A mathematical model of the absorption, distribution, metabolism, and elimination of benzene in the human body

by

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NOMENCLATURE

K_1 Rate constant of the reaction benzene → phenol

K_2 Rate constant of the reaction phenol → catechol

K_3 Rate constant of the reaction catechol → hydroxyquinol

K_4 Rate constant of the reaction phenol → quinol

$\dot{Q}$ Flow rate (ℓ/min)

$\dot{Q}_A$ Alveolar ventilation (ℓ/min)

$\dot{Q}_B$ Blood flow rate out of mixed venous pool (ℓ/min)

t Time (min)

V_A Alveolar volume of lung compartment (ℓ)

V_B Blood volume (ℓ)

V_T Tissue volume (ℓ)

x Concentration in liquid phase (ppm)

y Concentration in gaseous phase (ppm)

λ Partition coefficient

σ Lung shunt factor

Subscripts:

1 Denotes compartment of vessel rich group (VRG)

2 Denotes compartment of muscle group (MG)

3 Denotes compartment of fat group (FG)

a Denotes arterial

a' Denotes alveolar

ca Denotes metabolite catechol

hq Denotes metabolite hydroxyquinol

ℓ Denotes liver compartment

p Denotes lung compartment

ph Denotes metabolite phenol

qu Denotes metabolite quinol

v Denotes venous pool

λ_{TB} Denotes tissue-blood partition coefficient

I. INTRODUCTION

Benzene, C_6H_6, is a volatile, colorless, flammable aromatic hydrocarbon, which possesses a very characteristic odor. It is used principally as a chemical raw material in the synthesis of compounds such as styrene (employed to manufacture the most widely used type of synthetic rubber), phenol, dodecylbenzene (used in the preparation of alkylarene-sulfonate detergent), nitrobenzene (for the synthesis of aniline), cyclohexane (for the manufacture of adipic acid and caprolactam), nonylphenol and other products used in the preparation of nonionic detergents, dichlorodiphenyltrichloroethane (D.D.T.), chlorobenzene, benzene hexachloride and maleic anhydride. Benzene is also extensively used as a solvent in the preparation of paints and coatings, particularly where good penetration and rapid evaporation or setting are desired. Benzene is an excellent solvent for rubber, and therefore finds its way into numerous preparations such as rubber cement.

Inhalation of benzene vapor may result in acute or chronic poisoning, depending upon the concentration of the vapor and the length of the exposure. The maximum acceptable concentration (MAC) of benzene in air varies with both time and location. For the standard of the American Conference of Governmental Industrial Hygienists, the MAC of benzene in air for an 8-hour day is set at 10 ppm. The body develops no tolerance to benzene and any damage can be cumulative and permanent. There is wide variation in the susceptibilities of individuals. Women appear to be more susceptible to benzene poisoning than men, and young persons more than older persons. Exposure to air containing benzene at

a concentration of 20,000 ppm causes death within a few minutes; concentrations of 7,500 ppm are dangerous to life in one-half to one hour.

Chronic benzene poisoning usually results from daily exposure to an unsafe concentration of vapor over a prolonged period. If chronic benzene poisoning has begun, the effect may be indicated by a decrease in the number of red blood corpuscles, white blood corpuscles and platelets. Chronic benzene poisoning affects the blood-forming function of the bone marrow. If bone marrow damage is slight, complete recovery usually occurs after removal of the individual from exposure to benzene. If the damage is severe, the poisoning is usually fatal, since no method is known for restoring the ability of bone marrow to manufacture the necessary blood constituents.

Benzene enters the circulation system primarily through the respiratory tract. The compound is distributed in the body organs and varies with time elapsed after exposure. Approximately 50% of absorbed benzene is excreted through the lung. The remainder is oxidized for the most part to phenol and polyphenols, which are then excreted as conjugated products with sulfuric and glucuronic acid. Consequently, the amount of ester sulfates in the urine, expressed as a percentage of the total amount of sulfate, increases with the inhalation of benzene vapor and the concentration of urinary sulfate, has been used as an index of exposure. The concentration of urinary phenols has been employed for a similar purpose. Both methods provide presumptive evidence of exposure to benzene, but they reveal nothing about the health of the individual.

The problem of the absorption and elimination of benzene in the human body was studied for the first time by Lehmann and his co-workers in 1910. But up to the present, the majority of literature on this subject was limited to the empirical method, to interpret the response from the experimental data, or to get a model by curve-fitting techniques. Recently, mathematical phenomenological models have been adopted in research on anesthetic agents in the human body. However, simulation research on benzene, which is widely used, is still lacking. The metabolic reaction of benzene in the human body is very complex. Due to the toxicity of benzene, most previous research on its metabolism is restricted to experimental animals, or to the pathological study of poisoned humans. Kinetic studies on this reaction are still lacking.

The object of this research project is the development and refinement of a mathematical model for the absorption, distribution, metabolism and elimination of benzene in the human body, using a digital computer to simulate the transient response of benzene and its metabolites in the various organs and tissues. The metabolic reaction is simulated under several assumptions. The kinetics of the metabolic reaction are also derived in the analytical method. In this research, we simulate the case of exposure to a benzene concentration of 100 ppm. We have compared absorption and elimination of benzene for a hard-working person and a resting person. We also compared the cases of an obese person and a normal person under benzene exposure. The situation of repeated exposure, which is likely to happen in industry, has also been studied in this research. From the results derived from this model, we expect not only agreement with the results reported in other

papers, but also a prediction of the time necessary for benzene to be practically eliminated from the body. This is of importance in determining the degree of work hazard and in recommending working periods and leaves.

II. LITERATURE REVIEW

Benzene has been recognized since 1897 as a toxic chemical which causes chronic poisoning, and over the years a very comprehensive literature on its industrial toxicology has developed. Published information on human exposure is principally restricted to pathological studies on poisoned humans, though metabolism and toxicology has been extensively studied in experimental animals.

A. Absorption, Distribution and Elimination

Benzene vapor gains access to the circulation through the respiratory tract. The absorption of benzene through the lungs is dependent on the solubility in blood, the permeability and volume of the lung, the volumetric rate of ventilation, the volume and flow rate of blood in the lung, the speed of absorption and the difference in concentration of the vapors in the inhaled gas and in the blood. The concentration gradient determines the exchange in regard to direction and speed. The greater the partial pressure of the vapor in the air, the more rapidly the content in the blood increases. The speed of absorption and the degree of solubility are of great practical interest in the evaluation of the toxic effect.

Schrenk, et al. (1941) studied the absorption, distribution and elimination of benzene by body tissues and fluids, using dogs as experimental subjects. They found that the initial rate of absorption of benzene by the blood was extremely rapid, but final values were obtained slowly; there was a linear relationship between the

concentration of benzene in air and the equilibrium blood concentration of exposed animals. The coefficient of distribution was reported as 6.58. As for the distribution of benzene throughout the body, it occurred rapidly, but equilibrium values were dependent on blood supply. The fat, bone marrow and urine contained approximately 20 times as much benzene as blood, while benzene concentrations in muscle and vital organs were about 1 to 3 times the blood concentration. The elimination occurred rapidly at first, but owing to the large amount of benzene stored in the fat and the poor blood supply to the fat, elimination was not complete until about 137 hours after termination of exposure.

Srbova, et al. (1950) worked with 23 human subjects and got similar results as those of Schrenk. The human subjects inhaled a mixture of air and benzene vapor in concentrations of 150 to 350 μg per liter (47 to 110 ppm). They stated that the rate of absorption of benzene was highest in the first few minutes of inhalation; afterwards it dropped quickly (Fig. 1). During the test period, an equilibrium between blood and air level of benzene was not achieved. In the desaturation period, 30%-50% of the absorbed benzene was eliminated by the lungs, while the quantity of benzene eliminated by the kidneys was insignificant (0.1-0.2%) and the elimination continued for a long time. Benzene which was not excreted by the lungs or the kidneys remained in the body and was metabolized.

Parke and Williams (1950, 1952) administered a single dose of 0.34-0.50 g/kg of C^{14}-benzene orally to rabbits. They discovered 84-89% of the original dose as radioactive in the expired air, urine, feces, and body tissues. In the expired air, 43% was recovered as unchanged

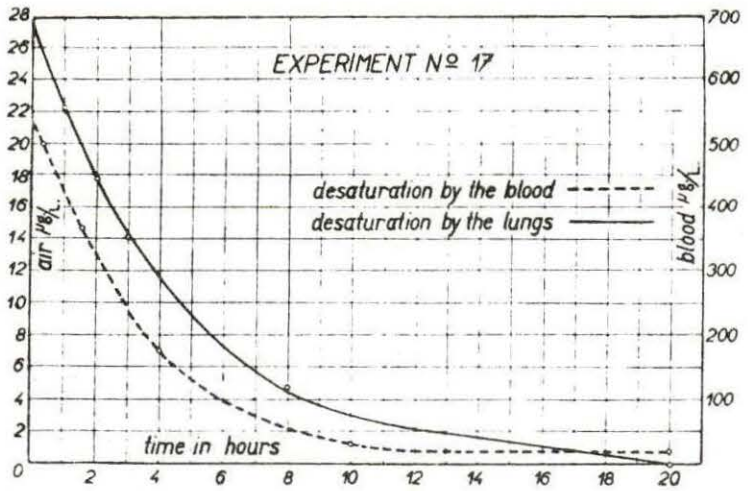


Fig. 1. Average rates at which inhaled benzene is eliminated from the blood and the lungs

benzene and 1.5% as $C^{14}O_2$. The elimination of the $C^{14}O_2$ began 12-18 hours after administration of the benzene, and continued for several days. The urine contained 34.5% of the original radioactivity, phenol accounting for 23.5%, quinol for 4.8%, catechol for 2.2%, hydroxyquinol for 0.3% and trans-trans-muconic acid for 0.5%. These determinations were based on samples collected over a 3-day period. After 3 days 5-10% of the original dose was still in the animal, distributed throughout the tissues.

Parke and Williams (1954) also applied radioactive labeled C^{14}-benzene to study the distribution of benzene in rabbit tissues. A total of 16% of the initial dose was recovered from the tissue one day after administration. The majority of the radioactivity was detected in the voluntary muscle (57%), the involuntary muscle (9%) and the blood (5%). No radioactivity was detected in the bone marrow, spleen or brain.

Hunter (1968) reported that a steady rate of absorption of benzene occurs quickly after the start of an exposure, the time to attain this state and the proportion of the exposure dose absorbed being a reflection of the individual and the energy expenditure. When exposure ceased, there was a rapid fall in the concentration of benzene, but benzene could still be detected in exhalations up to 24 hours after exposure with an instrument sensitive to 0.02 mg/m^3.

Sato, et al. (1975a, b) described the experimental human exposure of three male subjects inhaling 25 ppm of benzene. The results were graphically resolved into a sum of three exponential components; that is for benzene in the blood:

$$Y = 5.93\ e^{-0.418t} + 8.60\ e^{-0.0238t} + 2.87\ e^{-0.00317t}$$

for benzene in the end-tidal air:

$$Y = 0.532\ e^{-0.346t} + 0.585\ e^{-0.0309t} + 0.213\ e^{-0.00402t}$$

For this reason, they suggested an empirical three-compartment model for the absorption, distribution and elimination of benzene in the human body (Fig. 2).

Sato, et al. (1975a, b) also studied sex differences in the susceptibility to chronic benzene intoxication with special reference to body fat content. In an experiment with rats, they found that the rate of elimination of benzene was significantly lower in the fat males than in the lean males ($p < 0.01$) and also in the fat females than in the lean females ($p < 0.05$). In the experimental human exposure, they found that blood concentrations during exposure were consistently higher

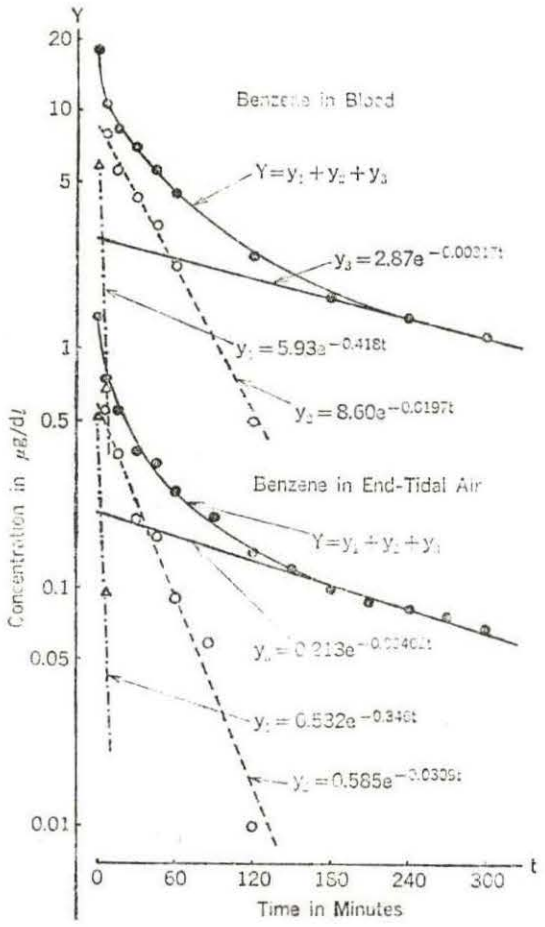


Fig. 2. Desaturation curves obtained from the human experimental exposure. Average concentrations in 3 subjects are plotted on a logarithmic scale against time (from Sato, et al., 1974)

in males than in females ($p < 0.005$). After the cessation of inhalation, the concentrations of benzene in both blood and end-tidal air began to decrease rapidly, with different rates between males and females; the concentration was higher in males than in females after the first 3 hours, and after 3 hours it was higher in females than in males (Fig. 3). They reasoned that since the human fat content is much greater in females than in males (Keys and Brozek, 1953), that benzene, which has a high affinity to fat tissue, has a distribution

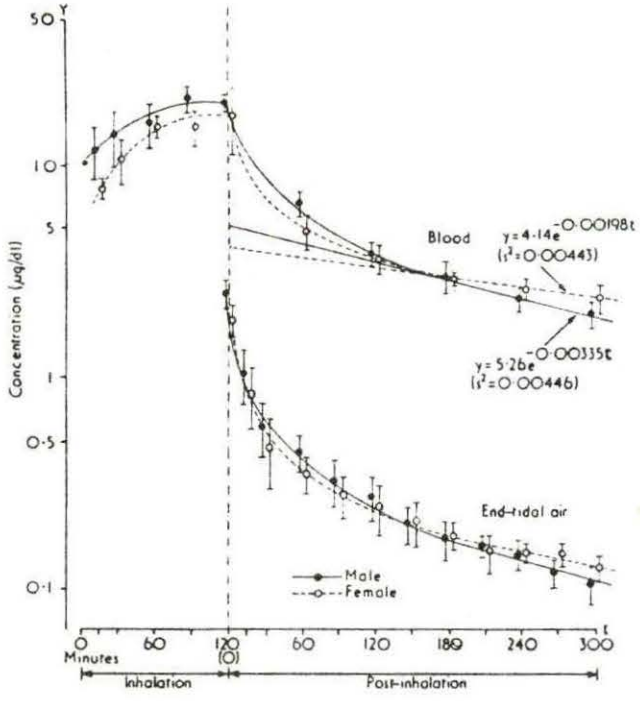


Fig. 3. Saturation and desaturation curves of benzene obtained from a human experimental exposure. The vertical line represents the mean value ± SD (s^2 = mean square of deviation from linear regression)

volume which is much greater in females than in males, and that the amount of absorbed benzene was not smaller in females than in males.

B. Metabolism

For many years studies have indicated a direct relationship between the level of benzene exposure and the level of total phenol excretion in the urine (Walkley, et al., 1961). Roush and Ott (1977) indicated that the urinary phenol levels of 52 employees exposed to benzene vapor of less than 5 ppm showed a positive statistically significant correlation with benzene exposure. Radojicia (1975) reported that the phenol content in urine of workers exposed to benzene

was proportional to benzene exposure, and the correlation coefficient of benzene exposure and urine phenol content was 0.78.

In other words, benzene, in part, is apparently converted to other forms of metabolites and is eliminated with urine. The major site of conversion appears to be the liver. The first major series of studies on the metabolic fate of benzene in animals was initiated in 1949 by Garton and Williams. They found that, following oral administration of benzene in rabbits, 21% of the dose was excreted as phenols. This consisted of a mixture of phenol, catechol, quinol and hydroxyquinol. A small amount of nonaromatic material trans-trans-muconic acid, was also found (Parke and Williams, 1952). Virtually all of the excreted phenols were conjugated either as glucuronides or as ethereal sulfates. Over 95% of the phenol was eliminated during the first 2 days. During same period, only 60% of the dihydroxyphenols, catechol and quinol were eliminated. The hydroquinol elimination did not reach a maximum until the third day. It was, therefore, suggested that the dihydroxyphenols were subsequent oxidation products of phenol and that the trihydroxyphenol was an even later oxidation product (Garton and Williams, 1949a, b).

In a series of experiments by Garton and Williams (1948, 1949a, b), phenol, catechol, resorcinol and quinol were administered to rabbits via a stomach tube. The urine was then examined for these compounds and for other possible metabolites. In all cases, the major metabolites were conjugated monoglucuronides. Ethereal sulfates were also formed. Only the urine of rabbits treated with catechol contained detectable amounts of hydroxyquinol, even though it could have been formed from further oxidation of all three dihydroxyphenols. Based on this

evidence, Porteous and Williams (1949) proposed the metabolic scheme shown in Fig. 4.

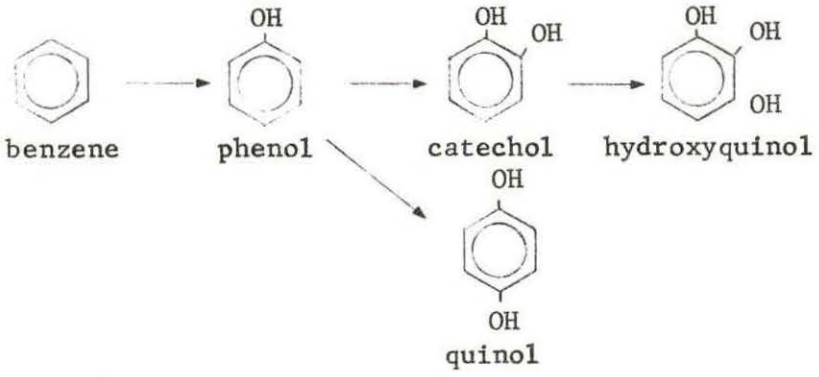


Fig. 4. Proposed in vivo benzene metabolic scheme

The metabolism in humans is apparently essentially the same as that in other animals. Teisinger, et al. (1952) exposed human subjects to approximately 100 ppm (340 mg/1) level of benzene for 5 hours daily. It was observed that the average retention of inhaled vapor was 46.3%. Of the retained benzene, approximately 12% was subsequently expired unchanged and approximately 0.1-0.2% was excreted in urine. The remainder was metabolized to various phenolic compounds previously described for animals.

From the biochemistry viewpoint, the suggested mechanism of hydroxylation of benzene is considered as follows (Jerina, 1973):

The mono-oxygenases enzymes are found in the endoplasmic reticulum of hepatic cells, the cytochrome P-450 system. Cytochrome P-450 is the electron transport chain from liver. In essence, the oxidized form of the hemoprotein ($P\text{-}450^{+++}$) binds the substrate (C_6H_6) and undergoes a one-electron reduction.

The reduced enzyme-substrate complex binds molecular oxygen at this point. Superoxide, the radical anion of the oxygen molecule, has been implicated in the scheme, since addition of the second electron leads to the oxidized substrate (C_6H_5OH) and water (Fig. 5).

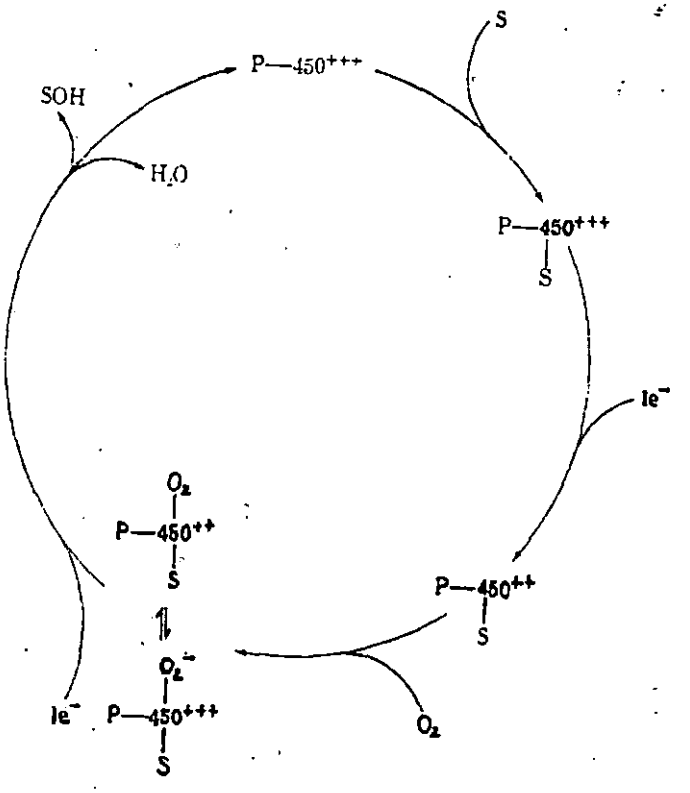


Fig. 5. Suggested mechanism of hydroxylation of benzene (from Jerina, 1973)

C. Analytical Methods

In recent times, the most successful determinations of benzene are made by nonvisible spectrophotometry and gas chromatography.

Spectrophotometric methods are adequate for determinations of benzene in air. The use of nonvisible spectrophotometric analyses

offers the advantage of fewer steps in sample preparation and therefore fewer chances for anomalous results.

The usefulness of gas chromatography lies in its ability to separate components in a mixture before analysis. It is a technique of choice for determining benzene in the blood and tissues and phenol in the urine. Benzene and other volatile compounds have been determined in blood (Sato, et al., 1972, 1974) and in other fluids with this method. Hunter (1968) also used this method to distinguish phenol from cresols during controlled exposures to benzene vapor.

D. Toxicology (Hamilton and Hardy, 1974)

1. Acute toxicity

The inhalation of a high concentration of benzene vapor may cause exhilaration followed by drowsiness, fatigue, dizziness, headache and nausea. The pulse rate increases, there may be a sensation of tightness in the chest accompanied by breathlessness, and ultimately the victim may lose consciousness. Convulsions and tremors occur frequently and death may follow in a few minutes or in several hours following severe exposure. From experiments on animals exposed to high concentrations of benzene, epinephrine is known to sensitize the myocardium to the action of benzene, and ventricular fibrillation may be induced. Post-mortem finding in case of acute benzene exposure include extensive petechial hemorrhages in the brain, pleurae, pericardium, urinary tract, mucous membranes and skin. There are no specific lesions pathognomonic of acute benzene intoxication.

Recovery from an acute exposure to benzene depends on the severity of the exposure. Breathlessness, nervous irritability and unsteadiness in walking may persist in severe cases for two or three weeks. Chronic effects of acute benzene intoxication may arise and persist long after the acute incident.

2. Chronic toxicity

The effects of inhaling small quantities of benzene vapor over a prolonged period of time are of the greatest importance in the industrial use of this hydrocarbon. These effects are probably due to the insidious injury to the blood-forming tissue at atmospheric concentrations which may not cause irritation of mucous membranes or any unpleasant sensory effects.

Early symptoms of chronic exposure to benzene vapors are varied and vague and not specific for benzene exposure. They may consist of headache, fatigue, dizziness, and loss of appetite. As the condition progresses, more specific signs of benzene intoxication become manifest, such as bleeding from the nose, the gum and mucous membranes and the development of purpuric spots and ecchymoses of the skin at the site of injury. The individual may complain of shortness of breath and appear to be anemic. In addition, there may be a slight elevation in temperature, a rapid pulse and a low blood pressure.

The most common persistent abnormalities in the blood of workers exposed to benzene are anemia and leukopenia. Many people believed leukopenia to be the earliest sign of chronic benzene intoxication. Macrocytosis and thrombocytopenia are also frequently found in benzene

poisoning. The bone marrow may be aplastic or hyperplastic and does not always correlate with peripheral blood findings indicating hypo- or hyperactivity of the blood-forming tissue.

Chronic benzene intoxication may appear after a few weeks or many years of exposure, or even many years after the actual exposure to benzene has ceased, and may prove fatal.

3. Therapy and control

The prevention of acute and chronic benzene poisoning is based on control of levels of benzene in air. Convenient survey detector tubes and other physical instruments are available for measuring benzene in ambient atmospheres. The recommended threshold limit value for benzene has dropped repeatedly in the last several decades, and a concentration of 10 ppm is now considered acceptable for eight-hour exposures at the work place. It is possible to measure metabolites of benzene in the urine of workers and thereby establish an index of exposure. The urinary sulfate ratio has been used for years to express that portion of urinary sulfate, normally at least 80%. In benzene exposure, the excretion of phenol sulfate increases so that the proportion of inorganic sulfate drops to less than 80%. Inorganic sulfate ratios of less than 80% are therefore considered indicative of excessive exposure.

E. Mathematical Model

The quantitative study of the time-course of absorption, distribution, excretion and metabolism of toxic substances is a useful tool in

studying the characteristics of toxic effects induced by them.

The hazards of ingesting or inhaling radioactive substances have been primarily assessed from the construction of a mathematical model. Such a technique has been extensively used to estimate uptake and elimination of anesthetic gases (Papper and Kitz, 1963).

Riley, et al. (1966) described the occupational exposure to methylene chloride with a compartment model. DiVincenzo, et al. (1972) applied the curve-fitting method to the experimental data of methylene chloride vapor exposure on human and canine and derived an empirical two-compartment model in that system. Peterson (1978) also modeled the uptake, metabolism and excretion of dichloromethane by man using the empirical regression method.

As industrial exposure to benzene vapor is typically highly variable, estimation of the burden of benzene in the body is enhanced when computer techniques are employed.

The process of uptake and washout of organic solvent vapors in humans has recently been studied using an analog (Fiserova-Bergerova, et al., 1974) or mathematical model (Fernandez, et al., 1977) to simulate the processes and gives an adequate prediction.

Such calculations require information on the uptake and release of benzene from body tissues which is not readily available. However, estimates can be made from a knowledge of the blood perfusion of the organs, and the partition coefficients for benzene in blood and the various tissues.

The partition coefficients of benzene for various body fluids and tissue homogenates of rabbits at 37°C are reported by Sato, et al.

(1974) as shown in Table 1. The coefficient of the vapor for fat is much higher than that for other tissues. The high solubility of benzene in fat compared with blood was also confirmed with human fat and blood. It indicated that fat tissue plays a very important role in the process of absorption, distribution and elimination of benzene.

Table 1. Partition coefficients of benzene for body fluids and tissue homogenates

		Benzene	
		m	s
A[a]	Blood	10.70	1.35
	Plasma	5.46	0.33
B[b]	Liver	1.61	0.18
	Kidney	1.13	0.28
	Brain, whole	1.93	0.50
	Lung	1.25	0.31
	Heart	1.44	0.38
	Muscle, femoral	1.08	0.17
	Bone marrow	16.18	2.45
	Fat, retroperitoneal	58.53	11.87
C[c]	Lecithin, from egg	196.42	9.30
	Triolein	535.68	31.14
	Cholesterol	20.95	0.85
	Cholesterol oleate	83.65	4.49
	Human fat, peritoneal[d]	406.22	10.10
	Human blood[e]	7.82	1.31

[a]A = Fluid-air partition coefficient. The figures are mean (m) and standard deviation (s) of 5 rabbits.

[b]B = Tissue-blood partition coefficient. The figures are mean (m) and standard deviation (s) of 5 rabbits.

[c]C = Material-air partition coefficient. The figures are mean (m) and standard deviation (s) of 5 determinations.

[d]The material was obtained from a 7-year-old boy who died of acute leukamia.

[e]Cited from Sato, et al. (1972).

III. MODEL DEVELOPMENT

A multi-compartment model is used in this study. To simulate the absorption and distribution, the whole body system is divided into the lung compartment and tissue compartment. Furthermore, the tissue compartment is divided into three groups of tissue according to Mapleson (1973). The first of these is the vessel-rich group (VRG), which is composed of those tissues most profusely supplied with blood vessels. These include heart, brain and spinal cord, hepatoportal system, kidney, and endocrine glands. The second group of tissues is the muscle group (MG), which is composed of muscle and skin. The third group of tissues is the fat group (FG), which is composed of adipose tissue. The fat group is very important in this study because benzene is a highly fat-soluble solvent, and has a very significantly high value of the tissue-blood partition coefficient. In addition, it is considered that benzene is quantitatively transformed in the liver to phenol, catechol, quinol and hydroxyquinol. Hence, the liver is separated in the model from the vessel-rich group. In the lung compartment, the shunting effect is included. To make up the concentrations in the various compartments, arterial and venous pools are included.

A. Theoretical Basis

The principal hypotheses used in this model are the same as those discussed by Mapleson (1973) and Cowles, et al. (1971):

1. The cardiac output and alveolar ventilation are considered to be continuous processes instead of cyclic processes;

2. Alveolar ventilation, blood flow rates and other physiological or physical parameters are constant;

3. Benzene diffuses freely through the entire surface of the capillary and alveolar walls;

4. All compartments are considered to be well-stirred, i.e., concentration within each compartment or tissue group is uniform;

5. The arterial blood concentration out of the lung compartment is in equilibrium with that of alveolar gas;

6. The concentration of benzene in venous blood is in equilibrium with that dissolved in the corresponding drained tissue;

7. For all tissues, the gas-tissue partition coefficient which determines the equilibrium between blood and tissue is independent of the solvent concentration;

8. All the rate constants of the metabolic reaction shown in Fig. 4 are considered to be first order for the concentration occurring during industrial exposure.

B. Model Equations

1. Absorption, distribution, and elimination of benzene

The equations describing this multi-compartment model are easily written by considering a material balance around each compartment

rate of accumulation = input rate - output rate

1. Lung compartment

$$(V_A + V_{Tp}\lambda_p + V_{Bp}\lambda_B)\frac{dy'_a}{dt} = \dot{Q}_A(y_i - y'_a) + \dot{Q}_B(1 - \sigma)(x_v - x'_a)$$

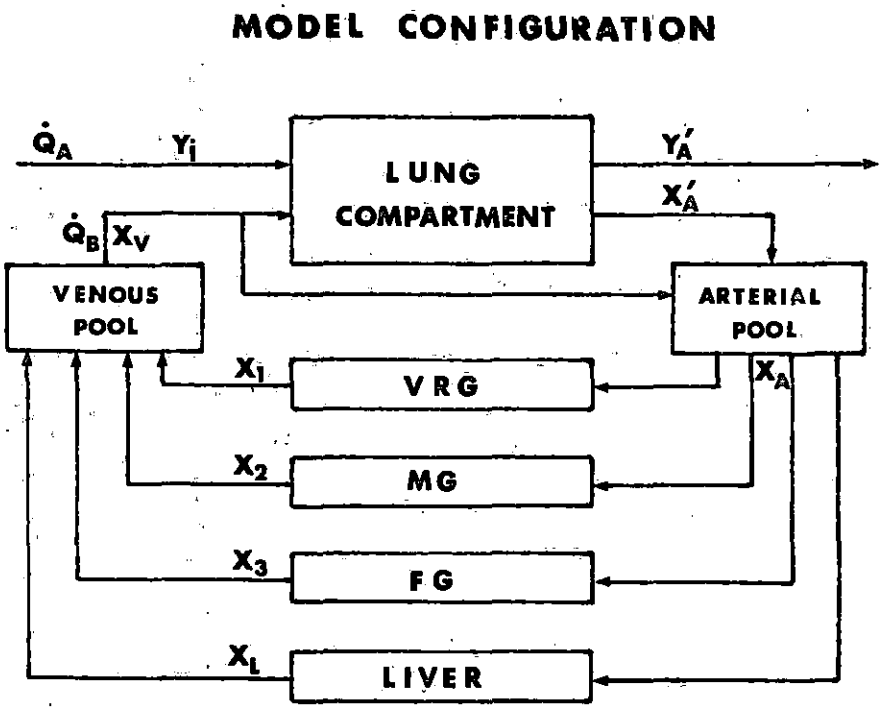


FIG. 6. FLOW CHART OF MULTI-COMPARTMENT MODEL

By assumption that the arterial blood concentration out of the lung compartment is in equilibrium with that of alveolar gas, i.e.,

$$x'_a = \lambda_B y'_a$$

Let $V_{peq} = V_A + V_{Tp}\lambda_p + V_{Bp}\lambda_B$

The model equation of lung compartment becomes:

$$V_{peq}\frac{dy'_a}{dt} = \dot{Q}_A(y_i - y'_a) + \dot{Q}_B(1 - \sigma)(x_v - \lambda_B y'_a) \qquad (1)$$

2. Tissue compartments

a. VRG compartment

$$(V_{T1}\lambda_{1B} + V_{B1})\frac{dx_1}{dt} = \dot{Q}_1(x_a - x_1)$$

Let

$$V_{1eq} = V_{T1}\lambda_{1B} + V_{B1}$$

The model equation of VRG compartment becomes:

$$V_{1eq}\frac{dx_1}{dt} = \dot{Q}_1(x_a - x_1) \qquad (2)$$

b. MG compartment

$$(V_{T2}\lambda_{2B} + V_{B2})\frac{dx_2}{dt} = \dot{Q}_2(x_a - x_2)$$

Let

$$V_{2eq} = V_{T2}\lambda_{2B} + V_{B2}$$

The model equation of MG compartment becomes:

$$V_{2eq} \frac{dx_2}{dt} = \dot{Q}_2(x_a - x_2) \tag{3}$$

c. FG compartment

$$(V_{T3}\lambda_{3B} + V_{B3}) \frac{dx_3}{dt} = \dot{Q}_3(x_a - x_3)$$

Let

$$V_{3eq} = V_{T3}\lambda_{3B} + V_{B3}$$

The model equation of FG compartment becomes:

$$V_{3eq} \frac{dx_3}{dt} = \dot{Q}_3(x_a - x_3) \tag{4}$$

3. Arterial pool

$$V_{Ba} \frac{dx_a}{dt} = \dot{Q}_B[(1 - \sigma)x'_a + \sigma x_v - x_a] \tag{5}$$

4. Venous pool

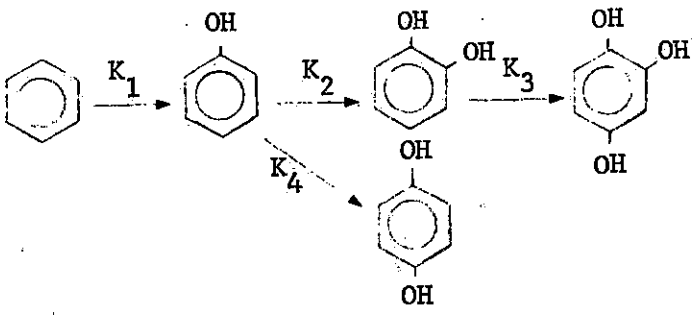
$$V_{Bv} \frac{dx_v}{dt} = \dot{Q}_1 x_1 + \dot{Q}_2 x_2 + \dot{Q}_3 x_3 + \dot{Q}_\ell x_\ell - \dot{Q}_B x_v \tag{6}$$

2. Metabolism of benzene

Assume the metabolic reaction takes place in the liver compartment after equilibrium according to partition coefficient:

$$\frac{x_\ell}{x_a} = \frac{V_{B\ell}}{V_{T\ell}\lambda_{\ell B} + V_{B\ell}} \tag{7}$$

Assume the metabolic pathway is as proposed by Porteous and Williams (1949) and all the rate constants are considered to be first order.



The differential equations expressing the rate of disappearance of benzene and each metabolite are then:

$$\frac{dx_{\ell}}{dt} = - K_1 x_{\ell} \tag{8}$$

$$\frac{dx_{ph}}{dt} = K_1 x_{\ell} - (K_2 + K_4) x_{ph} \tag{9}$$

$$\frac{dx_{ca}}{dt} = K_2 x_{ph} - K_3 x_{ca} \tag{10}$$

$$\frac{dx_{qu}}{dt} = K_4 x_{ph} \tag{11}$$

$$\frac{dx_{hq}}{dt} = K_3 x_{ca} \tag{12}$$

C. Data Used in the Model

For a standard man with a body weight of 70 kg., body surface area of 1.8 m^2, the volume of various tissues, as well as the volume of blood in equilibrium with them are shown in Table 2 (Cowles, et al., 1971). The volume of alveolar air is determined by the functional residual capacity (2.43 l) plus half the tidal volume (0.25 l).

The partition coefficient between gas and human blood are taken from the data of Sato, et al. (1972). The partition coefficients between gas and VRG/MG/FG are estimated to be 1.5, 1.0, and 52.6 as

Table 2. Tissue volumes, blood volumes, blood flow rates

	Lung compartment	VRG	MG	FG	Liver	Venous	Arterial
Tissue volume (l)	1.0	7.1	36.3	11.5	1.7	–	–
Blood volume (l)	1.4	2.59	0.63	0.18	0.6	0.6	0.95
Blood flow rate (l/min)	6.5	3.7	1.0	0.3	1.5	–	–

used in the model by Sato, et al. (1974).

The lung tissue-gas partition coefficient is estimated to be the same as the blood-gas partition coefficient and the liver-tissue partition coefficient is estimated to be the same as that of the vessel-rich group.

For the cardiac output of 6.5 l/min, the blood flow rates for various tissues are estimated by multiplying the cardiac output by the blood perfusion percentage (Cowles, et al., 1971).

The right-to-left shunt at the lung is assumed to be 2% of the cardiac output. The alveolar ventilation used corresponds to a value at rest of 5.5 l/min.

The mathematical analysis of the absorption, elimination, and metabolism of benzene leads to twelve first-order interdependent ordinary differential equations. We used the finite difference method and took the normal state as the steady state in our calculation. The variables in each equation were calculated in the form of the difference between the transient value and the steady-state value.

From the twelve equations and those variables at time t, we calculated the differences of the concentration between time t and $t + \Delta t$. By adding the concentrations at time t and the differences of concentration between t and Δt, the transient concentrations at time $t + \Delta t$ were obtained.

The time increment was taken to be 0.01 minute in our calculation. Once the initial condition was given, the digital computer provides us an efficient service to calculate the condition at any time.

Our program was written in FORTRAN IV to solve this problem on a VAX-11/780 system.

From previous literature, we know that the transient response of benzene in the human body can be approximated by the sum of several exponential components. Semi-log paper was adopted to plot those data.

IV. RESULTS AND DISCUSSION

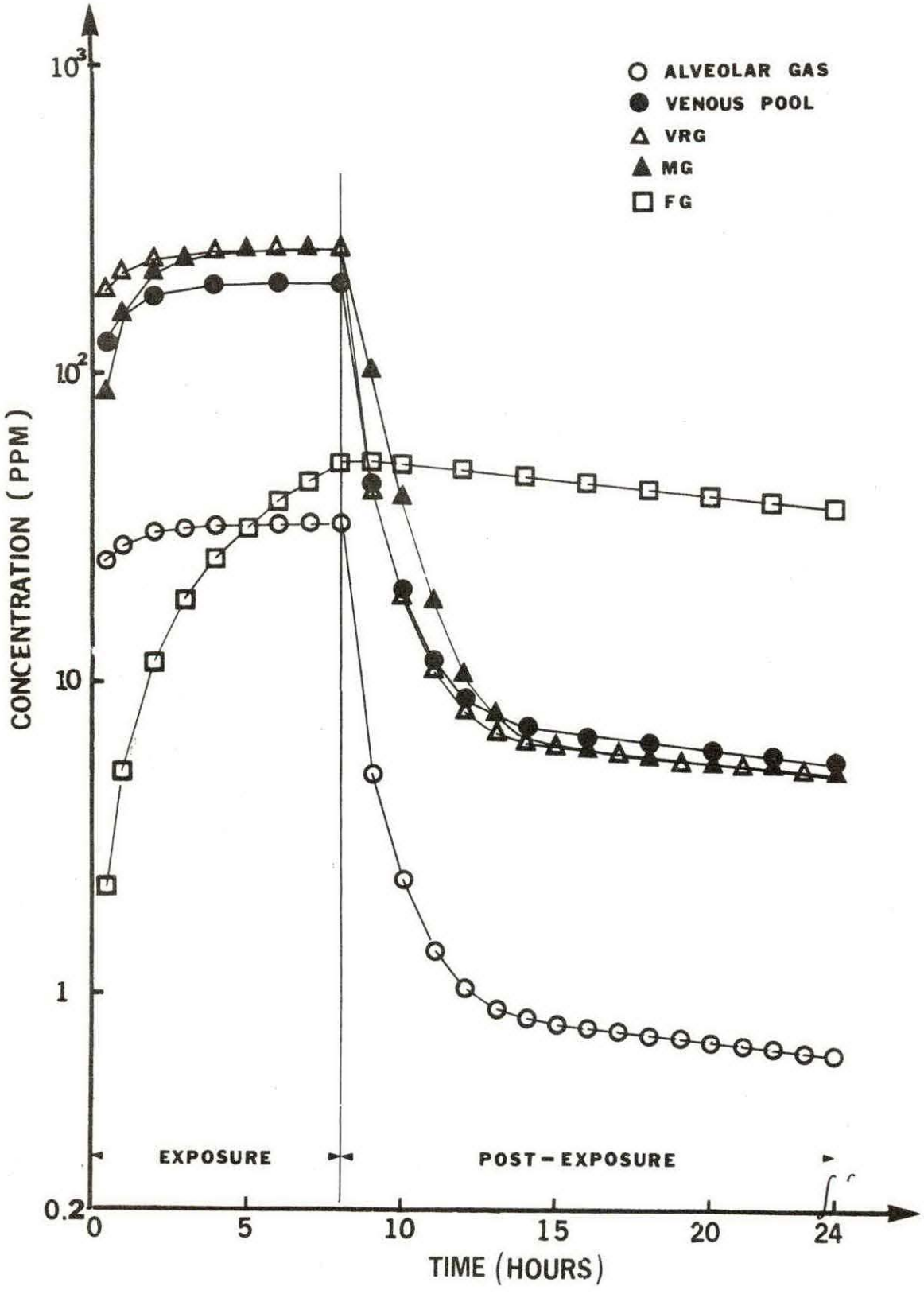
A. Absorption, Distribution and Elimination of Benzene in the Blood and Tissues for a Single Exposure

The kinetics of the saturation and desaturation of the tissues depends on their blood perfusion and apparent volumes of distribution. The predicted concentrations of benzene in alveolar gas, mixed venous pool and various body tissues during and after 8 hours exposure were plotted on semi-log paper against time (Fig. 7).

The concentration in alveolar gas increases very fast during the first hour and approaches saturation in the later period of exposure. This indicates that benzene in alveolar gas is absorbed by the pulmonary capillary blood and transported to the body tissues very easily at first, but when the tissues become more concentrated with benzene, the concentration in alveolar gas approaches an equilibrium state. During the post-exposure period, the elimination rate of benzene in alveolar gas is very rapid at first and decreases gradually as time goes on. It appears that due to the amount of benzene still remaining in the tissues, the elimination of benzene continues even after 24 hours.

Among the body tissues, the group of very vascular tissues, VRG, is almost always in equilibrium with the arterial blood, and has nearly the same concentration level as the alveolar gas both in exposure and in post-exposure periods. Contrarily, the concentration of benzene in adipose tissue, FG, which has the least blood perfusion is the lowest one compared with the other tissues, it increases constantly during the exposure, and decreases slowly in the post-exposure period, but never

FIG. 7. PREDICTED CONCENTRATIONS OF BENZENE IN ALVEOLAR GAS, MIXED VENOUS BLOOD, AND TISSUE GROUPS DURING AND AFTER 8 HOURS OF STEADY EXPOSURE


ALVEOLAR GAS
VENOUS POOL
VRG
MG
FG
CONCENTRATION (PPM)
10³
10²
10
1
0.2
EXPOSURE
POST-EXPOSURE
0
5
10
15
20
24
TIME (HOURS)

reaches the equilibrium state. The concentration in the group of muscle and skin tissues, MG, which has average physiological parameters is indicated as being intermediate between VRG and FG, but being more like the former.

For the whole body, the absorption of benzene by the blood was very rapid at first and reached equilibrium in the later exposure period. Similarly, the elimination in the post-exposure period occurs rapidly at first, and the rate decreases as time goes on, but due to the amount of benzene stored in adipose tissue, elimination continues even at the end of 24 hours.

It is also remarkable to find that the adipose tissue has only a minor effect on the alveolar gas concentration during exposure and the first few hours after exposure. On the other hand, the alveolar concentration 6 hours after the end of exposure shows variation directly proportional to the benzene concentration in FG. Consequently, the measurement of the concentration in alveolar gas during the first few hours after post-exposure mainly reflects the retention of the VRG and MG, but 6 hours after post-exposure, it reflects the retention of FG.

For the hard-working people in a benzene environment, the absorption and elimination of benzene in alveolar gas and in blood are shown in Fig. 8 and Fig. 9. We simulate this case by doubling the volumes of alveolar ventilation and cardiac output during the exposure period. We find that the concentrations of benzene both in alveolar gas and in blood for the hard-working person are higher than those for the resting person. It also shows that the absorption rate of benzene in the first few minutes of exposure is faster for the hard-working person,

FIG. 8. COMPARISON OF BENZENE CONCENTRATION BETWEEN THE ALVEOLAR GASES OF RESTING PERSON AND HARD-WORKING PERSON

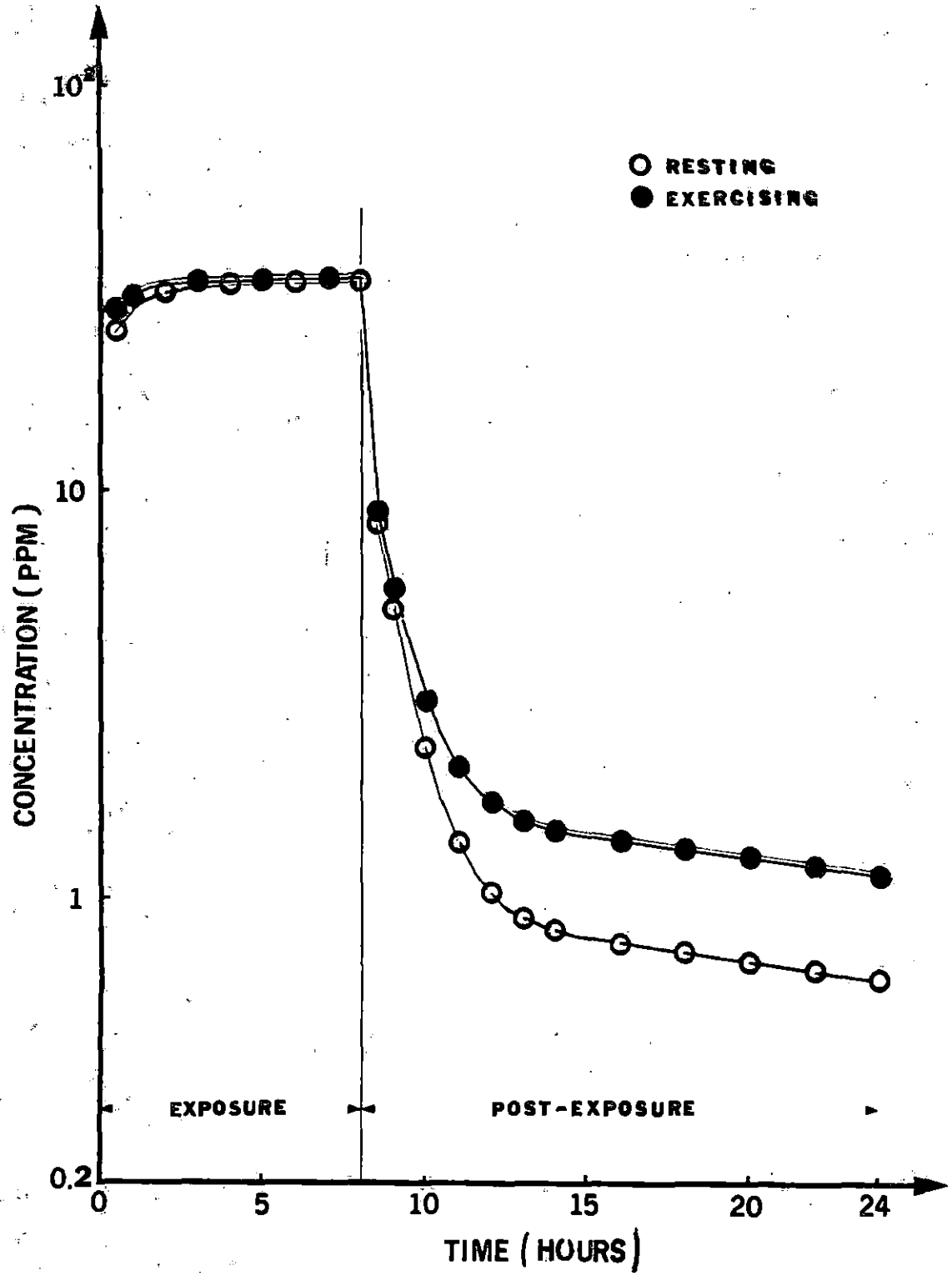
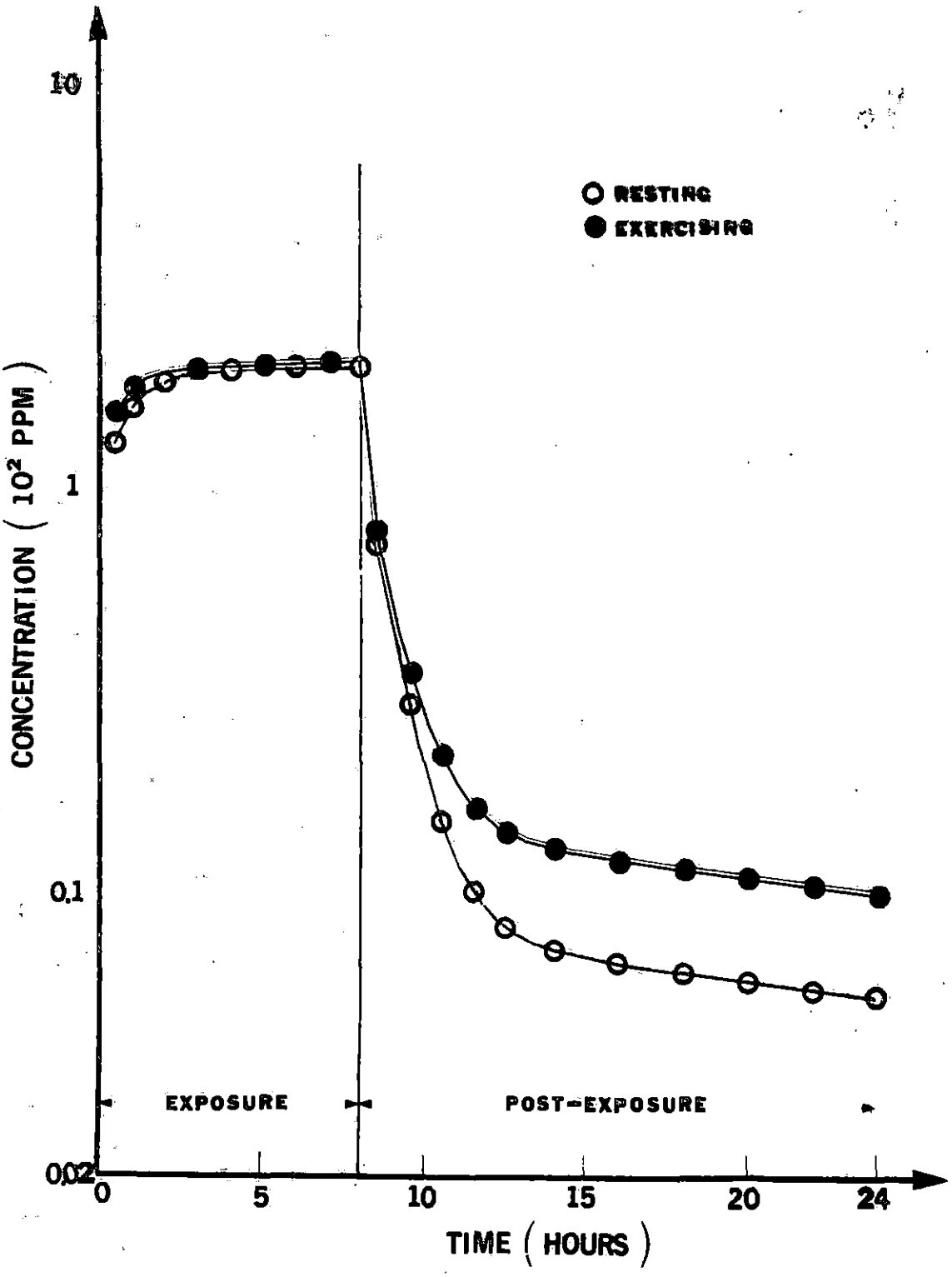

RESTING
EXERCISING
CONCENTRATION (PPM)
10
1
0.2
EXPOSURE
POST-EXPOSURE
0
5
10
15
20
24
TIME (HOURS)

FIG. 9. COMPARISON OF BENZENE CONCENTRATION BETWEEN THE VENOUS POOLS OF RESTING PERSON AND HARD-WORKING PERSON


10
1
0.1
0.02
CONCENTRATION (10^2 PPM)
RESTING
EXERCISING
EXPOSURE
POST-EXPOSURE
0
5
10
15
20
24
TIME (HOURS)

and then decreases with time. It becomes nearly the same for both cases after 3 hours of exposure. In the post-exposure period, the elimination rate is almost the same for the hard-working person and the resting person.

For the case of an obese person, the absorption and elimination of benzene in alveolar gas, blood and fat tissue are shown in Figs. 10-12. We simulate this case simply by doubling the volume of FG. We find that there is no significant difference between the concentrations of benzene in alveolar gas (Fig. 10) or in blood (Fig. 11) for the obese person and those for the normal person during the exposure period. The absorption rates are rapid in the first hour and then gradually approach an equilibrium state. When we examine the FG (Fig. 12), we can find that the benzene concentration in FG is consistently lower for the obese person than that for the normal person; we also see that the concentrations are far from saturation for both cases. The lower concentration in FG of the obese person can be easily explained by the larger fat tissue volume.

Throughout the whole post-exposure period, the concentration of benzene both in the alveolar gas and in blood is lower for the obese person than for the normal person. It seems inconsistent with the conclusion made by Sato, et al. (1975a, b). But if we examine the elimination curve of benzene in FG, we find that the slope of the curve for the normal person will be higher than that for the obese person. It is reasonable because the concentration gradient between the fat tissue and the capillary blood is higher for the normal person. Hence, the transport rate will be lower in the case of the obese person. In

FIG. 10. COMPARISON OF BENZENE CONCENTRATION BETWEEN THE ALVEOLAR GASES OF NORMAL PERSON AND OBESE PERSON

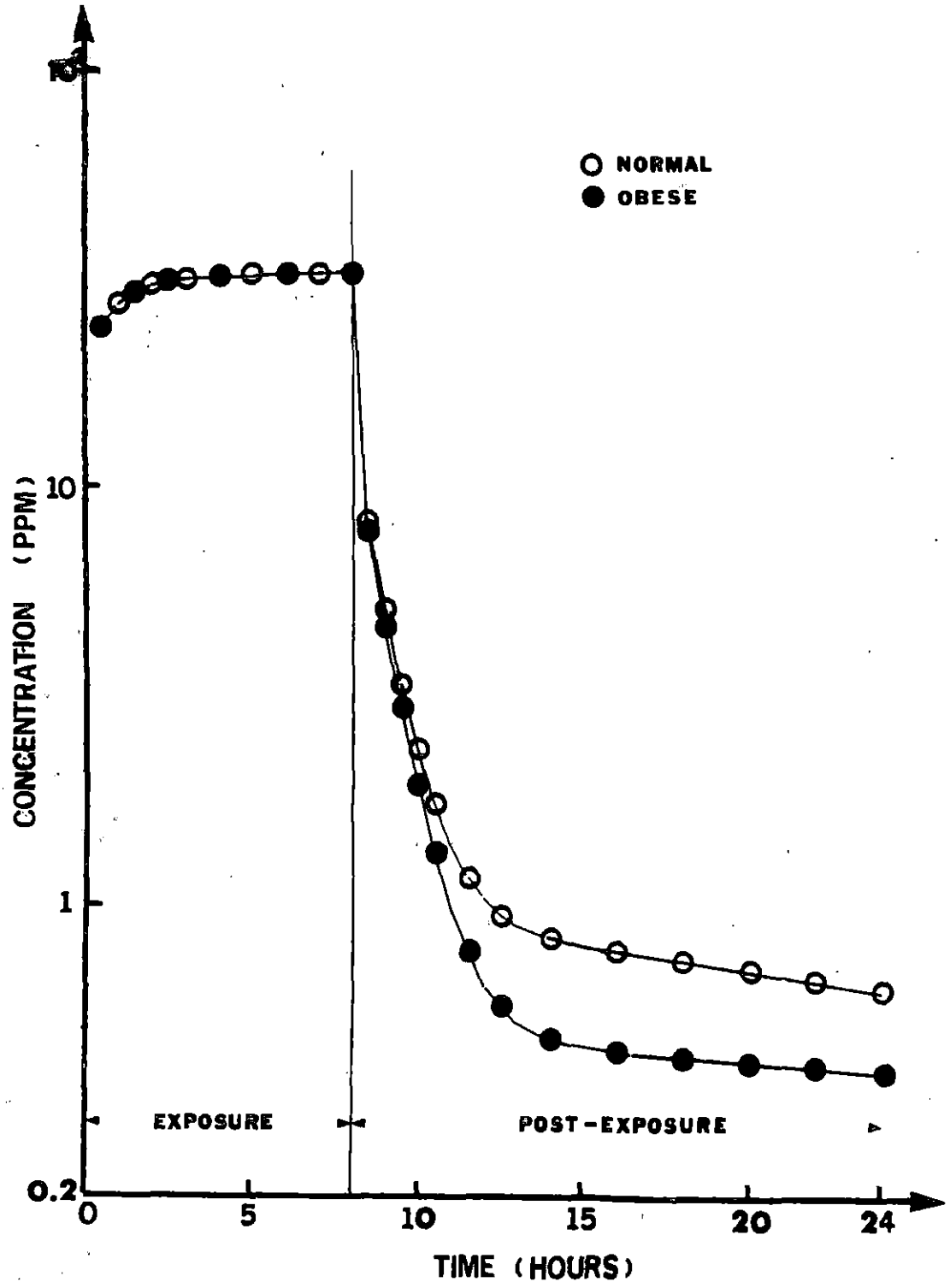
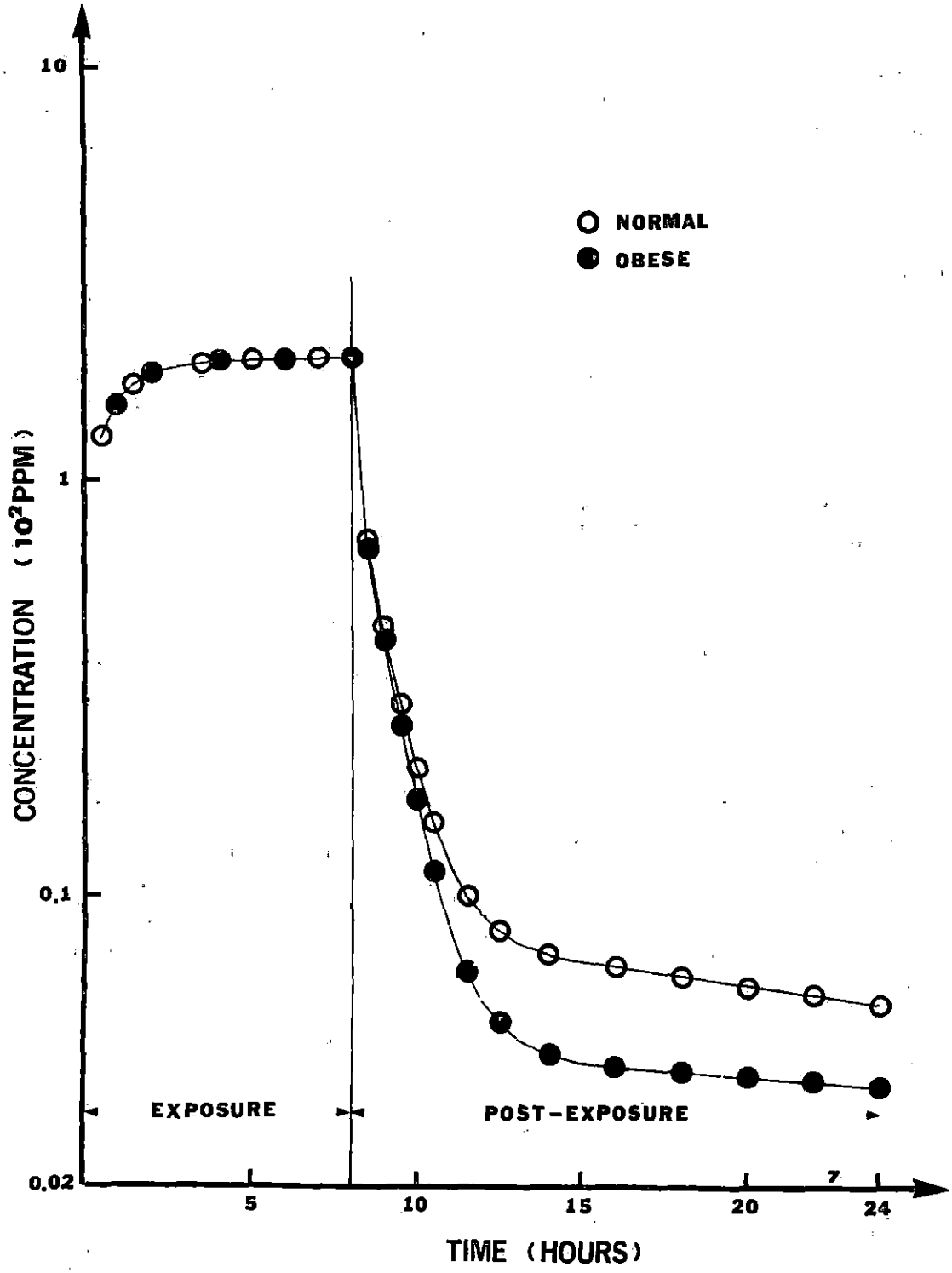

NORMAL
OBESE
CONCENTRATION (PPM)
10
1
0.2
EXPOSURE
POST-EXPOSURE
0
5
10
15
20
24
TIME (HOURS)

FIG. 11. COMPARISON OF BENZENE CONCENTRATION BETWEEN THE VENOUS POOLS OF NORMAL PERSON AND OBESE PERSON


10
1
0,1
0,02
CONCENTRATION (10²PPM)
NORMAL
OBESE
EXPOSURE
POST-EXPOSURE
5
10
15
20
24
7
TIME (HOURS)

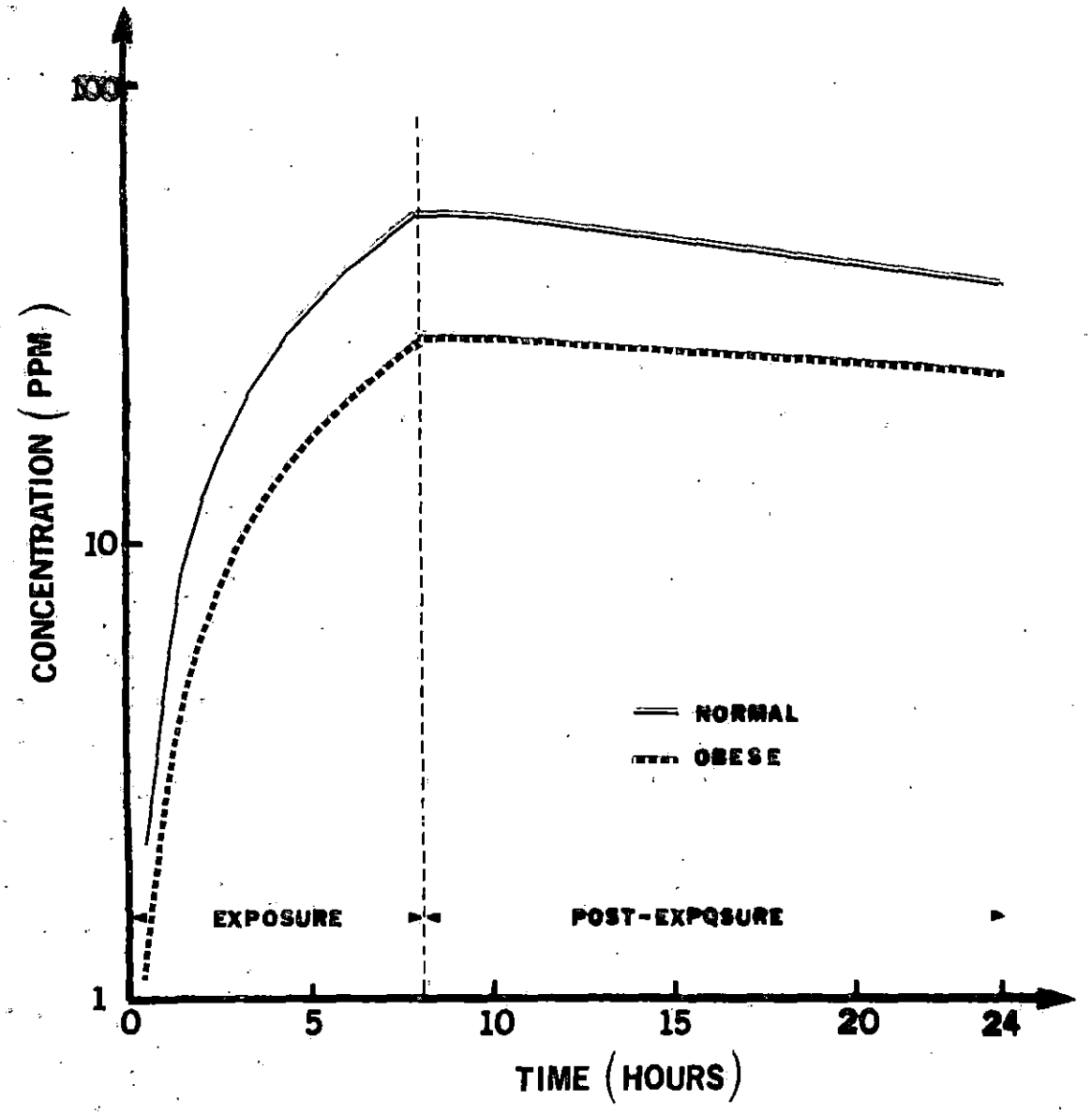


FIG. 12. COMPARISON OF BENZENE BETWEEN THE FAT TISSUES OF NORMAL PERSON AND OBESE PERSON

other words, benzene is difficult to eliminate from the fat tissue of the obese person and tends to accumulate in FG in case of repeated exposure. This explains the lower concentration in alveolar gas and blood of the obese person.

B. Repeated Exposure

In industry, exposure often occurs Monday through Friday and 8 hours per day. Figure 13 and Fig. 14 show the alveolar and venous blood concentrations obtained under repeated exposure of 100 ppm for five days and 8 hours per day. It can be seen that the concentrations of benzene in both alveolar gas and venous blood at the end of exposure vary only slightly from one day to another. As stated before, benzene levels in VRG and MG are practically in equilibrium with that in arterial blood at the end of exposure, the burden of benzene in these tissues increases very slightly.

On the other hand, due to the slow release of benzene during the elimination period, the quantity of benzene in adipose tissue increases progressively as shown in Fig. 15.

In Fig. 15, we also compare the concentration of benzene in obese persons with that in normal persons under repeated exposure. We find that during a five-day exposure, benzene concentration in FG of an obese person is consistently lower than that in a normal person, but because of the different elimination rates between FG of an obese person and a normal person, benzene concentration will be higher in FG of an obese person since the 6th day. In other words, the retention of benzene in an obese person will be longer than in a normal person.

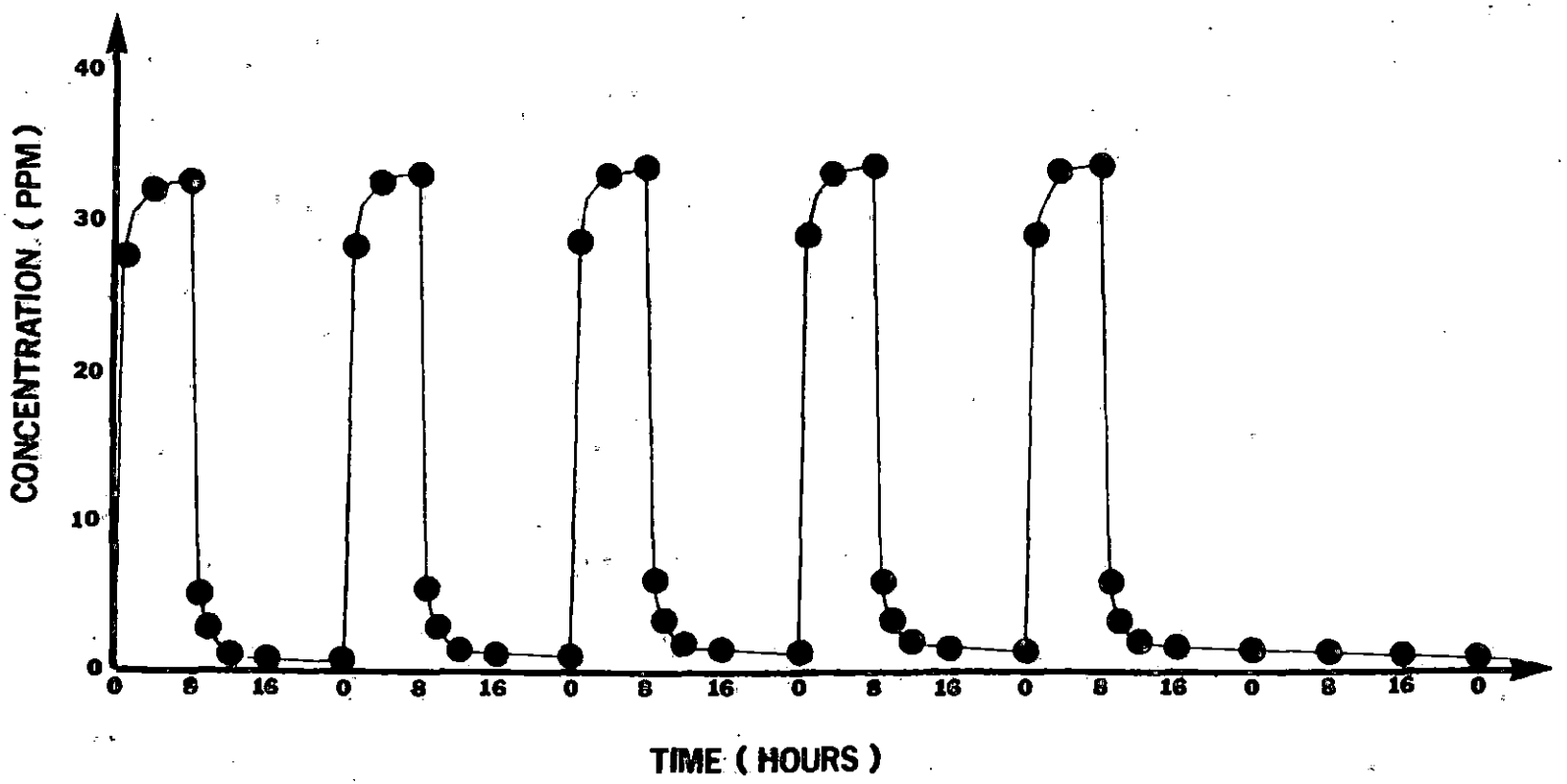


FIG. 13. PREDICTED CONCENTRATION OF BENZENE IN ALVEOLAR GAS UNDER REPEATED EXPOSURE

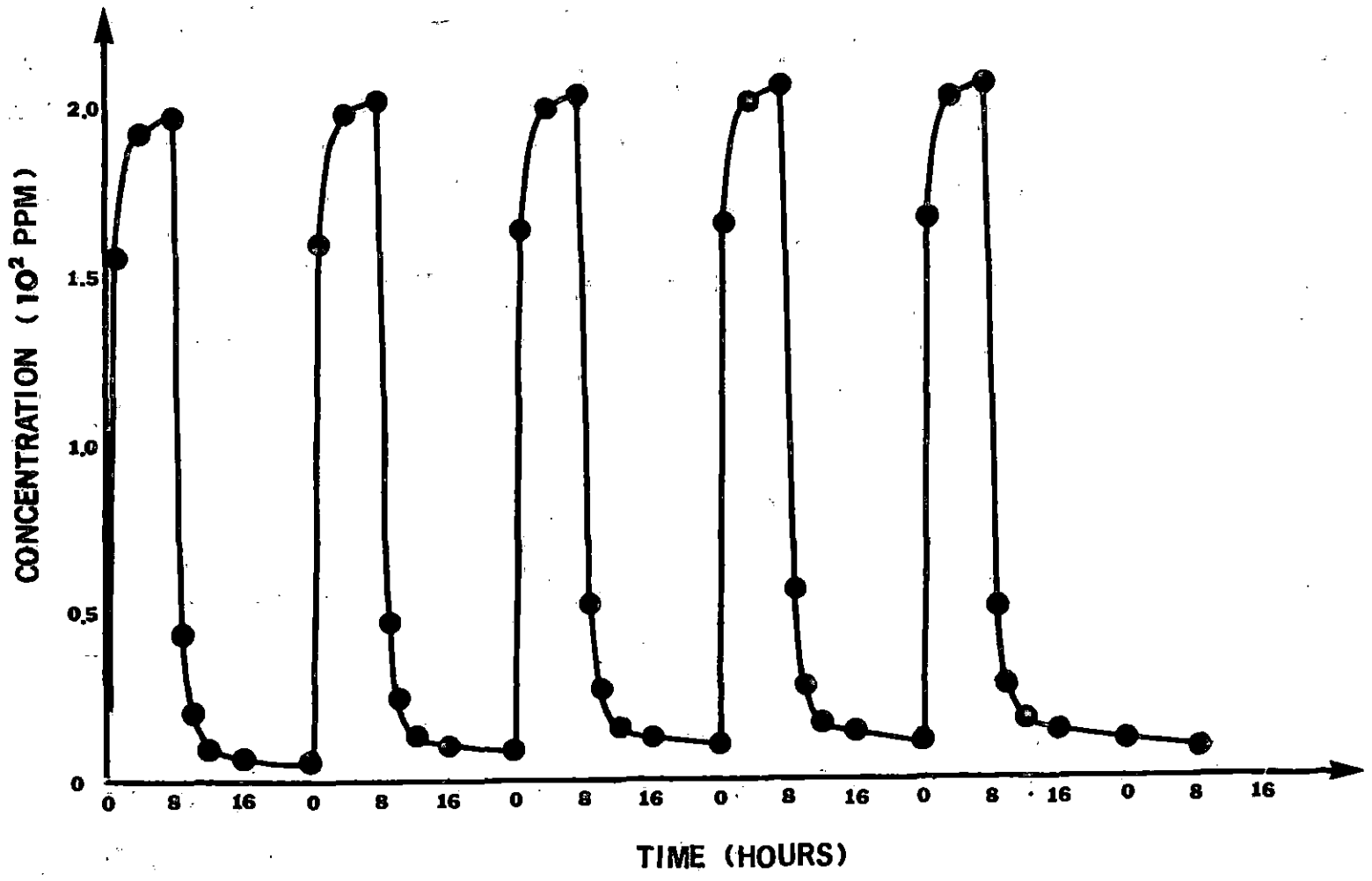


FIG. 14. PREDICTED CONCENTRATION OF BENZENE IN VENOUS BLOOD UNDER REPEATED EXPOSURE

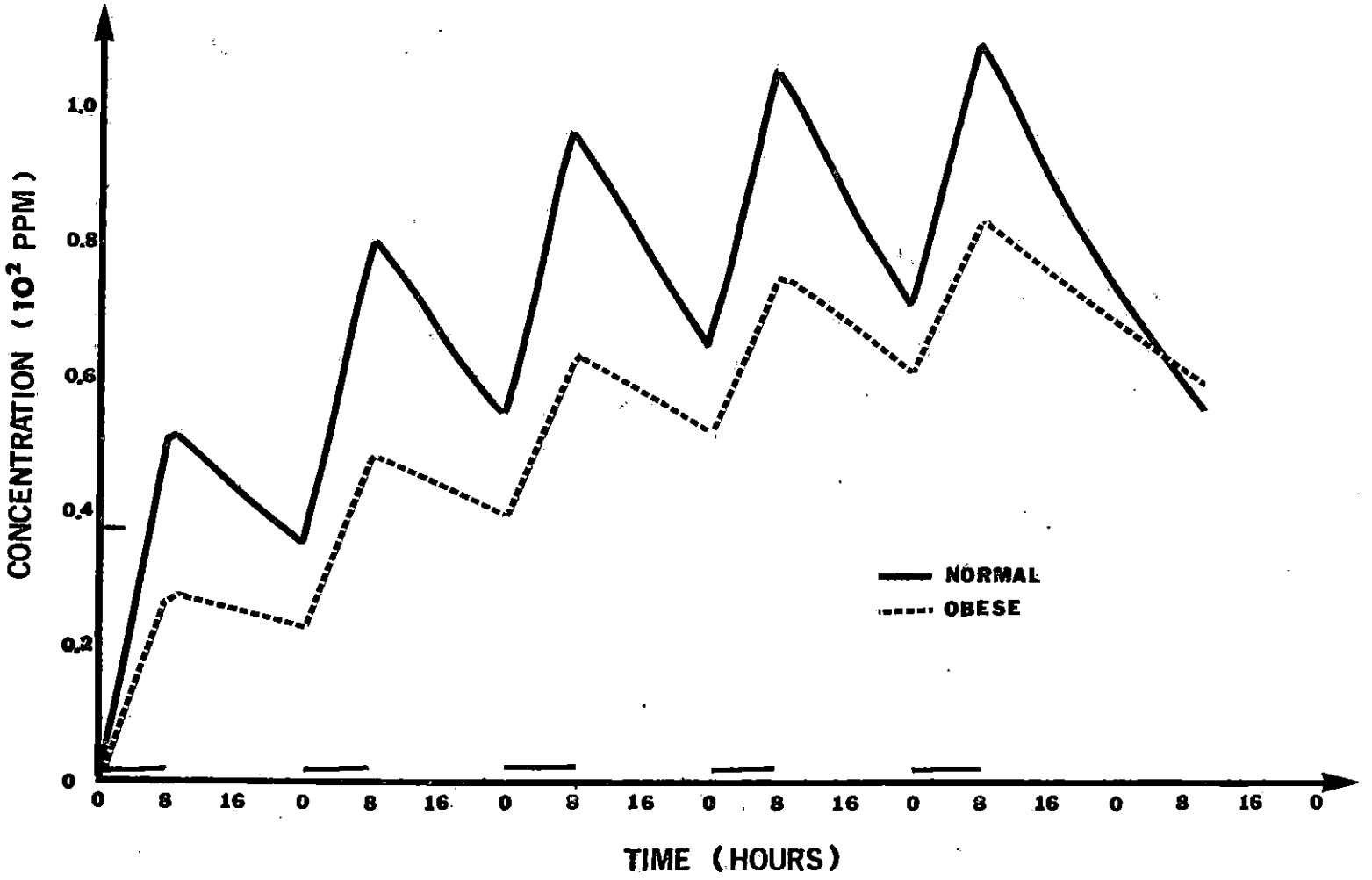


FIG. 15. COMPARISON OF BENZENE CONCENTRATION BETWEEN ADIPOSE TISSUES OF NORMAL PERSON AND OBESE PERSON UNDER REPEATED EXPOSURE

In human beings, the body fat content is larger on the average in females than in males (Keys and Brozek, 1953). Accordingly, our result can explain the general belief that females have a higher degree of susceptibility than males to haematopoietic disorders induced by benzene.

C. Response of Metabolites in the Body

Figures 16-19 illustrate the concentrations of phenol, catechol, quinol, and hydroxyquinol in the body during and after 8 hours of exposure to 100 ppm of benzene. We assume that the rate constants of this consecutive reaction are the same and of the order of 10^{-2}, 10^{-3}, 10^{-4} with the units of $[\text{min.}^{-1}]$.

The concentration of each metabolite depends on the rate constant of each metabolic reaction, respectively. For the rate constant of the order of 10^{-2}, the concentrations of all the metabolites increase with time during the exposure period. Furthermore, since the decomposing rates of phenol and catechol are also increasing, the concentrations of these two species approach an equilibrium state before the cessation of exposure. During the post-exposure period, the concentrations of phenol and catechol drop continuously, while those of quinol and hydroxyquinol increase slowly to attain the equilibrium state.

If the rate constants are of the order of 10^{-3}, the concentration of all metabolites will become lower in the exposure period. But due to the lower decomposing rate of phenol and catechol, their concentrations increase continuously and do not reach the equilibrium state through the whole exposure period. During the post-exposure period,

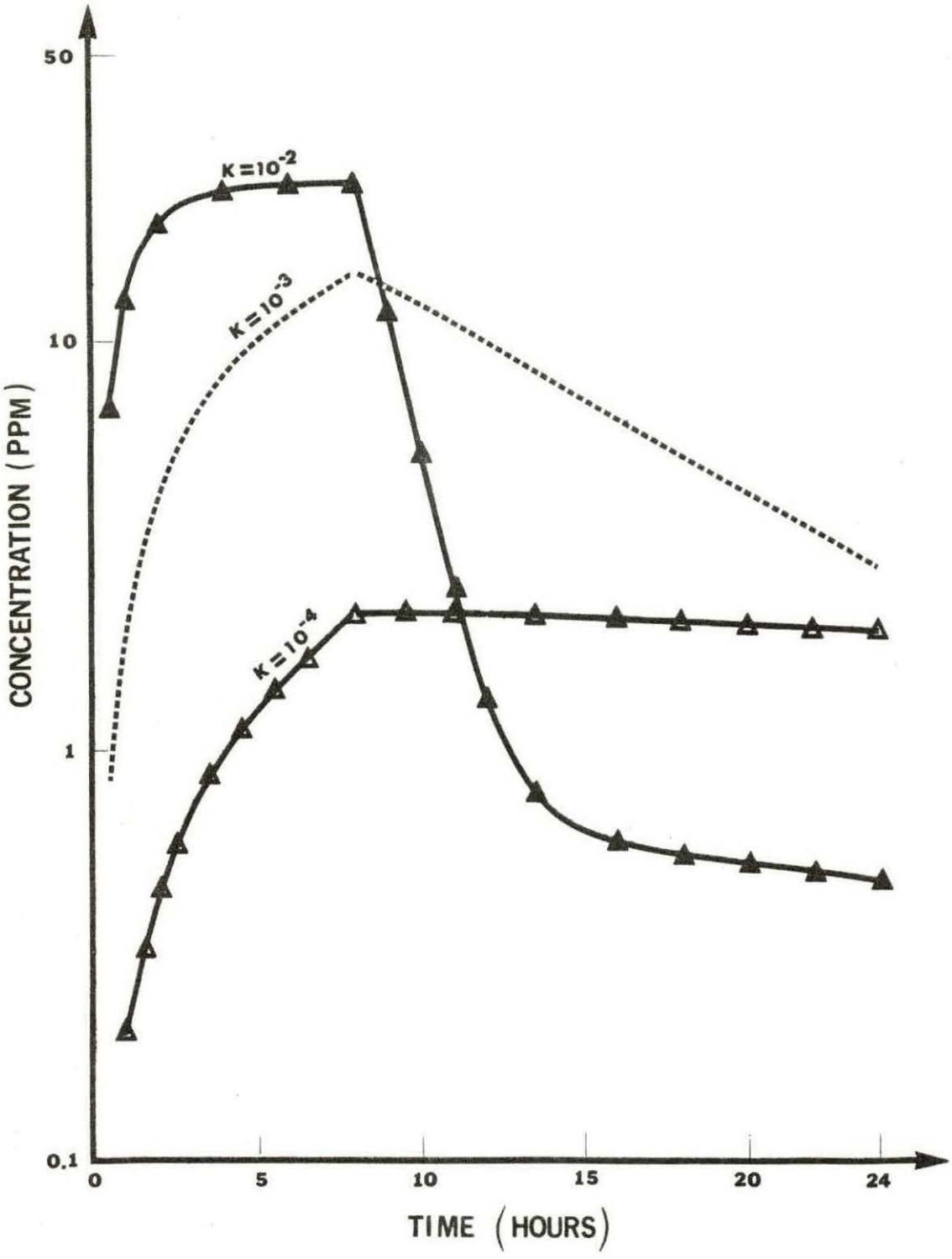


FIG. 16. PREDICTED CONTRATION OF PHENOL IN THE HUMAN BODY

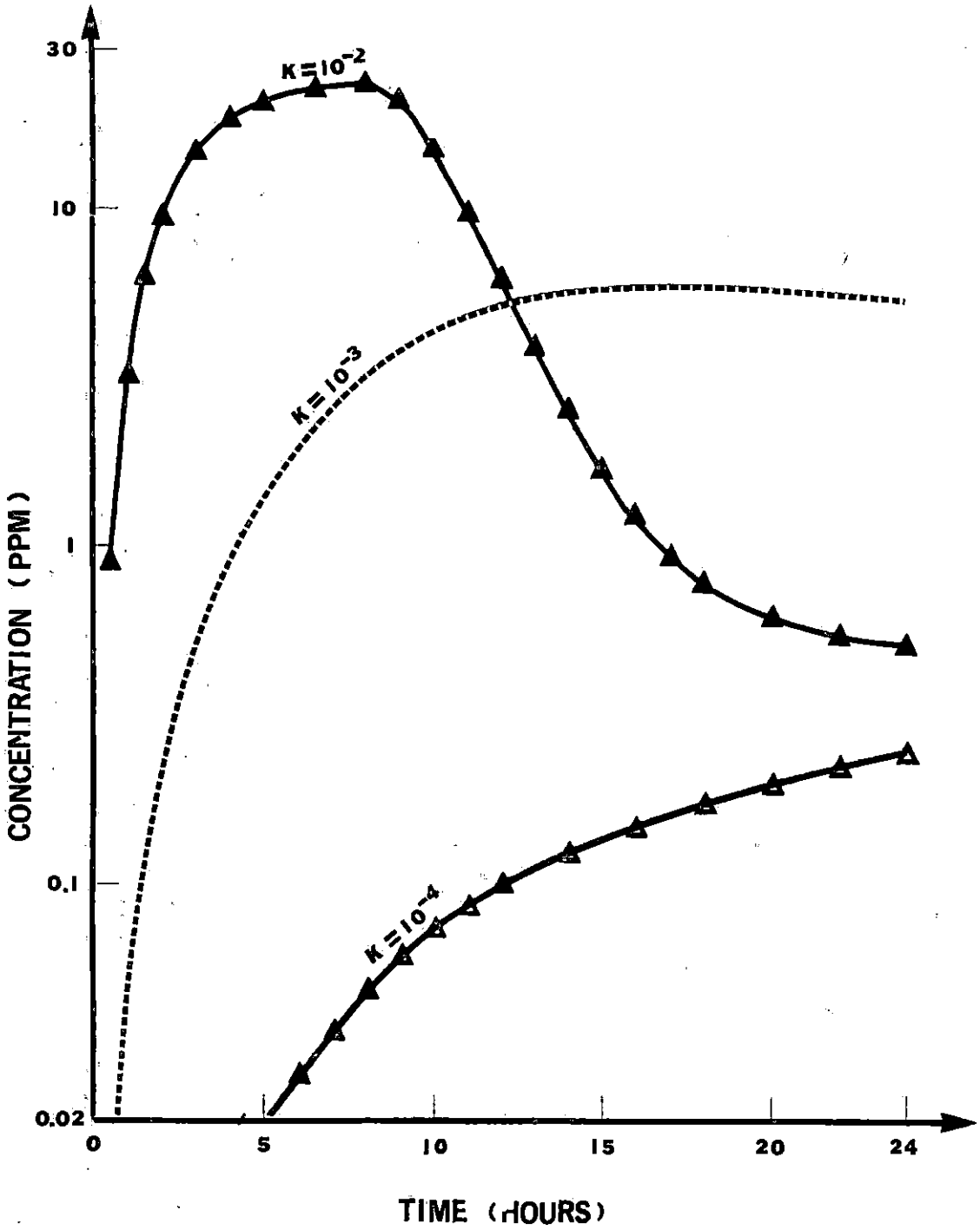


FIG. 17. PREDICTED CONCENTRATION OF CATECHOL IN THE HUMAN BODY

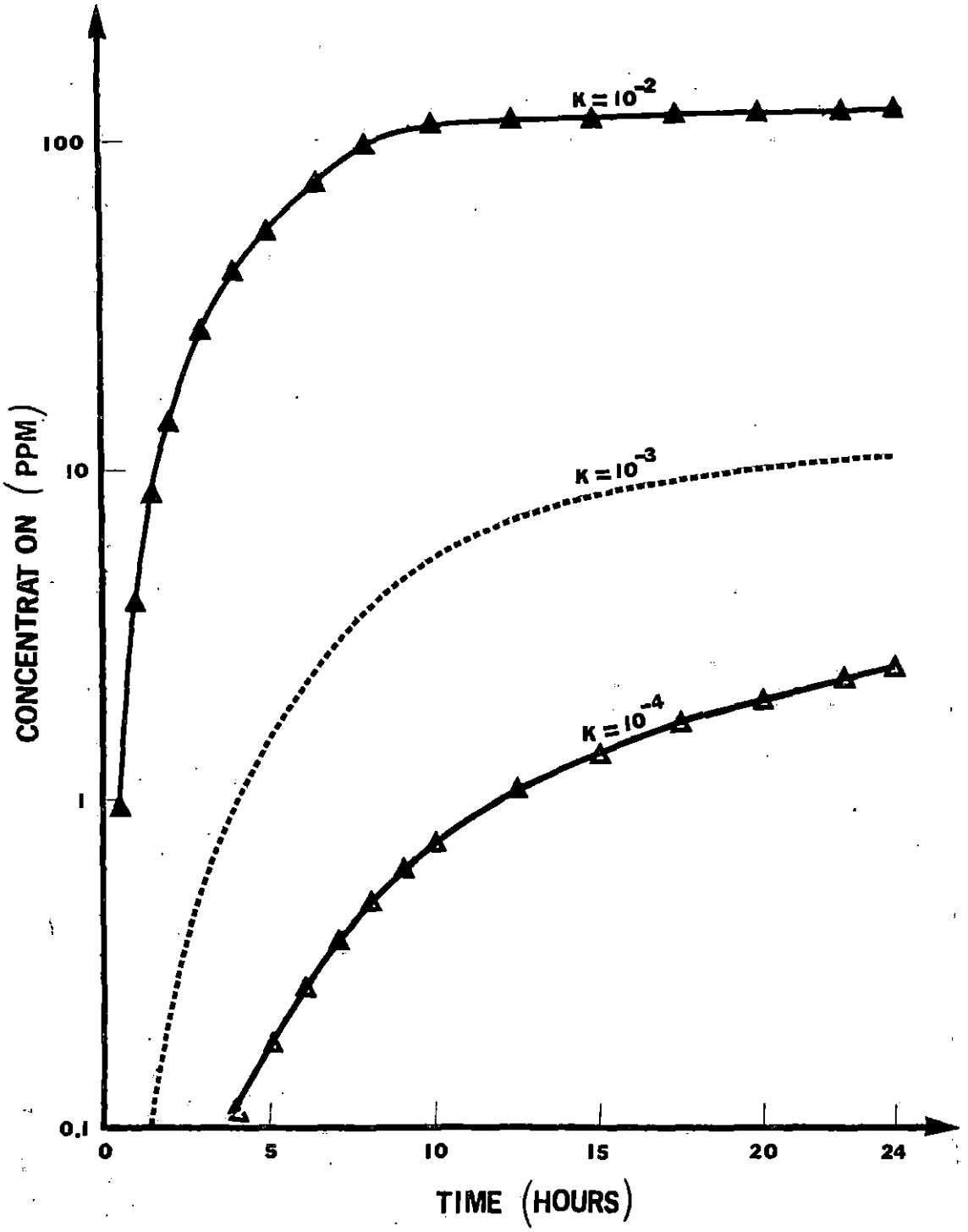


FIG. 18. PREDICTED CONCENTRATION OF QUINOL IN THE HUMAN BODY

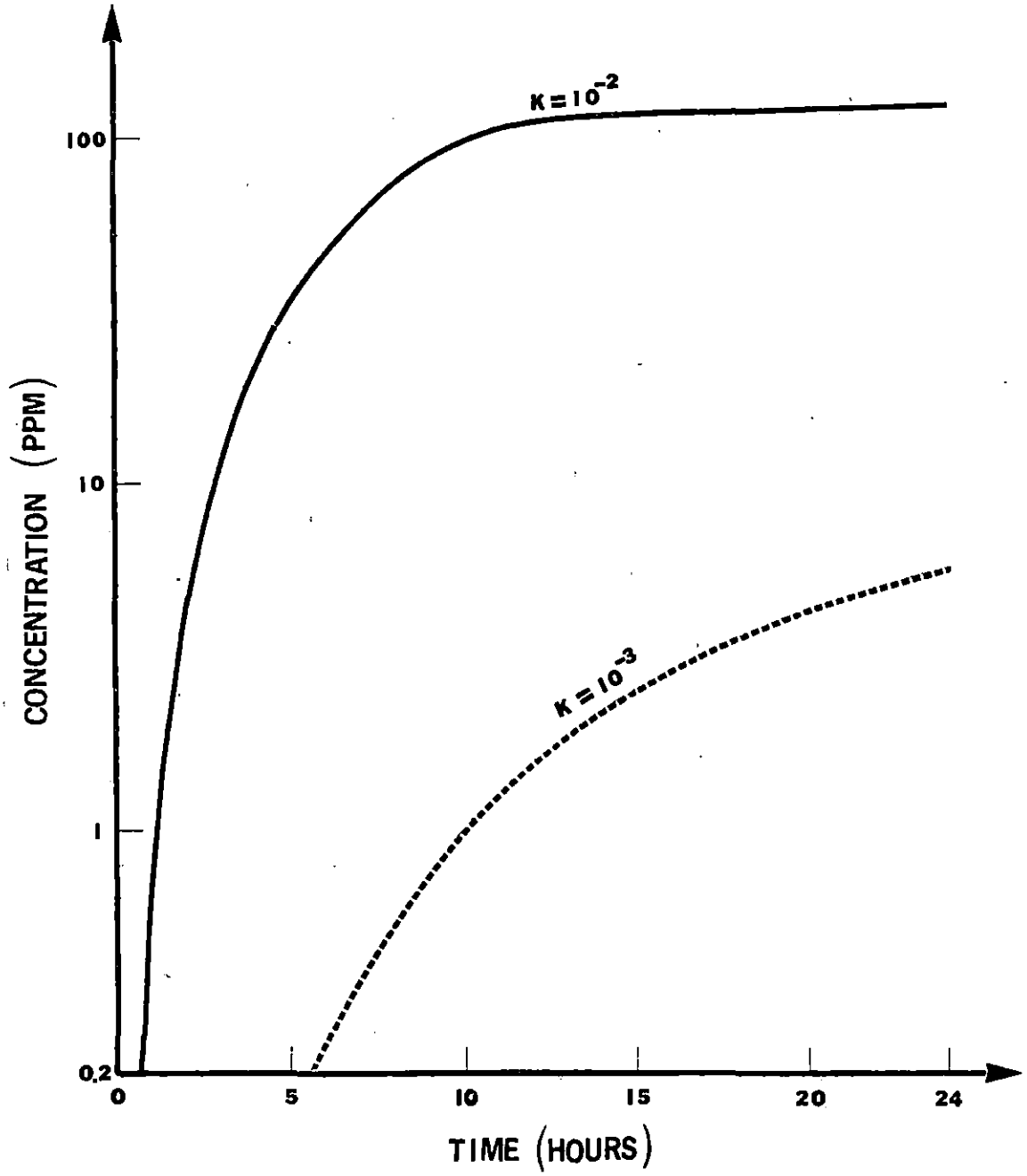


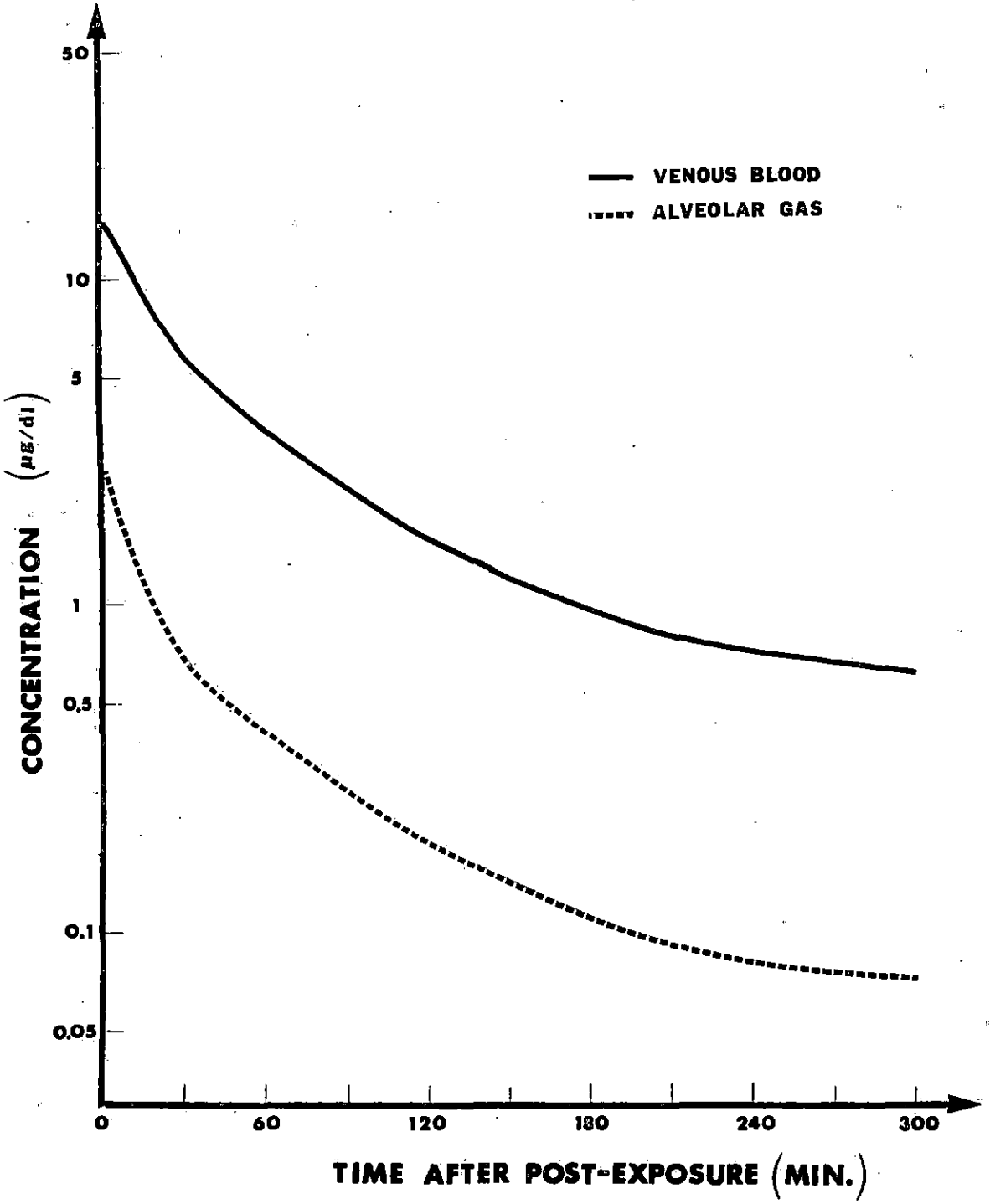
FIG. 19. PREDICTED CONCENTRATION OF HYDROXYQUINOL IN THE HUMAN BODY

phenol concentration decreases constantly with a slow elimination rate, catechol concentration continues to increase until 7 hours after cessation of exposure. The concentrations of quinol and hydroxyquinol increase consistently through the whole post-exposure period.

If the rate constants are even smaller, on the order of 10^{-4}, the concentration of all metabolites are obviously low. All metabolites except phenol increase in the body with time. Phenol concentration decreases very slowly during the post-exposure period.

In order to compare the results calculated from our model with those of previous measurements by Sato, et al. (Fig. 2), we simulated the same condition by using 25 ppm benzene in the inhaling gas. The result is shown in Appendix C. We also converted the unit of concentration from ppm to $\mu g/d\ell$ by multiplying the conversion factor of 3.19, and plotted in Fig. 20. In this figure, both our data and those of Sato, et al. are included. It is remarkable that the curves from this model are very close to those from the experiment of Sato, et al. Hence, we confirmed that our multi-compartment model can properly explain the problem of absorption and elimination of benzene in the human body.

FIG. 20. DESATURATION CURVES OF BENZENE IN BLOOD AND ALVEOLAR GAS (FOR THE EXPOSURE OF 25 PPM BENZENE)


VENOUS BLOOD
ALVEOLAR GAS
50
10
5
1
0.5
0.1
0.05
CONCENTRATION (µg/dl)
0
60
120
180
240
300
TIME AFTER POST-EXPOSURE (MIN.)

V. CONCLUSIONS AND RECOMMENDATIONS

The mathematical model developed in this research provides a quantitative prediction of the absorption, distribution, metabolism and elimination of benzene in the human body. The results agree well with those of previous investigators.

During an industrial exposure of benzene, the calculated rate of absorption by blood is very fast during the first few minutes and decreases as the benzene concentration in the blood increases. Similarly, during the post-exposure period, the elimination rate by the blood is also very fast right after cessation of exposure and decrease as the concentration gradient drops.

For a standard person with constant blood flow rate, ventilation and other physical and physiological values, the computed distribution of benzene throughout the body depends mainly on the partition coefficients of the various tissues. The tissues of vessel-rich groups absorb and eliminate benzene most efficiently. Even for repeated exposure, the accumulation of benzene in these tissues is not of importance. Contrarily, the adipose tissue absorbs and eliminates benzene very slowly. The accumulation is very obvious in the case of repeated exposure.

For a hard-working person, both the absorption and elimination rates are faster than that of a normal person.

It is remarkable from this research that the elimination of benzene from alveolar gas or from the blood is faster for the obese person than for the normal person at first following exposure, and

decreases in later periods. The concentration of benzene in the fat group is lower for obese persons, but due to its slower elimination rate, the concentration of benzene will become higher for the obese person from the 6th day of repeated exposure.

Although previous research is lacking in the kinetic study of the metabolic reactions, we have tried to simulate the reaction under the assumption of a consecutive reaction and different rate constants. From the results, we find that the concentration curves of the metabolites vary with the relative values of the rate constants. When the rate constants are higher, the conversion reaction is facilitated, the concentration of phenol and catechol decreases, while quinol and hydroxyquinol tend to be accumulated. Contrarily, if the rate constants are lower, the conversion reaction is depressed, and phenol and catechol tend to be accumulated in the body as well. We could further investigate the reaction rate by designing experiments to compare the experimental result with the computed result.

In addition to benzene, we suggest the simulation by similar methods of the response of other solvents or chemical species in the body. This will be helpful in environmental control and in establishing the standards of various industrial chemicals.

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Garton, G. A., and R. T. Williams. 1949b. Studies in detoxication. The fates of phenol, phenylsulphuric acid and phenylglucuronides in the rabbit, in relation to the metabolism of benzene. Biochem. J. 45: 158-163.

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Finally, the author would like to express his gratitude to his parents for their love and encouragement.

VIII. APPENDIX A. KINETICS OF METABOLISM OF BENZENE

In order to derive the kinetics of metabolism mathematically, we simulate the metabolic pathway by the following symbols:

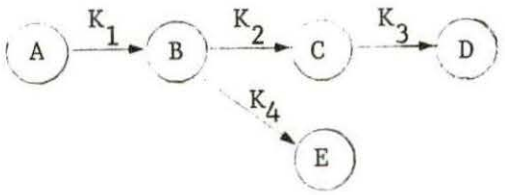

Fig. 21. Symbolic pathway of benzene metabolic reaction

where A: benzene in the liver compartment

B: free phenol converted from benzene

C: catechol converted from phenol

D: hydroxyquinol converted from catechol

E: quinol converted from phenol

K_1 - K_4: first-order rate constants.

Let x_A, x_B, x_C, x_D, x_E be the concentration of A, B, C, D, and E, respectively, at time t, which represent the time after cessation of the exposure. For simplification, we assume the initial concentrations of A, B, C, E, E are constants, x_{Ao}, x_{Bo}, x_{Co}, x_{Do}, and x_{Eo}.

The equations expressing the rate of disappearance of each species are:

$$\frac{dx_A}{dt} = K_1 x_A \tag{1}$$

$$\frac{dx_B}{dt} = K_1 x_A - (K_2 + K_4) x_B \tag{2}$$

$$\frac{dx_C}{dt} = K_2 x_B - K_3 x_C \tag{3}$$

$$\frac{dx_D}{dt} = K_3 x_C \tag{4}$$

$$\frac{dx_E}{dt} = K_4 x_B \tag{5}$$

Solving (1) for x_A,

$$x_A = x_{Ao} e^{-K_1 t} \tag{6}$$

Insert (6) into (2), and let $K_B = K_2 + K_4$ then (2) becomes

$$\frac{dx_B}{dt} + K_B x_B = K_1 x_{Ao} e^{-K_1 t}$$

Multiply the integrating factor $e^{K_B t}$, and solve for x_B, we obtain

$$x_B = -\frac{K_1 x_{Ao}}{K_1 - K_B} e^{-K_1 t} + (x_{Bo} + \frac{K_1 x_{Ao}}{K_1 - K_B}) e^{-K_B t} \tag{7}$$

Combining (7) and (3) generates

$$\frac{dx_C}{dt} + K_3 x_C = -\frac{K_1 K_2 x_{Ao}}{K_1 - K_B} e^{-K_1 t} + (K_2 x_{Bo} + \frac{K_1 K_2 x_{Ao}}{K_1 - K_B}) e^{-K_B t}$$

Multiply the integrating factor $e^{K_3 t}$, and solve for x_C, we obtain

$$x_C = \frac{K_1 K_2 x_{Ao}}{(K_1 - K_3)(K_1 - K_B)} e^{-K_1 t} - [\frac{K_2 x_{Bo}}{K_B - K_3} + \frac{K_1 K_2 x_{Ao}}{(K_B - K_3)(K_1 - K_B)}] e^{-K_B t}$$

$$+ [x_{Co} + \frac{K_2 x_{Bo}}{K_B - K_3} + \frac{K_1 K_2 x_{Ao}}{(K_1 - K_3)(K_B - K_3)}] e^{-K_3 t} \tag{8}$$

Inserting (8) into (4) generates

$$\frac{dx_D}{dt} = \frac{K_1 K_2 K_3 x_{Ao}}{(K_1 - K_3)(K_1 - K_B)} e^{-K_1 t} - [\frac{K_2 K_3 x_{Bo}}{K_B - K_3} + \frac{K_1 K_2 K_3 x_{Ao}}{(K_B - K_3)(K_1 - K_B)}] e^{-K_B t}$$

$$+ K_3 [x_{Co} + \frac{K_2 x_{Bo}}{K_B - K_3} + \frac{K_1 K_2 x_{Ao}}{(K_1 - K_3)(K_B - K_3)}] e^{-K_3 t}$$

Solving for x_D, we obtain

$$x_D = (x_{Do} + x_{Co} + \frac{K_2}{K_B} x_{Bo} + \frac{K_2}{K_B} x_{Ao}) - \frac{K_2 K_3 x_{Ao}}{(K_1 - K_3)(K_1 - K_B)} e^{-K_1 t}$$

$$+ [\frac{K_2 K_3 x_{Bo}}{K_B(K_B - K_3)} + \frac{K_1 K_2 K_3 x_{Ao}}{K_B(K_B - K_3)(K_1 - K_B)}] e^{-K_B t}$$

$$- [x_{Co} + \frac{K_2 x_{Bo}}{K_B - K_3} + \frac{K_1 K_2 x_{Ao}}{(K_1 - K_3)(K_B - K_3)}] e^{-K_3 t} \qquad (9)$$

Inserting (7) into (5) generates

$$\frac{dx_E}{dt} = - \frac{K_1 K_4 x_{Ao}}{K_1 - K_B} e^{-K_1 t} + (K_4 x_{Bo} + \frac{K_1 K_4 x_{Ao}}{K_1 - K_B}) e^{-K_B t}$$

Solving for x_E, we obtain

$$x_E = \frac{K_4 x_{Ao}}{K_1 - K_B} e^{-K_1 t} - [\frac{K_4}{K_B} x_{Bo} + \frac{K_1 K_4 x_{Ao}}{K_B(K_1 - K_B)}] e^{-K_B t}$$

$$+ [x_{Eo} - \frac{K_4 x_{Ao}}{K_1 - K_B} + \frac{K_4}{K_B} x_{Bo} + \frac{K_1 K_4 x_{Ao}}{K_B(K_1 - K_B)}] \qquad (10)$$

IX. APPENDIX B. FORTRAN PROGRAM ON THE VAX-11/780 SYSTEM

```
00100   c This program is to simulate the absorption, metabo-
00200   c lism and elimination of benzene in the human body,
00300   c which is exposed to an environment of 100 ppm ben-
00400   c zene for 8 hours.
00500
00600         real lmdb,lmdp,lmd1b,lmd2b,lmd3b,lmd1b
00700         real k1,k2,k3,k4
00800
00900   c read the volume of alveolar gas.
01000         read*, va
01100   c read the alveolar ventilation.
01200         read*, qa
01300   c read the volumes of various tissues.
01400         read*, vtp,vt1,vt2,vt3,vtl
01500   c read the blood volume in various tissues.
01600         read*, vbp,vb1,vb2,vb3,vbl,vbv,vba
01700   c read the blood flow rates through tissues.
01800         read*, qb,q1,q2,q3,ql
01900   c read the partition coefficients and lung shunt.
02000         read*, lmdb,lmdp,lmd1,lmd2,lmd3,lmdl,ssm
02100   c read the metabolic rate constants.
02200         read*, k1,k2,k3,k4
02300   c read the time increments.
02400         read*, dt,dtpr,tmax
02500
02600         vpeq=va+vtp*lmdp+vbp*lmdb
02700         v1eq=vt1*lmd1b+vb1
02800         v2eq=vt2*lmd2b+vb2
02900         v3eq=vt3*lmd3b+vb3
03000         h=vb1/(vt1*lmd1b+vb1)
03100
03200         write  (6,1) 'TIME','ALVEOLAR','VENOUS','VRG',
03300        $'MG','FG','LIVER'
03400   1     format(' ',1x,a4,4x,a8,3x,a6,7x,a3,8x,a2,9x,a2,
03500        $7x,a5)
03600
03700   c     initialization
03800         xa=0
03900         dxs=0
04000         xv=0
04100         dxv=0
04200         yap=0
04300         dyap=0
04400         x1=0
```

```
04500           dx1=0
04600           x2=0
04700           dx2=0
04800           x3=0
04900           dx3=0
05000           x1=0
05100           dx1=0
05200           xph=0
05300           dxph=0
05400           xca=0
05500           dxca=0
05600           xau=0
05700           dxau=0
05800           xha=0
05900           dxha=0
06000           t=0
06100           tfr=30
06200
06300     c     Calculation of the transient response of ben-
06400     c     zene in various organs and tissues.
06500
06600     2     if(t.ge.0.and.t.lt.480)then
06700             yi=0.100E-03
06800             else
06900             if(t.ge.480.and.t.lt.1440)then
07000               yi=0
07100               endif
07200             endif
07300
07400     c     Assume the steady state to be the normal state,
07500     c     ie., the concentration of benzene in alveolar
07600     c     gas and tissues are all zero.
07700
07800           yap=yap+dyap
07900           xv=xv+dxv
08000           x1=x1+dx1
08100           x2=x2+dx2
08200           x3=x3+dx3
08300           xa=xa+dxa
08400           x1=xa*b
08500           x1=x1+dx1
08600
08700           dyap=dt*(qa*(yi-yap)+qb*(1-ssm)*(xv-lmdb*yap))
08800          $/vpeq
08900           dx1=dt*q1*(xa-x1)/v1eq
09000           dx2=dt*q2*(xa-x2)/v2eq
09100           dx3=dt*q3*(xa-x3)/v3eq
09200           dxa=dt*qb*((1-ssm)*lmdb*yap+ssm*xv-xa)/vba
09300           dxv=dt*(q1*x1+q2*x2+q3*x3+ql*xl-qb*xv)/vbv
09400
09500     c     Calculation of the transient response of the
```

```
09600     c       benzene metabolites in the human body.
09700
09800             xph=xph+dxph
09900             xca=xca+dxca
10000             xqu=xqu+dxqu
10100             xha=xha+dxha
10200
10300             dx1=-dt*k1*x1
10400             dxph=dt*(k1*x1-(k2+k4)*xph)
10500             dxca=dt*(k2*xph-k3*xca)
10600             dxqu=dt*k4*xph
10700             dxha=dt*k3*xca
10800
10900             t=t+dt
11000             if ((t-tpr)-0.01) 2,3,3
11100     3       write (6,4) t,xph,xv,x1,x2,x3,x1
11200     4       format(' ',f6.0,2x,E9.3,2x,E9.3,2x,E9.3,2x,
11300            $E9.3,2x,E9.3,2x,E9.3)
11400             write (6,5) 'ph=',xph,'ca=',xca,'qu=',xqu,
11500            $'ha=',xha
11600     5       format(' ',8x,a4,E9.3,3x,a4,E9.3,3x,a4,E9.3,
11700            $3x,a4,E9.3)
11800             tpr=tpr+dtpr
11900             if ((t-tmax)-0.01) 2,6,6
12000     6       stop
12100             end
*
```

X. APPENDIX C.

TRANSIENT RESPONSE OF BENZENE IN THE HUMAN BODY

A. Transient Response of Benzene (100 ppm) in a Normal Person

TIME	ALVEOLAR	VENOUS	VRG	MG	FG
30.	0.245E-04	0.127E-03	0.185E-03	0.877E-04	0.222E-05
60.	0.277E-04	0.155E-03	0.213E-03	0.153E-03	0.520E-05
90.	0.295E-04	0.170E-03	0.228E-03	0.193E-03	0.842E-05
120.	0.305E-04	0.179E-03	0.237E-03	0.216E-03	0.117E-04
150.	0.312E-04	0.185E-03	0.242E-03	0.230E-03	0.151E-04
180.	0.316E-04	0.188E-03	0.246E-03	0.238E-03	0.185E-04
210.	0.319E-04	0.190E-03	0.248E-03	0.243E-03	0.219E-04
240.	0.320E-04	0.192E-03	0.249E-03	0.246E-03	0.252E-04
270.	0.322E-04	0.193E-03	0.250E-03	0.248E-03	0.286E-04
300.	0.323E-04	0.194E-03	0.251E-03	0.250E-03	0.318E-04
330.	0.323E-04	0.195E-03	0.252E-03	0.251E-03	0.351E-04
360.	0.324E-04	0.195E-03	0.252E-03	0.251E-03	0.383E-04
390.	0.325E-04	0.196E-03	0.253E-03	0.252E-03	0.414E-04
420.	0.325E-04	0.196E-03	0.253E-03	0.253E-03	0.445E-04
450.	0.326E-04	0.197E-03	0.254E-03	0.253E-03	0.476E-04
480.	0.326E-04	0.197E-03	0.254E-03	0.254E-03	0.507E-04
510.	0.821E-05	0.707E-04	0.699E-04	0.166E-03	0.515E-04
540.	0.504E-05	0.436E-04	0.419E-04	0.101E-03	0.514E-04
570.	0.333E-05	0.287E-04	0.274E-04	0.623E-04	0.512E-04
600.	0.232E-05	0.200E-04	0.189E-04	0.395E-04	0.507E-04
630.	0.172E-05	0.149E-04	0.139E-04	0.261E-04	0.502E-04
660.	0.136E-05	0.118E-04	0.109E-04	0.181E-04	0.496E-04
690.	0.115E-05	0.994E-05	0.916E-05	0.134E-04	0.491E-04
720.	0.102E-05	0.882E-05	0.807E-05	0.106E-04	0.485E-04
750.	0.936E-06	0.812E-05	0.740E-05	0.893E-05	0.479E-04
780.	0.884E-06	0.767E-05	0.697E-05	0.791E-05	0.473E-04
810.	0.849E-06	0.737E-05	0.669E-05	0.727E-05	0.467E-04
840.	0.825E-06	0.716E-05	0.648E-05	0.687E-05	0.461E-04
870.	0.806E-06	0.700E-05	0.633E-05	0.660E-05	0.455E-04
900.	0.791E-06	0.687E-05	0.621E-05	0.640E-05	0.449E-04
930.	0.778E-06	0.676E-05	0.611E-05	0.626E-05	0.443E-04
960.	0.767E-06	0.666E-05	0.602E-05	0.614E-05	0.438E-04
990.	0.756E-06	0.656E-05	0.593E-05	0.604E-05	0.432E-04
1020.	0.746E-06	0.647E-05	0.585E-05	0.595E-05	0.427E-04
1050.	0.736E-06	0.639E-05	0.578E-05	0.587E-05	0.421E-04
1080.	0.726E-06	0.631E-05	0.570E-05	0.579E-05	0.416E-04
1110.	0.717E-06	0.622E-05	0.563E-05	0.571E-05	0.411E-04
1140.	0.708E-06	0.614E-05	0.556E-05	0.564E-05	0.405E-04
1170.	0.699E-06	0.607E-05	0.548E-05	0.556E-05	0.400E-04
1200.	0.690E-06	0.599E-05	0.541E-05	0.549E-05	0.395E-04
1230.	0.681E-06	0.591E-05	0.535E-05	0.542E-05	0.390E-04
1260.	0.672E-06	0.584E-05	0.528E-05	0.535E-05	0.385E-04
1290.	0.664E-06	0.576E-05	0.521E-05	0.529E-05	0.380E-04
1320.	0.655E-06	0.569E-05	0.514E-05	0.522E-05	0.375E-04
1350.	0.647E-06	0.562E-05	0.508E-05	0.515E-05	0.370E-04
1380.	0.639E-06	0.554E-05	0.501E-05	0.509E-05	0.366E-04
1410.	0.630E-06	0.547E-05	0.495E-05	0.502E-05	0.361E-04
1440.	0.622E-06	0.540E-05	0.489E-05	0.496E-05	0.357E-04

1. Transient response of metabolites in a normal person

TIME	PHENOL	CATECH	QUINOL	HYDROQ
30.	0.670E-05	0.861E-06	0.943E-06	0.828E-07
60.	0.125E-04	0.321E-05	0.388E-05	0.667E-06
90.	0.165E-04	0.619E-05	0.826E-05	0.207E-05
120.	0.191E-04	0.924E-05	0.136E-04	0.439E-05
150.	0.208E-04	0.120E-04	0.196E-04	0.759E-05
180.	0.219E-04	0.145E-04	0.261E-04	0.116E-04
210.	0.227E-04	0.165E-04	0.328E-04	0.162E-04
240.	0.231E-04	0.182E-04	0.396E-04	0.215E-04
270.	0.234E-04	0.195E-04	0.466E-04	0.271E-04
300.	0.236E-04	0.205E-04	0.537E-04	0.331E-04
330.	0.238E-04	0.214E-04	0.608E-04	0.394E-04
360.	0.239E-04	0.220E-04	0.679E-04	0.459E-04
390.	0.240E-04	0.225E-04	0.751E-04	0.526E-04
420.	0.240E-04	0.229E-04	0.823E-04	0.594E-04
450.	0.241E-04	0.232E-04	0.895E-04	0.663E-04
480.	0.241E-04	0.234E-04	0.967E-04	0.733E-04
510.	0.175E-04	0.228E-04	0.103E-03	0.803E-04
540.	0.117E-04	0.206E-04	0.107E-03	0.868E-04
570.	0.779E-05	0.177E-04	0.110E-03	0.925E-04
600.	0.520E-05	0.148E-04	0.112E-03	0.974E-04
630.	0.351E-05	0.120E-04	0.113E-03	0.101E-03
660.	0.244E-05	0.967E-05	0.114E-03	0.105E-03
690.	0.175E-05	0.770E-05	0.115E-03	0.107E-03
720.	0.132E-05	0.610E-05	0.115E-03	0.109E-03
750.	0.105E-05	0.482E-05	0.116E-03	0.111E-03
780.	0.883E-06	0.382E-05	0.116E-03	0.112E-03
810.	0.776E-06	0.304E-05	0.116E-03	0.113E-03
840.	0.707E-06	0.245E-05	0.116E-03	0.114E-03
870.	0.662E-06	0.199E-05	0.117E-03	0.115E-03
900.	0.632E-06	0.164E-05	0.117E-03	0.115E-03
930.	0.611E-06	0.138E-05	0.117E-03	0.116E-03
960.	0.595E-06	0.118E-05	0.117E-03	0.116E-03
990.	0.583E-06	0.102E-05	0.117E-03	0.116E-03
1020.	0.572E-06	0.908E-06	0.118E-03	0.117E-03
1050.	0.563E-06	0.820E-06	0.118E-03	0.117E-03
1080.	0.555E-06	0.753E-06	0.118E-03	0.117E-03
1110.	0.548E-06	0.700E-06	0.118E-03	0.117E-03
1140.	0.540E-06	0.660E-06	0.118E-03	0.118E-03
1170.	0.533E-06	0.628E-06	0.118E-03	0.118E-03
1200.	0.526E-06	0.602E-06	0.119E-03	0.118E-03
1230.	0.519E-06	0.582E-06	0.119E-03	0.118E-03
1260.	0.513E-06	0.565E-06	0.119E-03	0.118E-03
1290.	0.506E-06	0.550E-06	0.119E-03	0.119E-03
1320.	0.500E-06	0.538E-06	0.119E-03	0.119E-03
1350.	0.493E-06	0.527E-06	0.119E-03	0.119E-03
1380.	0.487E-06	0.518E-06	0.119E-03	0.119E-03
1410.	0.481E-06	0.509E-06	0.120E-03	0.119E-03
1440.	0.475E-06	0.501E-06	0.120E-03	0.119E-03

B. Transient Response of Benzene (100 ppm) in a Working Person

TIME	ALVEOLAR	VENOUS	VRG	MG	FG
30.	0.277E-04	0.155E-03	0.213E-03	0.153E-03	0.520E-05
60.	0.305E-04	0.179E-03	0.237E-03	0.216E-03	0.117E-04
90.	0.316E-04	0.188E-03	0.246E-03	0.238E-03	0.185E-04
120.	0.320E-04	0.192E-03	0.249E-03	0.246E-03	0.252E-04
150.	0.323E-04	0.194E-03	0.251E-03	0.250E-03	0.318E-04
180.	0.324E-04	0.195E-03	0.252E-03	0.251E-03	0.383E-04
210.	0.325E-04	0.196E-03	0.253E-03	0.253E-03	0.446E-04
240.	0.326E-04	0.197E-03	0.254E-03	0.254E-03	0.507E-04
270.	0.328E-04	0.198E-03	0.255E-03	0.254E-03	0.567E-04
300.	0.329E-04	0.199E-03	0.256E-03	0.255E-03	0.625E-04
330.	0.330E-04	0.200E-03	0.256E-03	0.256E-03	0.682E-04
360.	0.331E-04	0.201E-03	0.257E-03	0.257E-03	0.737E-04
390.	0.331E-04	0.201E-03	0.258E-03	0.258E-03	0.791E-04
420.	0.332E-04	0.202E-03	0.259E-03	0.258E-03	0.843E-04
450.	0.333E-04	0.203E-03	0.259E-03	0.259E-03	0.894E-04
480.	0.334E-04	0.204E-03	0.260E-03	0.260E-03	0.944E-04
510.	0.896E-05	0.773E-04	0.759E-04	0.172E-03	0.947E-04
540.	0.579E-05	0.500E-04	0.477E-04	0.107E-03	0.941E-04
570.	0.406E-05	0.351E-04	0.332E-04	0.682E-04	0.933E-04
600.	0.304E-05	0.263E-04	0.246E-04	0.453E-04	0.923E-04
630.	0.243E-05	0.211E-04	0.196E-04	0.318E-04	0.913E-04
660.	0.207E-05	0.179E-04	0.165E-04	0.238E-04	0.902E-04
690.	0.185E-05	0.160E-04	0.146E-04	0.190E-04	0.891E-04
720.	0.171E-05	0.148E-04	0.135E-04	0.161E-04	0.879E-04
750.	0.162E-05	0.140E-04	0.127E-04	0.144E-04	0.868E-04
780.	0.156E-05	0.135E-04	0.122E-04	0.133E-04	0.857E-04
810.	0.151E-05	0.131E-04	0.119E-04	0.126E-04	0.847E-04
840.	0.148E-05	0.128E-04	0.116E-04	0.121E-04	0.836E-04
870.	0.145E-05	0.126E-04	0.114E-04	0.117E-04	0.825E-04
900.	0.143E-05	0.124E-04	0.112E-04	0.115E-04	0.815E-04
930.	0.141E-05	0.122E-04	0.111E-04	0.113E-04	0.804E-04
960.	0.139E-05	0.121E-04	0.109E-04	0.111E-04	0.794E-04
990.	0.137E-05	0.119E-04	0.108E-04	0.109E-04	0.784E-04
1020.	0.135E-05	0.117E-04	0.106E-04	0.108E-04	0.774E-04
1050.	0.133E-05	0.116E-04	0.105E-04	0.106E-04	0.764E-04
1080.	0.132E-05	0.114E-04	0.103E-04	0.105E-04	0.754E-04
1110.	0.130E-05	0.113E-04	0.102E-04	0.104E-04	0.745E-04
1140.	0.128E-05	0.111E-04	0.101E-04	0.102E-04	0.735E-04
1170.	0.127E-05	0.110E-04	0.995E-05	0.101E-04	0.726E-04
1200.	0.125E-05	0.109E-04	0.982E-05	0.996E-05	0.717E-04
1230.	0.124E-05	0.107E-04	0.970E-05	0.984E-05	0.707E-04
1260.	0.122E-05	0.106E-04	0.957E-05	0.971E-05	0.698E-04
1290.	0.120E-05	0.105E-04	0.945E-05	0.959E-05	0.690E-04
1320.	0.119E-05	0.103E-04	0.933E-05	0.947E-05	0.681E-04
1350.	0.117E-05	0.102E-04	0.921E-05	0.935E-05	0.672E-04
1380.	0.116E-05	0.101E-04	0.909E-05	0.923E-05	0.664E-04
1410.	0.114E-05	0.993E-05	0.898E-05	0.911E-05	0.655E-04
1440.	0.113E-05	0.980E-05	0.886E-05	0.899E-05	0.647E-04

C. Transient Response of Benzene (100 ppm) in an Obese Person

TIME	ALVEOLAR	VENOUS	VRG	MG	FG
30.	0.245E-04	0.127E-03	0.185E-03	0.877E-04	0.111E-05
60.	0.277E-04	0.154E-03	0.213E-03	0.153E-03	0.262E-05
90.	0.294E-04	0.169E-03	0.228E-03	0.192E-03	0.425E-05
120.	0.305E-04	0.178E-03	0.236E-03	0.215E-03	0.595E-05
150.	0.311E-04	0.184E-03	0.241E-03	0.229E-03	0.768E-05
180.	0.315E-04	0.187E-03	0.245E-03	0.237E-03	0.943E-05
210.	0.317E-04	0.189E-03	0.246E-03	0.242E-03	0.112E-04
240.	0.318E-04	0.190E-03	0.248E-03	0.245E-03	0.129E-04
270.	0.319E-04	0.191E-03	0.249E-03	0.247E-03	0.147E-04
300.	0.320E-04	0.192E-03	0.249E-03	0.248E-03	0.164E-04
330.	0.321E-04	0.192E-03	0.250E-03	0.249E-03	0.181E-04
360.	0.321E-04	0.193E-03	0.250E-03	0.249E-03	0.198E-04
390.	0.322E-04	0.193E-03	0.250E-03	0.250E-03	0.216E-04
420.	0.322E-04	0.193E-03	0.250E-03	0.250E-03	0.232E-04
450.	0.322E-04	0.193E-03	0.251E-03	0.250E-03	0.249E-04
480.	0.323E-04	0.194E-03	0.251E-03	0.251E-03	0.266E-04
510.	0.780E-05	0.672E-04	0.667E-04	0.163E-03	0.272E-04
540.	0.463E-05	0.400E-04	0.386E-04	0.979E-04	0.273E-04
570.	0.292E-05	0.252E-04	0.242E-04	0.591E-04	0.273E-04
600.	0.191E-05	0.165E-04	0.158E-04	0.363E-04	0.273E-04
630.	0.132E-05	0.114E-04	0.108E-04	0.229E-04	0.271E-04
660.	0.966E-06	0.835E-05	0.784E-05	0.150E-04	0.270E-04
690.	0.758E-06	0.657E-05	0.611E-05	0.103E-04	0.269E-04
720.	0.635E-06	0.551E-05	0.508E-05	0.756E-05	0.267E-04
750.	0.562E-06	0.487E-05	0.446E-05	0.593E-05	0.265E-04
780.	0.517E-06	0.449E-05	0.409E-05	0.496E-05	0.264E-04
810.	0.490E-06	0.425E-05	0.386E-05	0.439E-05	0.262E-04
840.	0.473E-06	0.410E-05	0.372E-05	0.404E-05	0.260E-04
870.	0.461E-06	0.401E-05	0.363E-05	0.382E-05	0.259E-04
900.	0.454E-06	0.394E-05	0.356E-05	0.369E-05	0.257E-04
930.	0.448E-06	0.389E-05	0.352E-05	0.360E-05	0.256E-04
960.	0.443E-06	0.385E-05	0.348E-05	0.354E-05	0.254E-04
990.	0.439E-06	0.382E-05	0.345E-05	0.349E-05	0.252E-04
1020.	0.436E-06	0.379E-05	0.342E-05	0.346E-05	0.251E-04
1050.	0.433E-06	0.376E-05	0.340E-05	0.343E-05	0.249E-04
1080.	0.430E-06	0.373E-05	0.337E-05	0.340E-05	0.247E-04
1110.	0.427E-06	0.371E-05	0.335E-05	0.338E-05	0.246E-04
1140.	0.424E-06	0.368E-05	0.333E-05	0.335E-05	0.244E-04
1170.	0.422E-06	0.366E-05	0.331E-05	0.333E-05	0.243E-04
1200.	0.419E-06	0.364E-05	0.328E-05	0.331E-05	0.241E-04
1230.	0.416E-06	0.361E-05	0.326E-05	0.329E-05	0.240E-04
1260.	0.413E-06	0.359E-05	0.324E-05	0.327E-05	0.238E-04
1290.	0.411E-06	0.357E-05	0.322E-05	0.325E-05	0.237E-04
1320.	0.408E-06	0.354E-05	0.320E-05	0.322E-05	0.235E-04
1350.	0.406E-06	0.352E-05	0.318E-05	0.320E-05	0.234E-04
1380.	0.403E-06	0.350E-05	0.316E-05	0.318E-05	0.232E-04
1410.	0.400E-06	0.348E-05	0.314E-05	0.316E-05	0.231E-04
1440.	0.398E-06	0.345E-05	0.312E-05	0.314E-05	0.229E-04

D. Transient Response of Benzene (25 ppm) in a Normal Person

TIME	ALVEOLAR	VENOUS	VRG	MG	FG
30.	0.612E-05	0.317E-04	0.462E-04	0.219E-04	0.555E-06
60.	0.693E-05	0.386E-04	0.533E-04	0.384E-04	0.130E-05
90.	0.737E-05	0.425E-04	0.570E-04	0.482E-04	0.210E-05
120.	0.764E-05	0.447E-04	0.592E-04	0.540E-04	0.294E-05
150.	0.780E-05	0.461E-04	0.606E-04	0.574E-04	0.378E-05
180.	0.790E-05	0.470E-04	0.614E-04	0.595E-04	0.463E-05
210.	0.796E-05	0.476E-04	0.619E-04	0.608E-04	0.547E-05
240.	0.801E-05	0.480E-04	0.623E-04	0.616E-04	0.631E-05
270.	0.804E-05	0.482E-04	0.626E-04	0.621E-04	0.714E-05
300.	0.807E-05	0.485E-04	0.628E-04	0.624E-04	0.796E-05
330.	0.809E-05	0.486E-04	0.629E-04	0.627E-04	0.877E-05
360.	0.810E-05	0.488E-04	0.631E-04	0.629E-04	0.957E-05
390.	0.812E-05	0.489E-04	0.632E-04	0.630E-04	0.104E-04
420.	0.813E-05	0.490E-04	0.633E-04	0.632E-04	0.111E-04
450.	0.815E-05	0.492E-04	0.634E-04	0.633E-04	0.119E-04
480.	0.816E-05	0.493E-04	0.635E-04	0.634E-04	0.127E-04
510.	0.205E-05	0.177E-04	0.175E-04	0.416E-04	0.129E-04
540.	0.126E-05	0.109E-04	0.105E-04	0.253E-04	0.129E-04
570.	0.832E-06	0.719E-05	0.686E-05	0.156E-04	0.128E-04
600.	0.579E-06	0.501E-05	0.474E-05	0.988E-05	0.127E-04
630.	0.429E-06	0.372E-05	0.348E-05	0.652E-05	0.126E-04
660.	0.340E-06	0.295E-05	0.274E-05	0.453E-05	0.124E-04
690.	0.287E-06	0.249E-05	0.229E-05	0.335E-05	0.123E-04
720.	0.254E-06	0.220E-05	0.202E-05	0.265E-05	0.121E-04
750.	0.234E-06	0.203E-05	0.185E-05	0.223E-05	0.120E-04
780.	0.221E-06	0.192E-05	0.174E-05	0.198E-05	0.118E-04
810.	0.212E-06	0.184E-05	0.167E-05	0.182E-05	0.117E-04
840.	0.206E-06	0.179E-05	0.162E-05	0.172E-05	0.115E-04
870.	0.202E-06	0.175E-05	0.158E-05	0.165E-05	0.114E-04
900.	0.198E-06	0.172E-05	0.155E-05	0.160E-05	0.112E-04
930.	0.195E-06	0.169E-05	0.153E-05	0.156E-05	0.111E-04
960.	0.192E-06	0.166E-05	0.150E-05	0.154E-05	0.109E-04
990.	0.189E-06	0.164E-05	0.148E-05	0.151E-05	0.108E-04
1020.	0.186E-06	0.162E-05	0.146E-05	0.149E-05	0.107E-04
1050.	0.184E-06	0.160E-05	0.144E-05	0.147E-05	0.105E-04
1080.	0.182E-06	0.158E-05	0.143E-05	0.145E-05	0.104E-04
1110.	0.179E-06	0.156E-05	0.141E-05	0.143E-05	0.103E-04
1140.	0.177E-06	0.154E-05	0.139E-05	0.141E-05	0.101E-04
1170.	0.175E-06	0.152E-05	0.137E-05	0.139E-05	0.100E-04
1200.	0.172E-06	0.150E-05	0.135E-05	0.137E-05	0.988E-05
1230.	0.170E-06	0.148E-05	0.134E-05	0.136E-05	0.975E-05
1260.	0.168E-06	0.146E-05	0.132E-05	0.134E-05	0.963E-05
1290.	0.166E-06	0.144E-05	0.130E-05	0.132E-05	0.950E-05
1320.	0.164E-06	0.142E-05	0.129E-05	0.130E-05	0.938E-05
1350.	0.162E-06	0.140E-05	0.127E-05	0.129E-05	0.926E-05
1380.	0.160E-06	0.139E-05	0.125E-05	0.127E-05	0.914E-05
1410.	0.158E-06	0.137E-05	0.124E-05	0.126E-05	0.903E-05
1440.	0.156E-06	0.135E-05	0.122E-05	0.124E-05	0.891E-05