BIOAVAILABILITY OF ORGANIC SOLVENTS IN SOILS. INPUT INTO BIOLOGICALLY-BASED DOSE-RESPONSE MODELS FOR HUMAN RISK ASSESSMENT

Ronald C. Wester, Xiaoying Hui, Howard I. Maibach

Department of Dermatology,

University of California, San Francisco, CA

Karla Thrall, Torka S. Poet, Richard A. Corley

Battelle Pacific Northwest National Laboratory, Richland, WA

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RESEARCH OBJECTIVE

The purpose of this study is to determine the bioavailability of organic solvents following dermal exposures to contaminated soil and water. Breath analysis will be used to obtain real–time measurements of volatile organics in expired air following exposure in rats and humans. Rhesus monkeys will be used as surrogates for humans in benzene exposures. The exhaled breath data will be analyzed using physiologically–based pharmacokinetic (PBPK) models to determine the dermal bioavailability of organic solvents under realistic exposure conditions.

The end product of this research will be a tested framework for the rapid screening of real and potential exposures while simultaneously developing physiologically–based pharmacokinetic (PBPK) models to comprehensively evaluate and compare exposures to organics from either contaminated soil or water.

INTRODUCTION

Numerous sites with the DOE Complex have significant levels of organic contaminants in soil. The contaminants in these soils are slowly released and provide a potential long–term source for chemical exposures. Remediation cleanup costs for soil contaminants on DOE sites will vary dramatically with the level to which soil must be decontaminated. The difficulty in establishing soil cleanup levels stems, in part, from our lack of knowledge of the human bioavailability of chemicals following exposure to environmental media.

If no literature is available on dermal absorption, then a value of applied dose rather than absorbed dose can be used for human health risk assessment. In essence, the government can assume 100% absorption when assessing human exposure to a chemical in a medium. This practice may be far from realistic when the chemical exposure in question is to a volatile solvent. Therefore, a fundamental understanding of the kinetics and bioavailability of solvent–laden water and solvent–laden soils is necessary.

MATERIALS AND METHODS

Significant levels of trichloroethylene, perchloroethylene, benzene, and trichloroethane (methyl chloroform: MC) are found as soil contaminants at numerous sites within the DOE complex. Accordingly, these solvents have been chosen for examination in this study. Each chemical will be fully investigated sequentially across all specific aims. In this manner, analysis of each chemical will build upon the methodologies and results from previous chemicals. MC is not extensively metabolized, thus the detection of parent compound may be easier for MC than the other organic solvents chosen for the study. Therefore, MC was the volatile organic chosen to begin the study.

An ideal noninvasive methodology for assessing bioavailability of volatile organics is the analysis of exhaled breath. Breath measurements are useful in environmental exposure studies, particularly when repeated samples collected in real time allows for the tracking of trends in the changing matrix. Exhaled breath repeatedly collected during the rapid kinetic changes that occur during, and immediately aftert exposure, provides a noninvasive means for comparing differences between

exposures to single versus multiple chemicals under various conditions. A new breath–inlet system allows for continuous real–time analysis of undiluted exhaled air from rats and humans. The system uses a Teledyne 3DQ Discovery ion trap mass spectrometer (MS/MS) equipped with an atmospheric sampling glow discharge ionization source (ASGDI). The MS/MS system can provide an appraisal of individual chemical components in the breath stream in the single–digit parts–per–billion (ppb) detectable range for each of the compounds proposed for study here, while maintaining linearity of response over a wide dynamic range.

RESULTS

Photo 1 shows a volunteer during study. The volunteer breathes fresh air from a compressed air tank, and a special breathing apparatus directs only exhaled breath away from the volunteer. An aliquot of the exhaled air is directed to the mass spectrometer detector while excess exhaled breath discharges into the hood. Figure 1 illustrates the solvent–laden soil patch system and Photos 2 and 3 show the patch on the forearm of the volunteer. Photo 4 shows a volunteer with a hand immersed in a bucket which contains either solvent–laden water or solvent–laden soil.

Figure 2 shows a dose–response of methyl chloroform (MC) absorption from a volunteer with his hand in a bucket containing water and MC. AT 1% concentration (above solubility limit) MC is rapidly absorbed through skin and into the body. At 0.1% (all MC is soluble in the water) the initial absorption is delayed 30–60 minutes. At 0.01% concentration MC levels are barely above background. Methyl chloroform in exhaled breath continued to rise until 120 minutes, when the volunteer removed his hand from the bucket. Methyl chloroform levels then decreased with time.

Figure 3 shows human dermal exposure to 0.1% MD in soil in a bucket. Exhaled MC peaked at 120 minutes when the hand was removed from the soil in the bucket.

Figure 4 illustrates the setup to measure solvent from water or soil applied to the skin of living rat and measured in exhaled air. Dead rats serve as control and show that the patch system does not leak solvent into the air. Figure 5 shows methyl chloroform in expired breath following 0.3% MC in soil applied to a rat. Figure 6 shows the physiologically–based pharmacokinetic model which will be used to describe solvent bioavailability in animals in man. The model's components are determined from solvent administration to animals with timed sacrifice and organ solvent concentration determination. The curved line in Figure 5 is the model's simulation of methyl chloroform absorption and excretion from soil on the rat.

DISCUSSION

These first results shows that methyl chloroform (MC) from MC–laden soil and MC–laden water will penetrate both human and rat skin, and that the absorbed MC can be detected in exhaled breath. Methods to study both short–term exposure (hand in bucket containing either solvent–laden soil or solvent–laden water) and longer term exposure (soil and water patch) have been shown to work. The "bucket" and soil "patch" systems are conceived such that the solvent–laden media is exposed to an atmosphere (bucket to open air; patch to activated charcoal) as exists in the real world. The physiologically–based pharmacokinetic model has been fit to the first rat data. There have been no adverse effects reported from any of the human volunteers.

Planned Activities

Following collection and analysis of all the MC exposure data for rats and humans, studies will be implemented to describe the dosimetry for perchlorethylene, trichlorethylene, and benzene following dermal exposures. A working PBPK model for MC will be used as the basis for PBPK models that describe the next three chemicals. Breath exhalation profiles will be determined for these volatile chemicals in rats and humans, except for benzene, where Rhesus monkeys will be used to replace humans as study subjects.

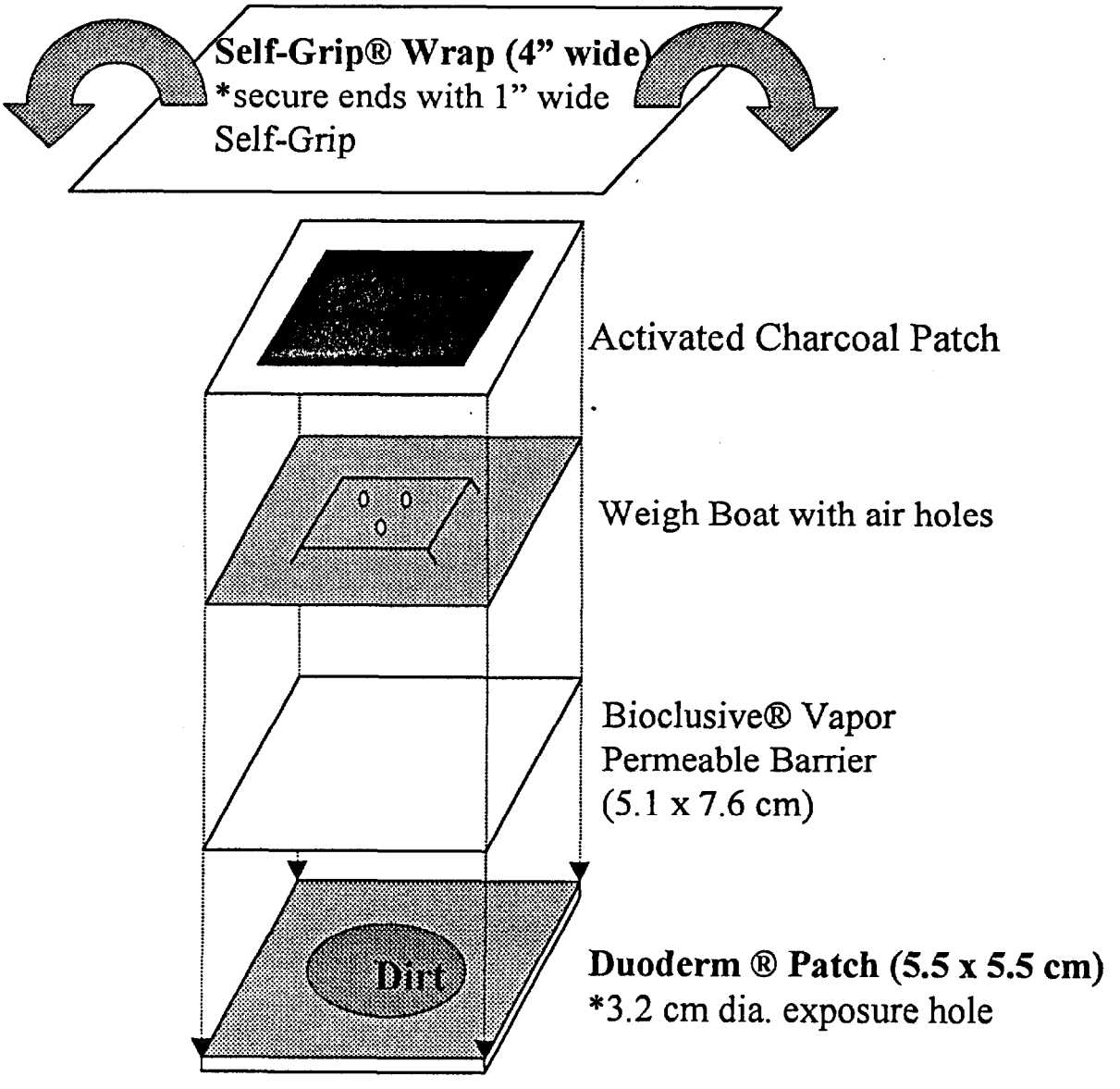

Figure 1 Patch system used for dermal exposures to methyl chloroform in soil.

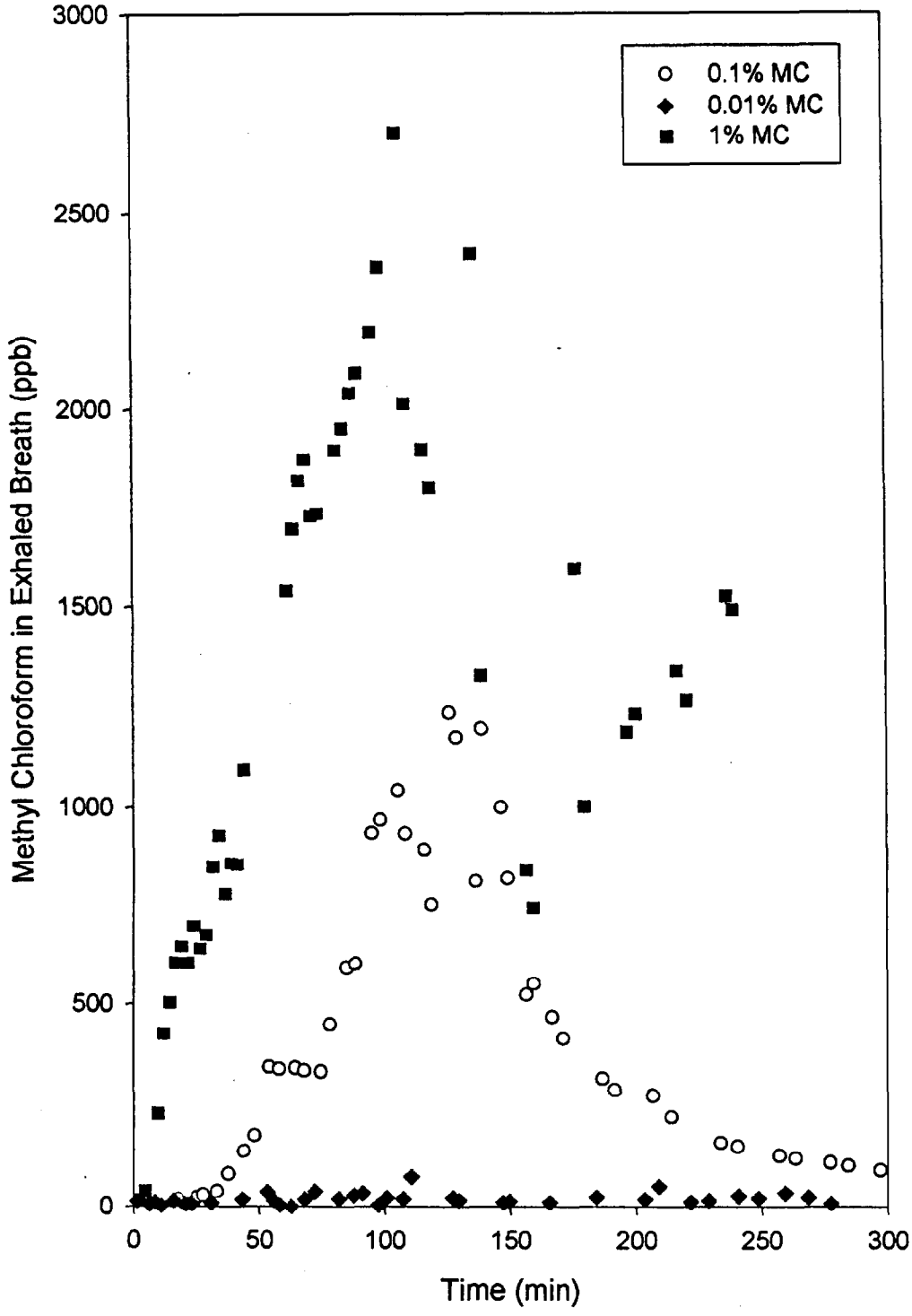

Figure 2 Dose–response of methyl chloroform absorption in volunteer with his hand in bucket containing water and methyl chloroform. AT 1% concentration (above MC solubility limit) MC is rapidly absorbed through skin into the body. At 0.1% (within MC solubility) less MC is absorbed. Note initial delay in MC absorption when all MC is soluble in water.

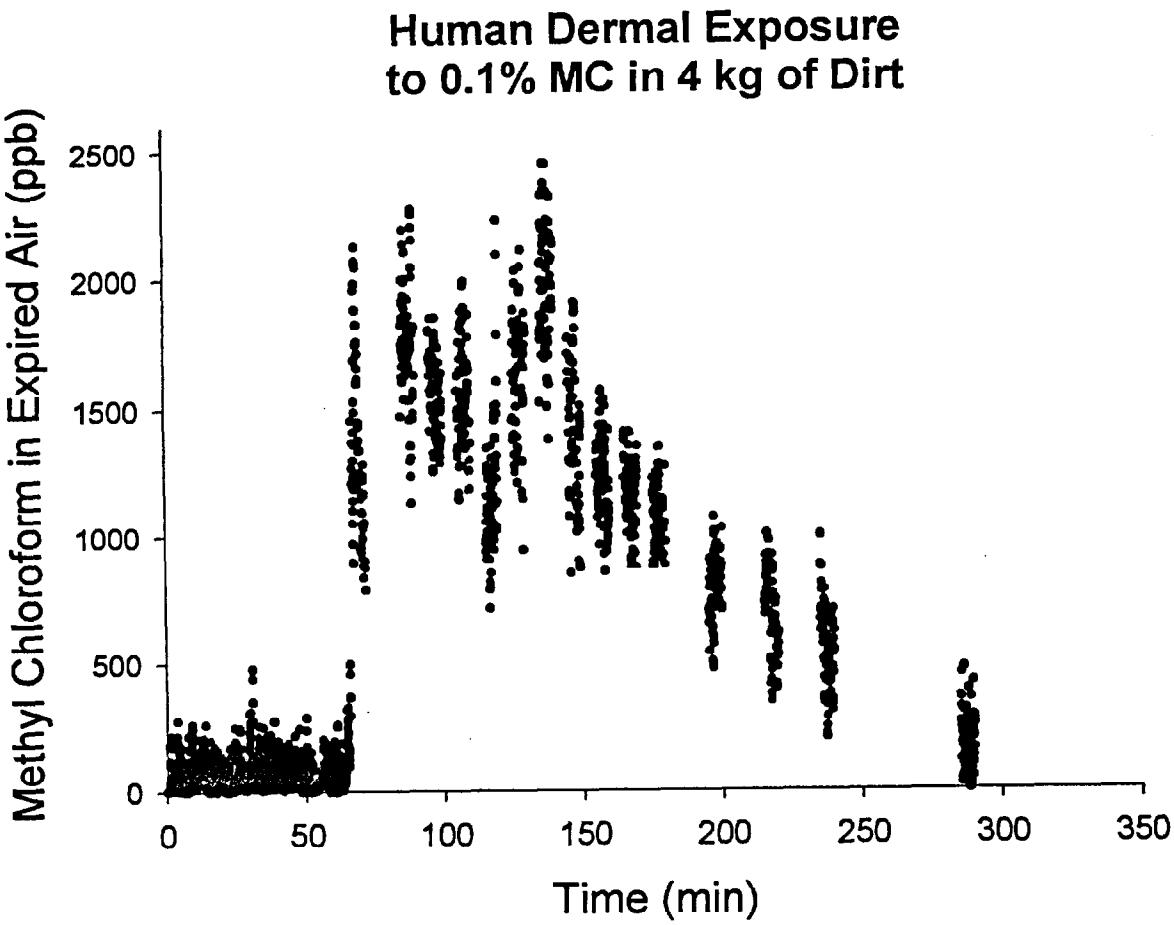

Figure 3 Human exposure to 0.1% methyl chloroform in 4 kg of dirt. A male subject placed his left hand into a bucket that contained MC–laden soil for 2 hr. The amount of MC in expired air was measured for a total of 4 hr. Points represent the expired air concentration measured every 3.8 sec.

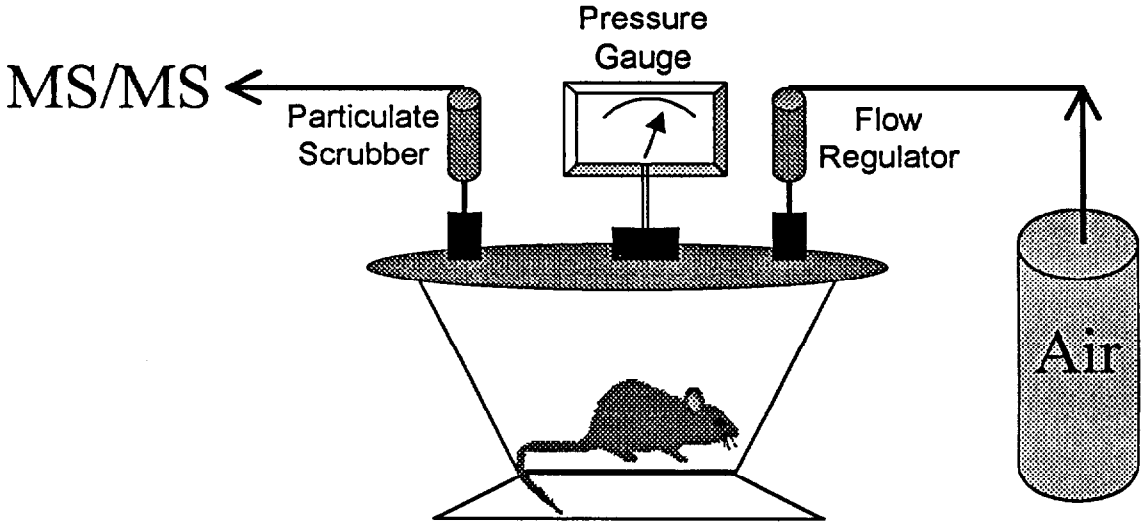

Figure 4 **Diagram of an off–gassing chamber used to measure methyl chloroform in expired air of dermally exposed rats.**

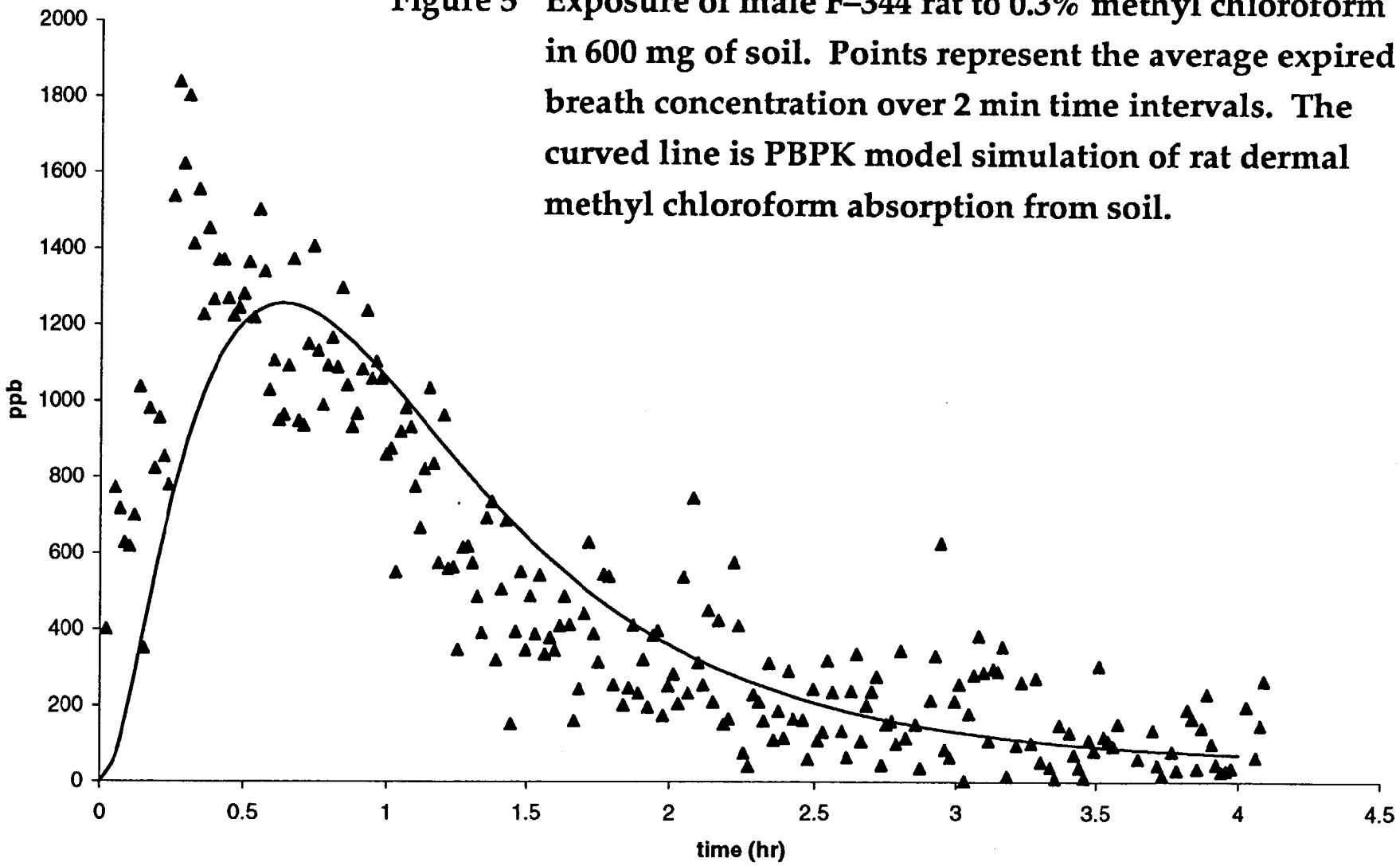

Figure 5 Exposure of male F–344 rat to 0.3% methyl chloroform in 600 mg of soil. Points represent the average expired breath concentration over 2 min time intervals. The curved line is PBPK model simulation of rat dermal methyl chloroform absorption from soil.

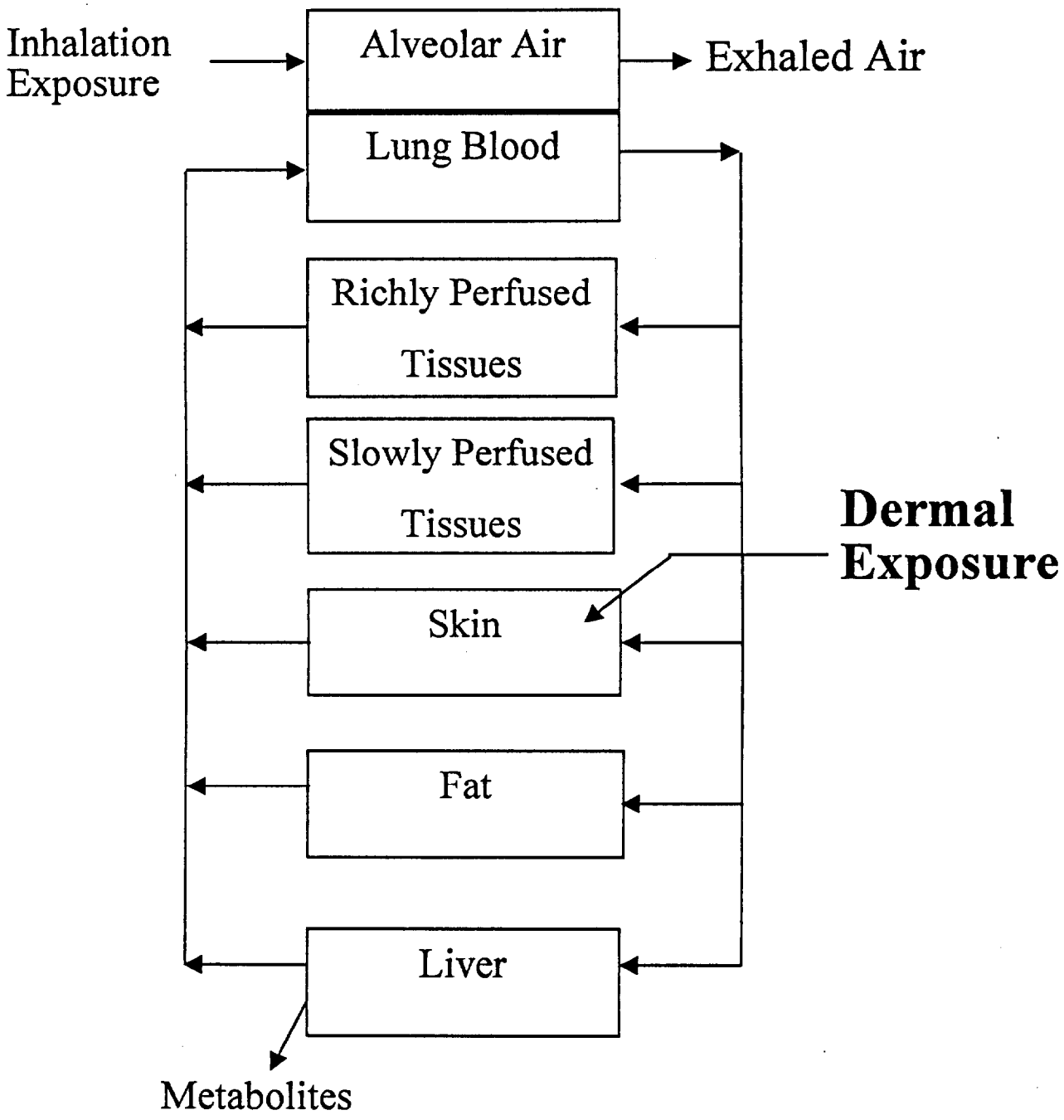

Figure 6 **Physiologically–based pharmacokinetic model used to described the pharmacokinetics of methyl chloroform in rats and humans during dermal exposures.**

Photo 1 A volunteer inhales fresh air from compressed air tanks. Exhaled air is directed to instrumentation, an aliquot of which is assayed every 3.8 seconds for solvent content.

Photo 2 **Solvent–laden soil is secured to volunteer's forearms. Solvent is absorbed through skin into body, then exhaled into breathing apparatus.**

Photo 3 Solvent–laden soil is placed on skin within a circular well of dermal tape. The soil is covered with a nonocclusive membrane which contains the soil but allows solvent evaporation to a charcoal unit placed over the membrane. A plastic weigh boat with holes physically separates soil/membrane from charcoal. Total unit is secured to forearm with overlaid wrapping. Solvent in soil can freely partition between human skin and charcoal–collecting atmosphere. A glass dish containing solvent–laden water can be used in place of soil unit.

Photo 4 **Volunteer's hand is placed within bucket which contains solvent–laden circulating water or solvent–laden soil. Solvent is absorbed through skin into body, then exhaled into breathing apparatus.**