Kg)=	11.360													
COMPOUND:	C2HCl3		BLOOD					R.B.C					PLASMA		Accum.	PLASMA	R.B.C	BLOOD
SAMPLE	SAMPLE	T.P.E	Total(g)	R.B.C	R.B.C	R.B.C	R.B.C	Net	PLASMA	PLASMA	PLASMA	PLASMA	Net	BLOOD	Inhaled	%	%	%
Type	TIME	(hours)		(g)	C.S(g)	C.S.(DPM)	nCi/g	nCi/g	(g)	C.S(g)	C.S.(DPM)	nCi/g	nCi/g	nCi/g(net	nCi	TOTAL	TOTAL	Total
BLOOD	16/10:38	0	2.055	1.011	0.064	39.400	0.277		1.044	1.044	41.960	0.018			0	45.911	ision by	ision by
BLOOD	11:08	0.500	2.521	1.110	0.080	59.860	0.337	0.060	1.411	1.411	417.460	0.133	0.115	0.087	3.947	1.326	0.688	2.014
BLOOD	11:38	1.000	2.354	1.044	0.066	66.130	0.451	0.174	1.310	1.310	902.950	0.310	0.292	0.233	7.885	1.685	1.003	2.688
BLOOD	12:08	1.500	2.551	1.075	0.061	78.560	0.580	0.303	1.476	1.476	1,691.090	0.516	0.498	0.400	11.891	1.903	1.157	3.060
BLOOD	12:38	2.000	2.430	1.035	0.062	86.460	0.628	0.351	1.395	1.395	2,066.870	0.667	0.649	0.500	15.367	1.920	1.037	2.957
BLOOD	1:08	2.500	2.510	1.049	0.068	105.230	0.697	0.420	1.461	1.461	2,989.900	0.897	0.879	0.649	19.229	2.077	0.992	3.069
BLOOD	1:38	3.000	2.582	1.066	0.062	114.510	0.832	0.555	4.516	4.516	3,651.800	0.364	0.346	0.450	22.596	0.696	1.115	1.812
BLOOD	2:08	3.500	2.167	0.855	0.073	122.530	0.756	0.479	4.312	4.312	3,432.820	0.359	0.341	0.410	22.596	0.685	0.963	1.648
BLOOD	3:08	4.500	2.667	1.292	0.063	103.920	0.743	0.466	4.375	4.375	3,647.600	0.376	0.357	0.412	22.596	0.719	0.937	1.655
BLOOD	4:08	5.500	2.456	1.235	0.061	114.560	0.846	0.569	1.221	1.221	3,709.300	1.368	1.350	0.959	22.596	2.716	1.144	3.859
BLOOD	7/17	24.000	3.156	1.734	0.073	86.450	0.533	0.256	1.422	1.422	4,094.930	1.297	1.279	0.768	22.596	2.572	0.515	3.087
BLOOD	7/18	48.000	3.157	1.631	0.064	62.080	0.437	0.160	1.526	1.526	2,326.870	0.667	0.669	0.414	22.596	1.345	0.321	1.666
BLOOD	7/19	72.000	3.232	1.762	0.069	51.030	0.333	0.056	1.470	1.470	1,484.190	0.455	0.437	0.246	22.596	0.878	0.112	0.990
BLOOD	7/20	96.000	3.207	1.729	0.083	59.100	0.321	0.043	1.478	1.478	1,202.170	0.366	0.348	0.196	22.596	0.700	0.087	0.788
BLOOD	7/21	120.000	3.167	1.454	0.071	44.530	0.283	0.005	1.713	1.713	932.550	0.245	0.227	0.116	22.596	0.457	0.010	0.467

EXP#15	DATE:	7/16/85	COMPOUND:	C2HCl3	DOG I.D:	76K01B			
	SAMPLE	T.P.E	Tot.Vol	mL or g	DPM/	nCi	Net	Total	Total %
SAMPLE	DATE	(Days)	(mL)	Sample	C.sample	g or mL	nCi/ml	nCi	Inhaled
URINE	7/16/85	0	0.200	0.200	50.00				
URINE	7/17/85	1.000	86.010	0.200	16,954.80	38.186	38.186	3,284.420	14.536
URINE	7/18/85	2.000	251.790	0.200	4,475.040	10.079	10.079	2,537.771	11.231
URINE	7/19/85	3.000	476.000	0.200	732.840	1.651	1.651	785.657	3.477
TOTAL						ision by	N/A	6,607.848	29.244
FECAL	7/16/85	0	0.057	0.057	50.00				
FECAL	7/17/85	1.000	15.420	0.054	57.150	0.477	0.477	7.351	0.033
FECAL	7/18/85	2.000	62.610	0.057	462.850	3.658	3.658	229.011	1.014
FECAL	7/19/85	3.000	137.260	0.056	161.480	1.299	1.299	178.288	0.789
TOTAL						1.299	1.299	414.650	1.835
CAGE WASH	7/16/85	0	1.000	1.000	50.000	0.023			
CAGE WASH	7/17/85	1.000	194.360	0.200	710.800	1.601	1.578	306.774	1.358
CAGE WASH	7/18/85	2.000	114.050	0.200	91.770	0.207	0.184	21.004	0.093
CAGE WASH	7/19/85	3.000	195.720	0.200	48.940	0.110	0.088	17.165	0.076