Bull. Environ. Contam. Toxicol. (1990) 45:197–207

Bulletin of Environmental Contamination and Toxicology

Altered Pharmacokinetics of Soil-Adsorbed Benzene Administered Orally in the Rat

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An experimental study of the effect of soil absorption on the pharmacokinetics of benzene in orally exposed rats was recently conducted by Turkall et al. (1988). In this study, groups of male Sprauge-Dawley rats weighing 250-300 g were administered either benzene alone or soil-adsorbed benzene suspensions. Two New Jersey soils were chosen for testing in the study: a Cohansey aquifer soil ("sandy" soil) with organic carbon content of 4.4% and clay content of 2%, and a Keyport series soil ("clay" soil) with organic carbon content of 1.6% and clay content of 22%.

The treatment doses were prepared as suspensions using 150 μl of ^{14}C-labelled benzene solution (specific activity of 50 μCi/mmole) with or without .5 g of soil combined with 2.85 ml of aqueous 5% gum acacia. The intended benzene dosage in each of the suspensions was approximately 480 mg/kg. Volatilization losses of benzene during the suspension process were estimated to be 43, 57, and 61% of radioactivity for benzene, sandy, and clay treatments, respectively. Consequently, dosages presumed to be administered, i.e., the initial doses, were 275 mg/kg benzene alone, 205 mg/kg benzene in sandy soil, and 190 mg/kg benzene in clay soil. In all treatments, plasma concentrations of benzene were determined up to two hours after administration and cumulative excretion/metabolism profiles, expressed as percentages of initial dose in expired air, urine, and feces were determined up to 48 hours after administration. Percentage recoveries of initial dose during the initial 48 hour period were 84.9 ± 14.1, 104.4 ± 24.1 and 63.1 ± 23.7, for benzene alone (control), sandy soil, and clay soil, respectively.

The authors reported that absorption half-lives into blood plasma were not statistically different between treatment groups and that the elimination half-life of the clay treatment group was statistically different from the control treatment (Turkall et al. 1988). The elimination of radioactivity in urine was reported to be elevated in the presence of both

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Table 1. Nomenclature used to describe pharmacokinetic model

Q_{alv}	Alveolar ventilation rate (L air/h)
C_{inh}	Concentration in inhaled air (mg/L air)
C_{alv}	Concentration in alveolar air (mg/L air)
λ_b	blood/air partition coeffiecient (L air/L blood)
Q_b	Cardiac output (L blood/h)
C_{art}	Concentration in arterial blood (mg/L blood)
C_{ven}	Concentration in mixed venous blood (mg/L blood)
V_{max}	Michaelis-Menten metabolism rate (mg/h)
K_m	Michaelis constant (mg/L blood)
A_m	Amount metabolized in the liver (mg)
Q_i	Blood flow rate to tissue group i (L blood/h)
V_i	Volume of tissue group i (L)
C_i	Concentration in tissue group i (mg/L)
A_i	Amount in tissue group i (mg)
C_{vi}	Concentration in venous blood leaving tissue group i (mg/L blood)
λ_i	Tissue/blood partition coefficient for tissue i (L blood/L i)
$\lambda_{i/a}$	Tissue/air partition coefficient for tissue i (L air/L i)
	Gavage or oral rate constants (h^{-1}):
k_1	absorption from stomach and upper GI tract
k_2	transit, upper to lower GI tract
k_3	absorption from lower GI tract
k_4	transit from lower GI tract to feces
D_o	Total quantity of benzene absorbed via gavage (mg)

soils, suggesting that benzene is preferentially metabolized in the presence of soils. The authors concluded that percentages of initial dose expired and metabolized were altered in the presence of both soils.

The purpose of the present study was to investigate mechanisms by which the plasma concentration time course and excretion profile of benzene were altered by the presence of soils. We consider whether the changes in the pharmacokinetics of benzene between the treatment groups are due to differences in absorption and elimination rates as well as differences in dosages absorbed. Model based estimates of the half-lives of absorption from the gastrointestinal tract are derived.

MATERIALS AND METHODS

The model used in this study is a five-compartment physiologically based pharmacokinetic model for benzene patterned after the Ramsey-Andersen model (Ramsey and Anderson 1984). The model equations are shown in Figure 1 with corresponding nomenclature given in Table 1. The empirical

$$Q_{alv}C_{inh}dt + Q_bC_{ven}dt = Q_{alv}C_{alv}dt + Q_bC_{art}dt$$
$$C_{art} = \lambda_bC_{alv}$$

$$Q_iC_{art}dt = dA_i + Q_iC_{vi}dt$$
$$C_{vi} = C_i / \lambda_i$$
$$\lambda_i = \lambda_{i/a} / \lambda_b$$
$$C_i = A_i / V_i$$

$$\frac{dA_m}{dt} = \frac{V_{max}C_{vl}}{K_m + C_{vl}}$$

$$\frac{dA_l}{dt} = Q_l(C_{art} - C_{vl}) - \frac{dA_m}{dt} + \frac{dG}{dt}$$

$$C_{ven} = \frac{1}{Q_b}(\sum_i Q_iC_{vi})$$

$$\frac{dG}{dt} = k_1D_o\exp\{-(k_1+k_2)t\} + \frac{k_3k_2D_o}{k_4+k_3-k_2-k_1}(\exp\{(k_1+k_2)t\}+\exp\{(k_3+k_4)t\})$$

Figure 1. Pharmacokinetic model equations

physiological and chemical data used in the model are shown in Table 2. The model was coded in Fortran and integrated with the LSODE solver (Hindmarsh 1980) using an IBM PC AT.

For this study we have assumed a mean body weight of 275 g. Scaling of alveolar ventilation, cardiac output and V_{max} to this body weight was assumed to follow allometrically (Gunter 1975) from reference values (Arms and Travis 1988). Absorption of benzene from the gut was modelled as a two phase process in order to represent possible effects of differential uptake into the portal circulation. Since less than 1% of benzene administered orally appears in feces (Abou-el-Makarem et al. 1966), absorption into the portal circulation was considered complete. Thus, the gastrointestinal tract was considered as consisting of upper GI tract lumen (i.e., stomach and cecum) and lower GI tract lumen (i.e., large and small intestines) with a treatment independent rate constant characterizing the transit of dose from the upper GI tract into the lower GI tract.

Since each treatment consisted of suspensions of benzene with approximately 80% water content, the transit half-life was assumed to be relatively rapid. The half-life of water emptying from the human stomach is approximately 20 minutes

Table 2. Empirical physiological and chemical model parameters

	Parameter	Rat
Body Weight (kg)	BW	0.3
Alveolar Ventilation Rate (L/h)	Q_{alv}	7.0
Cardiac Output (L/h)	Q_b	5.0
Blood Flow Fractions		
liver	Q_l/Q_b	0.25
fat	Q_f/Q_b	0.09
bone marrow	Q_b/Q_b	0.04
organs	Q_o/Q_b	0.51
muscle	Q_m/Q_b	0.11
Tissue Group Volume Fractions		
liver	V_l/BW	0.04
fat	V_f/BW	0.07
bone marrow	V_b/BW	0.03
organs	V_o/BW	0.05
muscle	V_m/BW	0.72
Blood/air Partition Coefficient	λ_b	15.0
Tissue/Air Partition Coefficients		
liver/air	$\lambda_{l/a}$	17.0
fat/air	$\lambda_{f/a}$	500.0
bone marrow/air	$\lambda_{b/a}$	30.0
organ/air	$\lambda_{o/a}$	17.0
muscle/air	$\lambda_{m/a}$	15.0
Metabolic Parameters		
Maximum velocity (mg/h)	V_{max}	3.65
Michaelis constant (mg/L blood)	K_m	0.35

(Eve 1966). Scaling from a standard 70 kg man to 275 g animal (Gunther 1975), this value corresponds to about 5 minutes in the rat. Considering that treatments were suspensions containing solid constituents we have chosen 15 minutes as representative of the half-life of each treatment dose emptying into the lower GI tract. Based upon this assumption, source terms and rate constants of absorption into the portal circulation were adjusted until the variance between model predications and empirical data was minimized (Table 3). Model prediction of percentage of initial dose eliminated through expired air and urine were compared to the data based upon the presumed dosages adjusted for volatilization losses alone.

Table 3. Adjusted model parameters

	Benzene	Sandy	Clay
Partition Coefficients			
$\lambda_{blood/air}$	15.	15.	45.
$\lambda_{liver/air}$	17.	17.	102.
$\lambda_{fat/air}$	500.	500.	3000.
$\lambda_{bone/air}$	30.	30.	180.
$\lambda_{organ/air}$	17.	17.	102.
$\lambda_{muscle/air}$	15.	15.	90.
Absorption Rate Constants (min^{-1})			
Stomach and upper GI Tract	.0075	.009	.0155
Lower GI Tract	.0075	.0045	.0155
Upper to lower GI Tract	.0462	.0462	.0462
Estimated Dosage (mg/kg)	140.	215.	120.

RESULTS AND DISCUSSION

For benzene alone, modification of the source term and rate constants of absorption could not explain the peculiarly high levels of initial dose observed in expired air within the first 2-4 hours. Turkall et al. (1988) suggest that this effect might have been due to direct volatilization of benzene from the stomach up through the esophagus into expired air. Our analysis concurs with this interpretation. We estimate that only 140 mg/kg of dose was absorbed through the gastrointestinal system and that 90 mg/kg was volatilized into expired air within the first 4 hours after administration. Based upon an absorption source term of 140 mg/kg, the data were consistent with absorption from both the upper GI tract and the lower GI tract into the portal circulation with a half-life of 92 minutes. This absorption rate is 25% lower than previously estimated using data where benzene was administered orally to Fisher and Wistar rats (Travis *et al.*, 1989). Species differences may be responsible for this discrepancy. Model predictions of benzene plasma concentration and excretion profile are shown in Figures 2 and 3. As can be seen, model predictions for the control group (benzene alone) are consistent with measured pharmacokinetic parameters.

For benzene in sandy soil, a pulse rise and decay in benzene plasma concentration within the first 20 minutes suggested that the effect of the soil may have been to accentuate absorption of benzene from the stomach. Based upon a dose of 215 mg/kg, the data were consistent with an absorption from the upper GI tract into the portal circulation with a half-life of 77

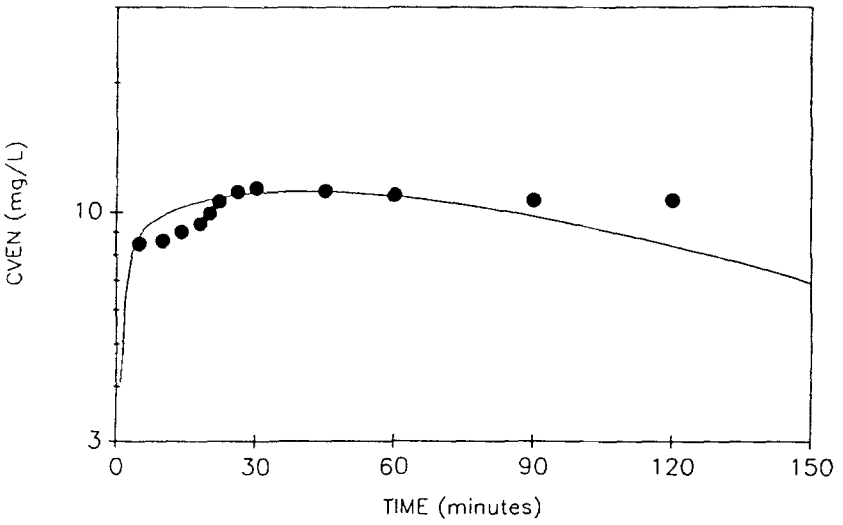

Figure 2. Blood concentration of benzene in the control group. Solid line represents model prediction. Experimental data from Turkall et al. (1988).

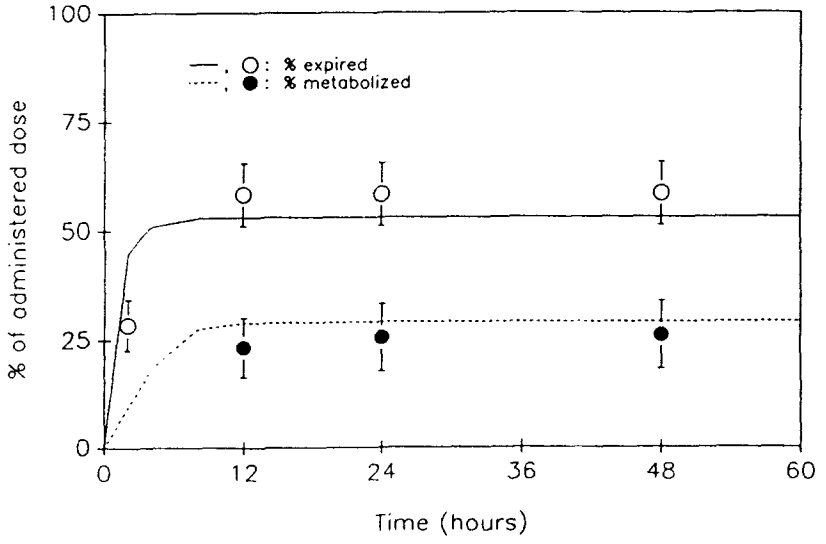

Figure 3. Cumulative excretion/metabolism profile of benzene in the control group. Solid and broken lines represents model prediction. Experimental data from Turkall et al. (1988).

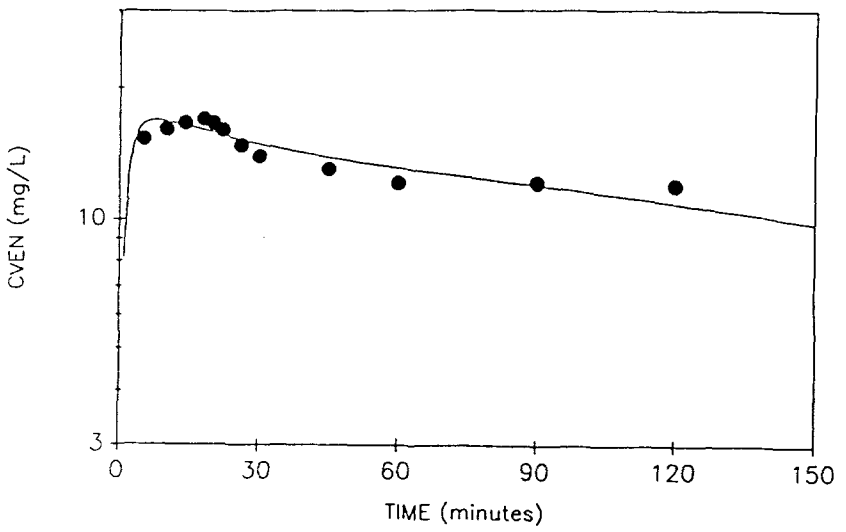

Figure 4. Blood concentration of benzene in the sandy soil treatment group. Solid line represents model prediction. Experimental data from Turkall et al. (1988).

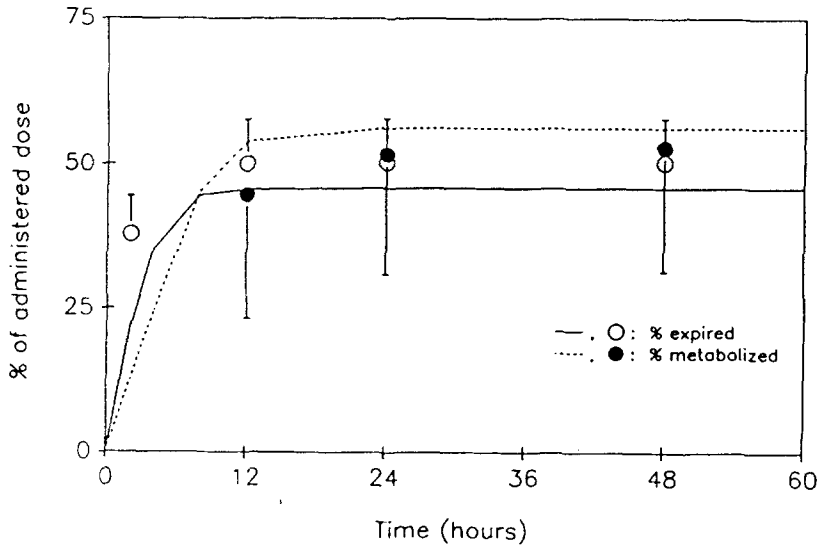

Figure 5. Cumulative excretion/metabolism profile of benzene in the sandy soil treatment group. Solid and broken lines represents model prediction. Experimental data from Turkall et al. (1988).

minutes and absorption from the lower GI tract into the portal circulation with a half-life of 154 minutes. Thus, it appeared that the sandy soil enhanced the absorption of benzene from the stomach and upper GI tract but depressed absorption from the lower GI tract as compared to treatment with benzene alone. Disposition and elimination of benzene in tissues after absorption appeared to be unaffected in the presence of the sandy soil. Model predictions of benzene plasma concentration and excretion profile are shown in Figures 4 and 5.

For the clay soil treatment group, the cumulative percentage of the initial dose either exhaled or metabolized over the 48 hours following administration was only 61.7%. Considering the rapid elimination half-life of benzene in the rat, it is unlikely that a substantial amount of benzene remained in the tissues after 48 hours. Consequently, we have interpreted the loss of recovery to indicate that volatilization losses during treatment preparation were higher than actually determined. A source term of 130 mg/kg and an half-life of 45 minutes from the gastrointestinal tract produced the best fit to the blood data. The model fit obtained based upon these assumptions is illustrated in Figures 6 and 7. As indicated by these figures, model predications for benzene equivalents in expired air and urine do not agree well with the measured data. The percentage of benzene metabolized is underpredicted.

To match both the measured benzene concentration in plasma and the excretion profile for this treatment group necessitates an elevation of metabolic elimination of benzene. This could be accomplished in two ways: increase the metabolic parameters (V_{max}) in the model or change the tissue partition coefficients in the model. There is no evidence that vehicle of administration can change the intrinsic rate of metabolism of a compound, but there is evidence that it can effect partition coefficients (Angelo and Pritchard 1984; Angelo et al. 1986). We therefore attempted to model the clay treatment group by increasing the partition coefficients. Accordingly, the blood/air partition coefficient was elevated three-fold and tissue/air partition coefficients were elevated six-fold. The source term was adjusted to 120 mg/kg. Based upon these assumptions the data were found to be consistent with absorption from both the upper GI tract and the lower GI tract into the portal circulation with a half-life of 45 minutes. Predictions of blood concentration and excretion profiles are illustrated in Figures 8 and 9. The adjusted model parameters are shown in Table 3.

Model based analysis of soil adsorption effect on benzene pharamacokinetics indicates that rates of absorption and elimination of benzene are likely to be altered in the presence of soils. Differences between soil-adsorbed and control treatment groups could not be explained due to the differences in administered dosages. It appears that, contrary to the data analysis conducted by Turkall et al. (1988), benzene uptake was

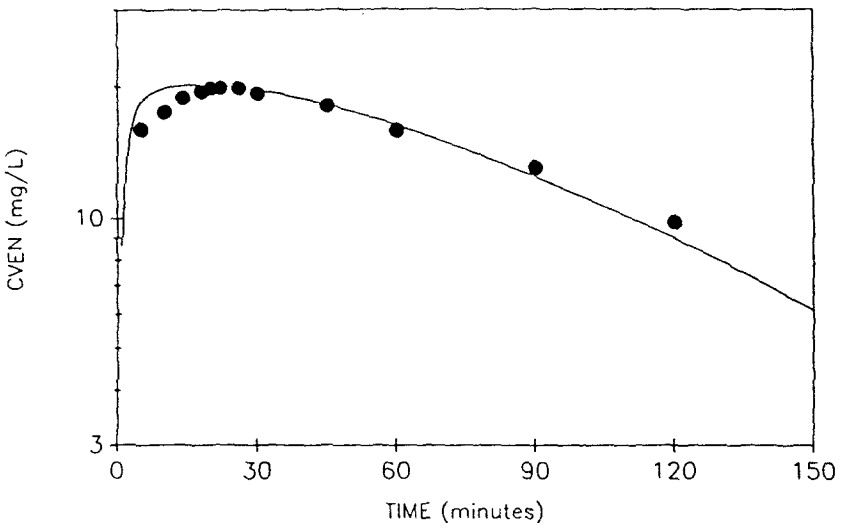

Figure 6. Blood concentration of benzene in the clay treatment group. Solid line represents model prediction without alteration of partition coefficients. Experimental data from Turkall et al. (1988).

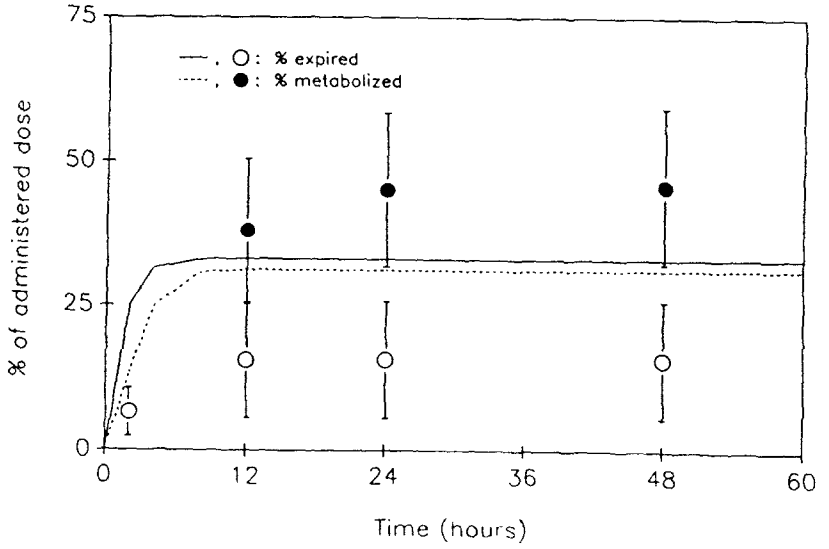

Figure 7. Cumulative excretion/metabolism profile of benzene in the clay treatment group. Solid and broken lines represents model prediction without alteration of partition coefficients. Experimental data from Turkall et al. (1988).

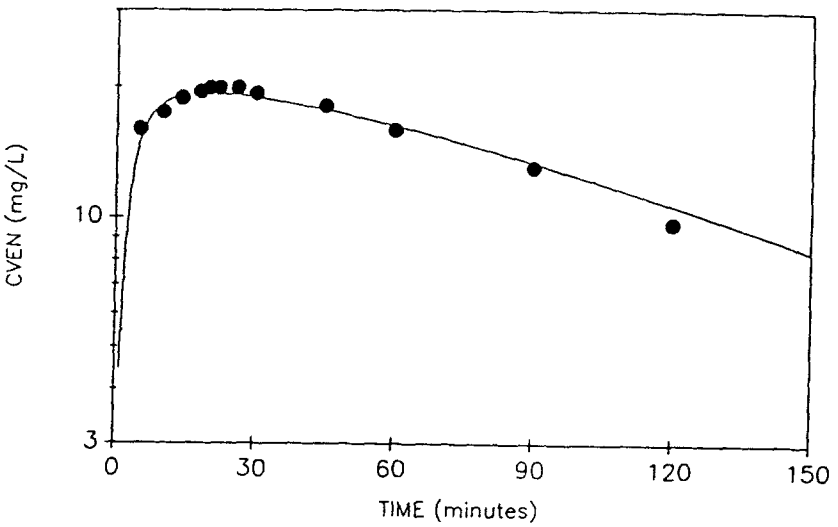

Figure 8. Blood concentration of benzene in the clay treatment group. Solid line represents model prediction with elevated partition coefficients. Experimental data from Turkall et al. (1988).

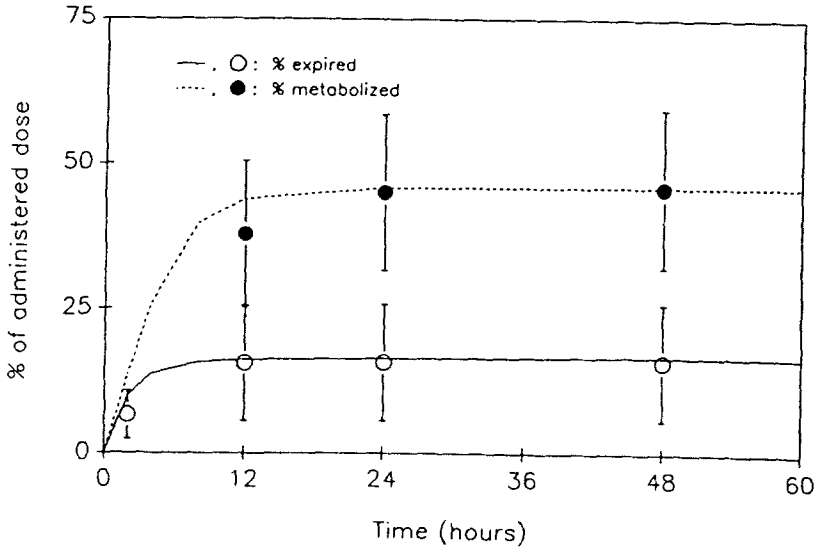

Figure 9. Cumulative excretion/metabolism profile of benzene in the clay treatment group. Solid and broken lines represents model prediction with elevated partition coefficients. Experimental data from Turkall et al. (1988).

altered in the presence of both the sandy and clay soils studied. Additionally, benzene elimination was slowed when administered in the presence of the clay soil. Alteration in the metabolic clearance of benzene between treatment groups appeared to be due to differences in absorption and elimination rates.

Acknowledgements. Research supported by the American Petroleum Institute under grant no. ERD-87-682, applicable under Martin Marietta Energy Systems, Inc., contract no. DE-AC05-84OR21400 with the U.S. Department of Energy.

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Received November 13, 1989; accepted February 7, 1990.