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Journal of Toxicology and Environmental Health Part A

ISSN: 1528-7394 (Print) 1087-2620 (Online) Journal homepage: https://www.tandfonline.com/loi/uteh20

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To cite this article: Karla D. Thrall , Jolen J. Soelberg , Karl K. Weitz & Angela D. Woodstock (2002) DEVELOPMENT OF A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL FOR METHYL ETHYL KETONE IN F344 RATS, Journal of Toxicology and Environmental Health Part A, 65:13, 881-896, DOI: 10.1080/00984100290071207

To link to this article: https://doi.org/10.1080/00984100290071207


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Journal of Toxicology and Environmental Health, Part A, 65:881–896, 2002
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1528-7394/02 $12.00 + .00
DOI: 10.1080/00984100290071207

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DEVELOPMENT OF A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL FOR METHYL ETHYL KETONE IN F344 RATS

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A physiologically based pharmacokinetic (PBPK) model to describe the absorption, distribution, metabolism, and elimination of methyl ethyl ketone (MEK) in rats was developed. Partition coefficients were experimentally determined in rat tissues and blood samples using an in vitro vial equilibration technique. These solubility ratios were in agreement with previous human-based estimates that MEK is uniformly soluble within all tissues. The in vivo metabolism of MEK was evaluated using groups of three F344 male rats exposed to 100–2000 ppm MEK in a closed, recirculating gas uptake system. An optimal fit of a family of uptake curves was obtained by adjusting Michaelis–Menten metabolic constants, K_m (affinity), and V_{max} (capacity) using the PBPK model. At the highest chamber concentration, the uptake curve could not be modeled without the addition of a first-order (K_{fo}) metabolic pathway. Pretreatment with pyrazole, an inhibitor of oxidative microsomal metabolism, decreased the slope of the gas uptake curve but did not abolish metabolism. Optimal model fit to the gas uptake curve from pyrazole-pretreated animals required the apparent K_m to be increased roughly 50 times the value determined in naive rats. The completed PBPK model was evaluated against real-time exhaled breath data collected from rats receiving an intravenous (iv) injection of MEK via a jugular vein cannula. Model simulation of the iv-treated animals required alveolar ventilation to be reduced 30% in order to match the data. Exhaled breath profiles from animals treated with MEK by oral gavage or intraperitoneal (ip) injection were evaluated and absorption rates was determined. Development of a comprehensive PBPK model for MEK in rats is the first step toward future extrapolations to apply to humans.

Methyl ethyl ketone (MEK; 2-butanone) is an industrial chemical used as a component of solvent mixtures for a wide variety of coatings (Yoshikawa et al., 1995). Human exposure to MEK can occur by ingestion of water contaminated by MEK, or by dermal and inhalation routes through the use of paints and other commercial coatings. In general, MEK is considered a relatively safe chemical, although at higher occupational exposure levels, effects similar to those reported for other organic solvents, including irritation, and

Received 28 August 2001; accepted 2 November 2001.
This work was supported by grant 1-RO1-OH03658-01A2 from the National Institute for Occupational Safety and Health (NIOSH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NIOSH.
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central nervous system depression have been observed (Bang, 1984). In combination, MEK appears to potentiate neurotoxicity of hexacarbons, including *n*-hexane (Altenkirch et al., 1977), 2,5-hexanedione (Ralston et al., 1985), and *n*-butyl ketone (Saida et al., 1976).

Both physiologically based pharmacokinetic (PBPK) and compartmental models have been developed to describe the dose-dependent kinetics of MEK in humans (Liira et al., 1990; Leung, 1992) and rats (Kessler et al., 1989; Dietz et al., 1981). However, the specificity of these previous models makes it difficult to extrapolate beyond the data set from which the model was developed. In an effort to better understand the dose-dependent and route-specific kinetics of MEK, the current objectives focused on development and validation of a PBPK model for the rat using controlled in vitro and in vivo animal studies. Development of an accurate representation of the rodent absorption, distribution, metabolism, and elimination kinetics will ultimately enable extrapolation of the PBPK model to describe human kinetic relationships.

MATERIALS AND METHODS

Animals

Adult male F344 rats (200–250 g body weight) were obtained from Charles River Breeding Laboratories (Raleigh, NC). The animals were housed in solid-bottom cages with hardwood chips, and were acclimated in a humidity- and temperature-controlled room with a 12-h light/dark cycle for at least 5 d prior to use. Certified Purina rodent chow (Ralston Purina Co., St. Louis, MO) and water were provided ad libitum throughout the acclimation period. A separate group of animals was purchased with indwelling jugular vein cannulas. Cannulas were maintained by periodic flushing with heparinized saline.

Test Material

Methyl ethyl ketone (MEK), of 99+% purity, was obtained from Aldrich Chemical Company (Milwaukee, WI). Pyrazole (1,2-diazole) of >98% purity was obtained from Fluka (Ronkonkoma, NY). All other chemicals were reagent grade or better.

Partition Coefficients

Substrate to air partition coefficients were determined for rat blood, epididymal fat, thigh muscle, and liver using a vial equilibration method as described by Sato and Nakajima (1979) and Gargas et al. (1989). Headspace concentrations were analyzed by gas chromatography (GC) using a Hewlett-Packard model 6890 system (Avondale, PA). The GC used a hydrogen flame ionization detector (FID) with nitrogen as the carrier gas. The column was a Restek RTX-Volatiles, 60 m, 1.5 μm film thickness (Restek, Bellefonte, PA). The detector was operated at 250°C, the inlet at 210°C, and the final oven temperature was 240°C. Under these conditions, MEK had a retention time of approximately 1.8 min. Tissue-to-blood partition coefficients were calcu-

lated by dividing tissue-to-air partition coefficients by blood-to-air partition coefficients.

Gas Uptake Studies

The closed-atmosphere exposure system was constructed as described by Gargas et al. (1986) with modifications as described by Thrall et al. (2000). In brief, the system consisted of a 9-L desiccator jar with gas inlet and outlet fittings fashioned into a $\frac{1}{4}$-inch-thick stainless-steel lid. A silicone rubber gasket was fitted between the glass rim of the desiccator and the stainless-steel lid, and the assembly was clamped in place using thumbscrew brackets placed around the perimeter. Preliminary studies conducted with an empty chamber found the nonspecific loss of MEK to be independent of concentration, and less than 6%/h. The chamber atmosphere was recirculated using a Bellows (model MB-41, Metal Bellows Corp., Los Angeles, CA) stainless-steel metal pump at 2 L/min. Carbon dioxide was removed with SodaSorb (W. R. Grace & Co., Atlanta, GA). Relative humidity was maintained by placing the glass chamber directly in ice, as described by Gargas et al. (1986). Oxygen concentration in the chamber was maintained at 19–21% by slowly adding ultra-high-purity (UHP) O_2 when an audible O_2 alarm (Cole-Parmer, Vernon Hills, IL) signaled concentrations dropped below 20%. The pressure in the chamber was continually monitored using a Cole-Parmer (Vernon Hills, IL) digital pressure gauge and stayed constant throughout the experiments.

Each experiment utilized three rats per exposure concentration. Animals were acclimated to the closed system prior to exposure. Methyl ethyl ketone was added as a liquid through a heated septum fitting 12 in upstream of the chamber in a volume to achieve the desired initial chamber concentrations. Chamber atmosphere was monitored prior to addition of MEK, and up to 5 h thereafter.

Atmospheric concentrations of MEK in the chamber were determined every 5 min by gas chromatography using a Hewlett-Packard model 5890 Series II system in place of the model 6890 system utilized in the partition coefficient studies. The 5890 Series II GC used a hydrogen flame ionization detector with nitrogen as the carrier gas with the same column and similar temperature settings as described previously. Specifically, the detector was operated at 250°C, the inlet valve at 150°C, and the final oven temperature was 200°C. Under these conditions, MEK had a retention time of approximately 0.8 min.

To evaluate the impact of inhibition of oxidative microsomal metabolism on the shape of the gas uptake curve, a separate group of animals were pretreated with a single intraperitoneal (ip) injection of aqueous pyrazole at 320 mg pyrazole/kg body weight $\frac{1}{2}$ h prior to gas uptake exposure as described previously by Gargas et al. (1986).

In Vivo Studies

Separate groups of naive animals received a single iv injection ($n = 4$; 25 mg/kg), ip injection ($n = 3$; 50 mg/kg), or oral gavage ($n = 3$; 50 mg/kg)

dose of aqueous MEK. Immediately following dosing, rats were individually placed in small off-gassing chambers and exhaled breath was continually monitored for up to 6 h postexposure, as described by Thrall et al. (1999). In brief, certified pure breathing air was supplied to the rat through the lid of the off-gassing chamber at a calibrated rate of 200 ml/min. A Teledyne Discovery II ion-trap mass spectrometer (MS/MS) equipped with an atmospheric sampling glow discharge ionization source (ASGDI) sampled directly from the off-gassing chamber approximately every 1.6 s. The intensity data from the MS/MS was converted to concentration (ppb) through the use of external standards prepared in Tedlar bags and a calibration curve. A new calibration curve was similarly generated for each day of experimentation.

Because chamber concentration is analyzed every 1.6 s, the resulting data have a tendency to appear variable. However, this variability likely reflects temporary variations in breathing rates and any movement by the animal. For model simulations, the breath data is averaged every 10 data points and the ion intensity for MEK is normalized to the intensity of the air peak (*m*/*z* ratio of 31) to minimize variability and accommodate any system drift.

PBPK Model

The structure of the rat PBPK model was similar to that used to describe styrene kinetics in rats (Ramsey & Andersen, 1984). For MEK, the PBPK model consisted of four compartments (fat, liver, rapidly perfused tissues, and slowly perfused tissues), plus the exchange of MEK between lung blood and alveolar air (Figure 1). In this model, metabolism of MEK was assumed to occur in the liver. Gas uptake inhalation exposures were modeled according to Gargas

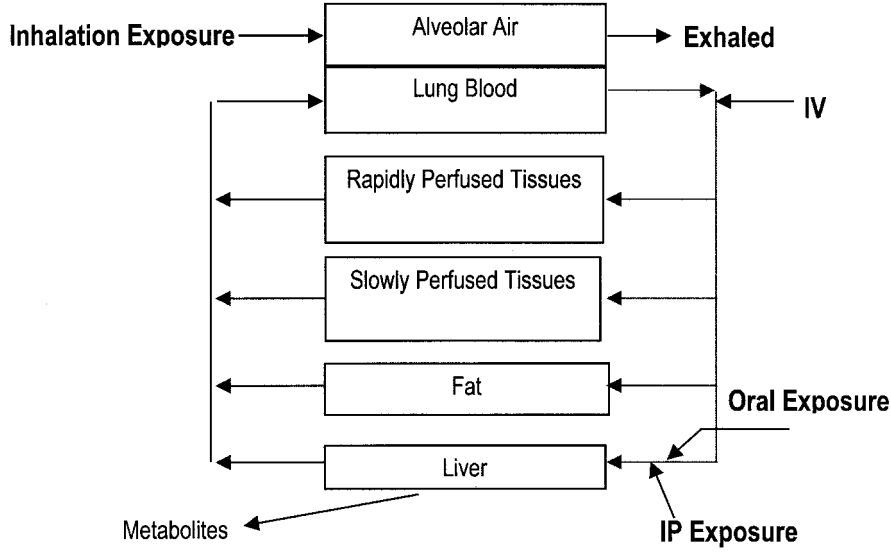

FIGURE 1. Schematic diagram of the PBPK model for MEK.

et al. (1986). Absorption of MEK following ip injection or oral gavage was described as a first-order process with a rate constant (h^{-1}) of k_a or k_{as}, for ip or oral exposures, respectively. For in vivo kinetic studies using the off-gassing chambers, the changing concentration of MEK in the off-gassing chamber (C_{CH}) was described in terms of input from the exhaled breath and removal from the chamber, either by rebreathing or to the MS/MS system. In the PBPK model, this is written as:

$$\frac{dA_{CH}}{dt} = (QP \times C_{EX} - QP \times C_{CH}) - F_{CH} \times C_{CH}$$

where A_{CH} is the amount of MEK in the chamber (μmol), QP is the alveolar ventilation rate (L/h), C_{EX} is the concentration of MEK exhaled from the animal (μmol/L), C_{CH} is the concentration of MEK in the chamber (μmol/L), and F_{CH} is the air flow through the chamber (L/h).

To develop and validate the rat PBPK model, partition coefficients were developed as already described. Values for breathing rate, organ volumes, and blood flow rates specific for the rodent (Table 1) were taken from the literature (Thrall et al., 2000). Metabolic parameters for MEK were obtained by computer optimization of the gas uptake data, as described previously (Gargas et al., 1986). In brief, a PBPK model containing all parameters except rate of chemical removal due to metabolism was used to simultaneously predict the family of gas uptake data. A maximum likelihood search algorithm in SimuSolv (version 3.0; Dow Chemical Co., Midland, MI) was used to vary values of the Michaelis–Menten constants K_m and V_{max} until an optimal fit was achieved that described all the time-course data with a single set of constants.

TABLE 1. Physiological Parameters for the Rat PBPK Model

Parameter	Rat[a]
Body weight (kg)	0.25
Cardiac output (L/h)	5.4
Alveolar ventilation (L/h)	5.4
Blood flow (% cardiac output)	
Liver	25
Fat	4
Rapidly perfused	51
Slowly perfused	20
Tissue volume (% body weight)	
Liver	4
Fat	8
Rapidly perfused	5
Slowly perfused	74

[a]From Thrall et al. (2000).

Statistical Analysis

Partition coefficient values are given as the mean and standard deviation of $n = 8$ to 23 samples. The variability of sample size was due to additional testing of some tissues in order to minimize the statistical error. All sets of gas uptake curves were simultaneously optimized; therefore, no statistical evaluation of variability in the optimized values was possible. Estimates of metabolic and absorption model parameters were based on the ability to describe data from the gas uptake and in vivo studies using the software optimization routines supplied with the commercial software package SimuSolv (Dow Chemical Company, Midland, MI). The percent variability explained for all optimized values was always $\geq$80%. The use of these routines has been described previously (Agin & Blau, 1982).

RESULTS

Partition Coefficients

Substrate-to-air partition coefficients for MEK were measured in saline, rat blood, liver, epidyimal fat, and thigh muscle (Table 2). Muscle was used to represent the slowly perfused tissue compartment, and the liver was considered representative of the rapidly perfused tissue compartment in the PBPK model. The blood-to-air partition coefficient reported here (138 $\pm$ 15) compared well with the rodent value (139 $\pm$ 6) reported by Beliveau and Krishnan (2000) and the human value (125 $\pm$ 10) reported by Fiserova-Bergerova and Diaz (1986).

TABLE 2. Substrate-to-Air Partition Coefficients for MEK (Mean $\pm$ SD)

Substrate to air	Rat	Human	Other
Blood	138 $\pm$ 15[a]	125 $\pm$ 10[b]	
	139 $\pm$ 6[c]	183 $\pm$ 12[d]	
		202 $\pm$ 10[e]	
Liver	152 $\pm$ 10[a]	180 $\pm$ 15[d]	
Fat	101 $\pm$ 6[a]	162 $\pm$ 28[b]	
		161 $\pm$ 14[d]	
Muscle	185 $\pm$ 30[a]	103 $\pm$ 10[b]	
		212 $\pm$ 30[d]	
Saline			143 $\pm$ 18[a]
			193 $\pm$ 7[d]
			254 $\pm$ 29[e]
			134[e]
Oil			131[f]

[a]Current data.
[b]Data from Fiserova-Bergerova and Diaz (1986).
[c]Beliveau and Krishnan (2000).
[d]Perbellini et al. (1984).
[e]Sato and Nakajima (1979).
[f]Kessler et al. (1989).

This high blood to air solubility ratio is consistent with reports that MEK is well absorbed during inhalation exposure (Saida et al., 1976; Perbellini et al., 1984).

Blood- and tissue-to-air partition coefficients for MEK did not differ significantly from saline-to-air values, which is in agreement with previous comparisons between water-to-air and olive oil-to-air ratios (Kessler et al., 1989). This is also in agreement with human partition coefficient values for samples obtained from cadavers, where tissue to blood ratios were found to be approximately 1 (Perbellini et al., 1984; Fiserova-Bergerova & Diaz, 1986). A comparison of the partition coefficient values determined in this study with literature values is provided in Table 2.

Gas Uptake Studies

Closed, recirculating chamber exposures of naive rats were conducted with initial exposure concentrations ranging from approximately 100 to 2000 ppm (Figure 2). An optimal fit of the family of uptake curves was obtained by adjusting the Michaelis–Menten metabolic constants K_m (affinity) and V_{max} (capacity) using the PBPK model. At the highest chamber concentration, the uptake curve could not be modeled without the addition of a first-order (K_{fo}) metabolic pathway. Model simulations incorporating two saturable pathways (high and low capacity, high and low affinity) to describe MEK metabolism did not improve the model prediction and were not pursued further (data not shown). The best fit of the family of uptake curves was achieved with a K_m (affinity) of 0.63 mg/L, V_{max} (capacity) of 5.44 mg/h/kg, and K_{fo} (first-order) of 4.1 h^{-1} (Table 3).

Pretreatment of animals with pyrazole decreased the slope of the gas uptake curve, but did not completely inhibit metabolism (Figure 3). The uptake curve for the pyrazole treated animals was modeled by adjusting K_m to fit the data, leaving both V_{max} and K_{fo} alone, as described by Gargas et al. (1986). The resulting apparent K_m for these pyrazole-pretreated animals was nearly 50 times higher than the K_m determined in naive animals (Table 3).

In Vivo Studies

To evaluate the PBPK model, a series of animals was exposed to aqueous MEK at 25 mg/kg by iv injection and the MEK concentration in exhaled breath was continually monitored for approximately 3 h thereafter. Peak MEK levels in exhaled breath were observed within minutes of injection and decreased sharply thereafter, with essentially the entire dose eliminated by 3 h postexposure (Figure 4, points). The PBPK model, incorporating partition-coefficient and metabolic parameters determined as already described, was used to simulate the iv exposure and predict exhaled breath levels. Initial model simulations greatly overestimated the amount of MEK exhaled immediately following administration of the compound for all animals exposed. Decreasing alveolar ventilation by approximately 30% (from 5.4 to 3.9 L/h) provided a much better fit between the PBPK model-predicted and experimentally observed exhaled

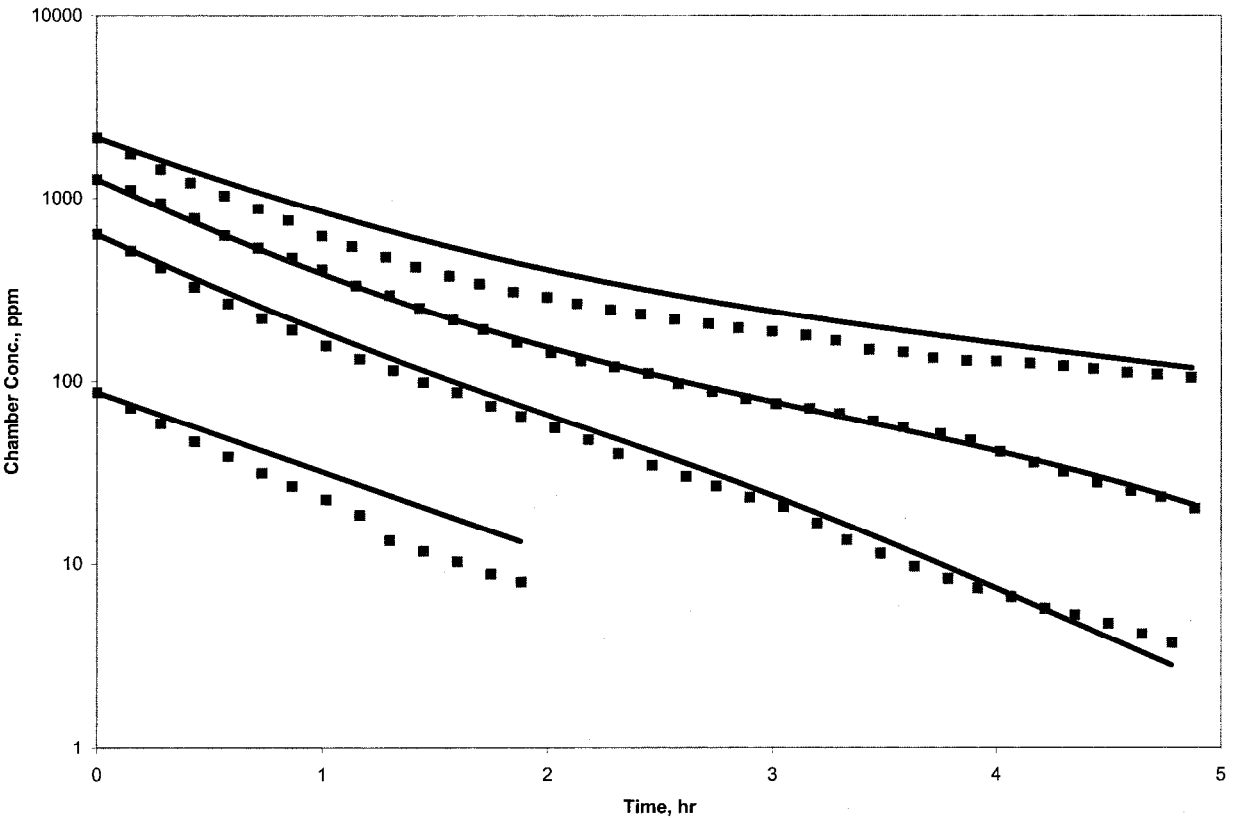

FIGURE 2. Uptake of MEK from a closed, recirculating atmosphere by three naive F344 male rats per exposure. The initial chamber concentrations were 87, 560, 1265, or 2121 ppm. The smooth curves were generated by the PBPK model using the constants given in Tables 1, 2, and 3.

TABLE 3. In Vivo Metabolic and Absorption Rate Constants

Parameter	Value
Metabolic rate constants	
V_{max} (mg/h/kg body weight)	5.44
K_m (mg/L)	0.63
K_m (mg/L)—pyrazole treated animals	30.32
K_{fo} ($h^{\odot 1}$)	4.1
Absorption rate constants	
K_a (ip absorption)	0.91
K_{as} (oral absorption)	1.86

breath data (Figure 4). No reduction in alveolar ventilation was necessary for any exhaled breath data sets from any exposure routes other than the iv route.

Additional series of in vivo studies were conducted with animals exposed to aqueous MEK at approximately 50 mg/kg by ip or oral gavage and exhaled breath monitored for MEK levels as before (Figures 5 and 6, points). Oral and ip absorption of MEK was assumed to occur in a first-order fashion, with uptake modeled as direct introduction into the liver. Exhaled breath data from one

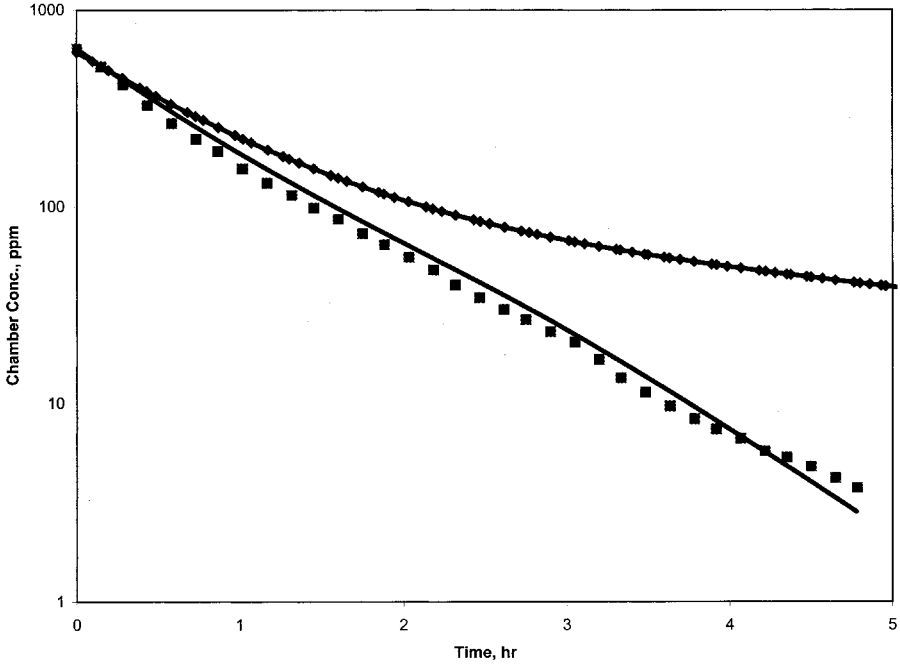

FIGURE 3. A comparison of MEK uptake from a closed, recirculating atmosphere at 560 ppm in pyrazole-pretreated (◆) and naive rats (■). The smooth curve for the pyrazole-pretreated rats was generated by the PBPK model using the kinetic constants given in Table 2.

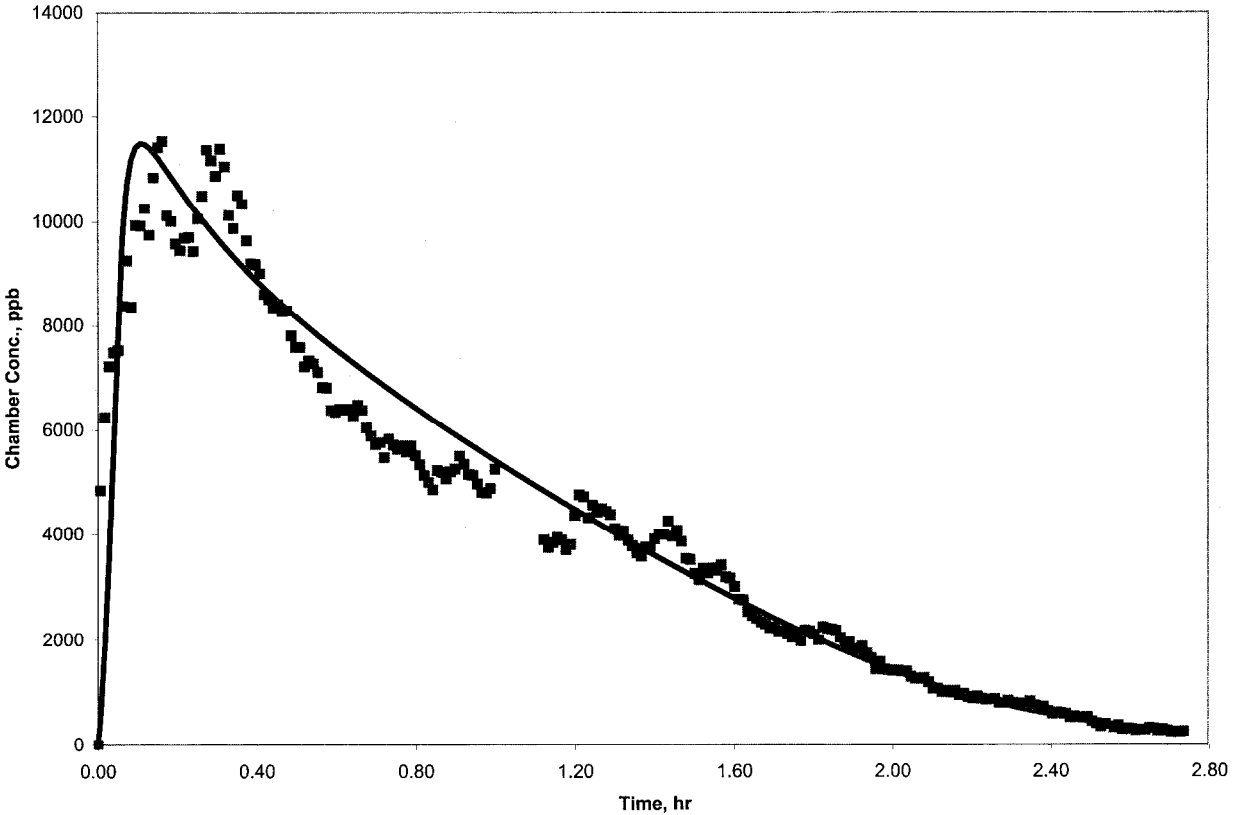

FIGURE 4. PBPK model prediction of the chamber concentration of MEK exhaled (ppb) from a rat receiving an iv injection of 25 mg/kg aqueous MEK (solid line) via a jugular vein cannula compared to the measured data from this study (points).

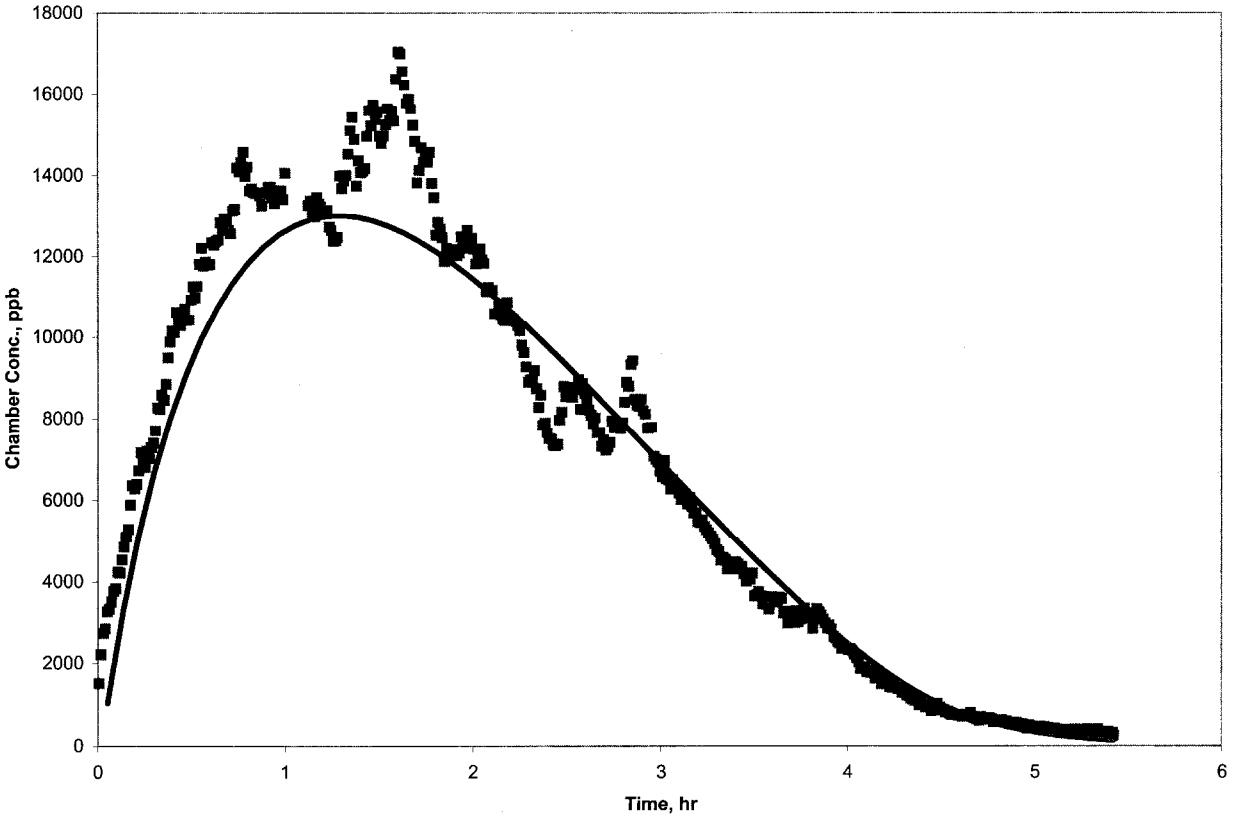

FIGURE 5. PBPK model prediction of the chamber concentration of MEK exhaled (ppb) from a rat receiving a single ip dose of 50 mg/kg aqueous MEK (solid line) compared to the measured data from this study (points).

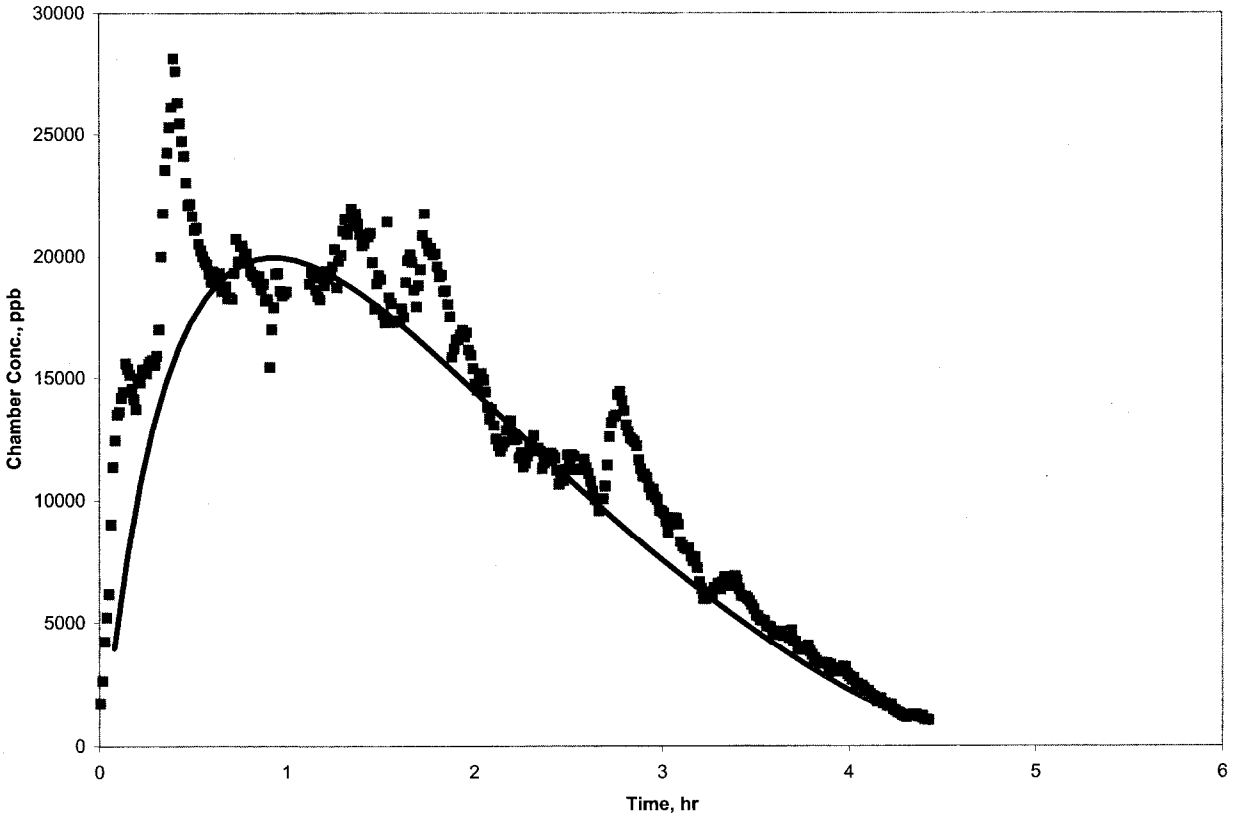

FIGURE 6. PBPK model prediction of the chamber concentration of MEK exhaled (ppb) from a rat receiving a single oral gavage dose of 50 mg/kg aqueous MEK (solid line) compared to the measured data from this study (points).

animal per exposure route was used to estimate the oral or ip absorption rate constants, and these absorption rates were used to simulate the remaining data sets. In this manner, one data set could be used for estimating the absorption rate constant and the other data sets could be used to test the validity of the estimated rate constant.

For ip exposures, peak exhaled breath concentrations of MEK were observed at just over 1 h postdosing and slowly decreased thereafter (Figure 5). The ip absorption constant (K_a) was estimated by the PBPK model to be 0.91 h^{-1} (Table 3), and the optimized absorption coefficient fit all ip exposure data sets from 3 animals. The PBPK model simulations predict that 99.3% of the injected amount of MEK was absorbed systemically, of which roughly 16% was exhaled during the 5 h the animals were monitored.

Following oral gavage doses, MEK was quickly and completely absorbed (Figure 6). Peak exhaled breath concentrations were achieved within 1 h postexposure, and decreased slowly over the next 3 h. The absorption rate constant (K_{as}) for oral exposure was estimated by the PBPK model to be 1.9 h^{-1} (Table 3) and provided a good fit to all 3 animal oral exposure exhaled breath profiles. The PBPK model simulations of these oral exposures predict that roughly 20% of the absorbed MEK was exhaled during the 5 h the animals were monitored postexposure.

DISCUSSION

A PBPK model can be used to describe the biokinetics of a chemical in experimental animals, and can be used to predict human tissue levels of a compound following occupational or environmental exposure. Thus, the objective of the present work was to systematically develop a PBPK model to describe the kinetics of MEK in rats following different routes of administration.

A limited number of studies are available to describe the uptake, distribution, metabolism, and elimination of MEK in experimental animals or humans. However, complete development of the rat PBPK model required generation of sufficient data to mathematically describe the interaction of MEK within the body, in terms of both relative tissue solubility and metabolism. In some cases, such as partition coefficient values, the data generated here were found to directly coincide with prior reports. In other cases, key data were not available in the literature, such as in vivo metabolic rate constants based on gas uptake studies.

Metabolic rate constants determined from gas uptake studies reported here indicate MEK is metabolized in both a saturable and first-order process. Pretreatment with pyrazole, an inhibitor of oxidative microsomal metabolism, decreased the slope of the gas uptake curve, but did not abolish metabolism, thus supporting the contribution of two metabolic pathways. The uptake curve from the animals pretreated with pyrazole was only adequately simulated when the K_m was increased over 50 times compared to the naive animals. Previous investigators have established that in rodents, MEK is metabolized

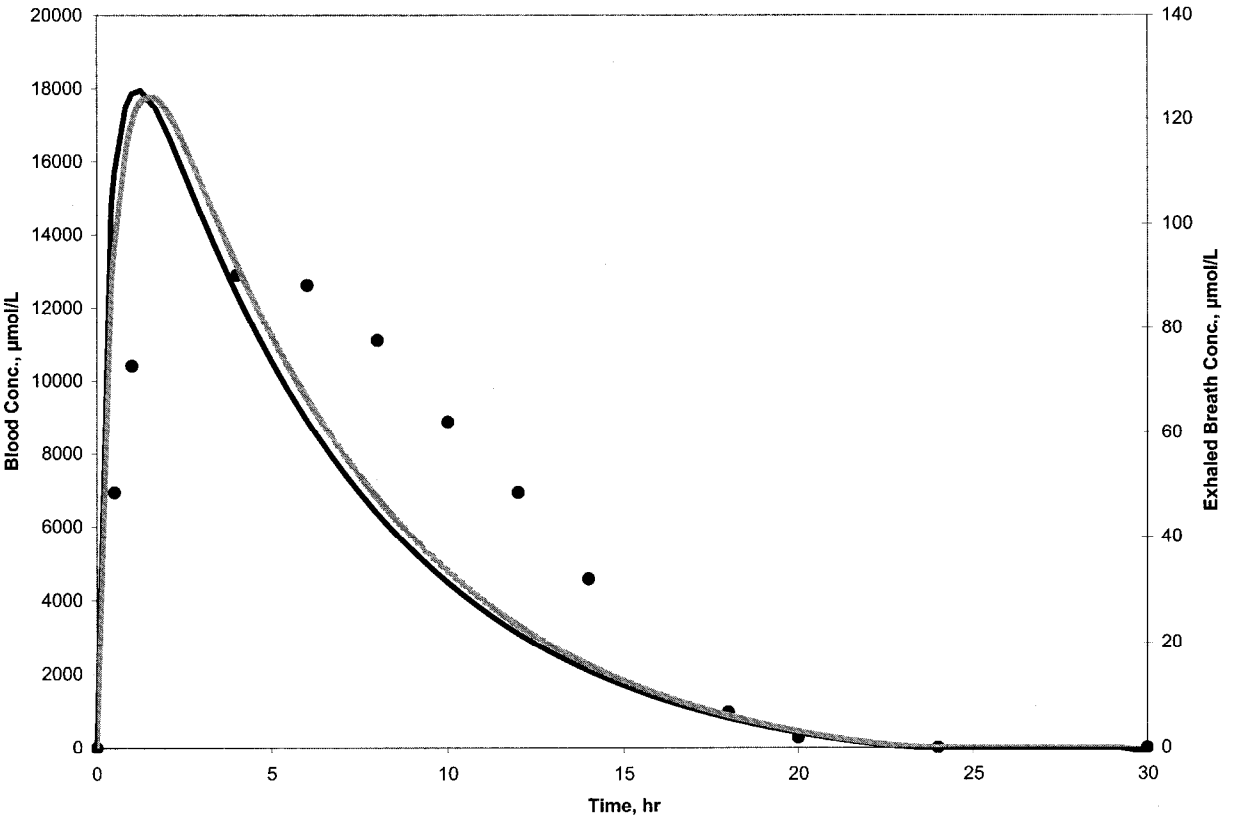

FIGURE 7. PBPK model prediction of the blood concentration (dark solid line) and exhaled breath concentration (gray solid line) from a rat exposed by oral gavage to 1690 mg/kg MEK using the oral absorption rate constant determined in the present studies, compared to the measured blood data (points) reported by Dietz et al. (1981).

reductively by alcohol dehydrogenase to 2-butanol and oxidatively to 3-hydroxy-2-butanone, presumably by cytochrome P-450-dependent monooxygenases (DiVicenzo et al., 1976; Dietz et al., 1981). Similarly, Kessler et al. (1989), using dithiocarb, an inhibitor of monooxygenases, inhibited but did not eliminate MEK metabolism in Wistar rats.

The real-time exhalation data demonstrate that MEK is rapidly absorbed following either oral or ip administration, with peak exhaled breath concentrations occurring approximately 1 h following exposure. In contrast, Dietz et al. (1981) reported peak blood concentrations of MEK at 4 h following oral exposure of aqueous MEK in Sprague-Dawley rats. Although the Dietz et al. (1981) oral study is similar in design to the study described here, there are some key differences. In particular, Dietz et al. (1981) utilized Sprague-Dawley rats, which were fasted overnight and administered an aqueous dose roughly 35 times higher (1690 mg/kg) in concentration than the current study (50 mg/kg). It is difficult to ascertain if these differences are sufficient to explain the discrepancies between our exhaled breath profiles and the blood MEK concentrations reported by Dietz et al. (1981). However, the MEK PBPK model described here predicts that the breath elimination profiles will reflect the blood concentration. Therefore, significant parameter changes are required to shift the peak blood or breath concentrations from 1 to 4 h postexposure to compare with the Dietz et al. (1981) data, as illustrated in Figure 7. Given that the measured blood concentrations in the Dietz et al. (1981) study are approximately 24 times greater than what is predicted from the oral studies conducted here, it is feasible that the current PBPK model may be limited to the range of exposures explored here.

The studies described here provide kinetic information on MEK following inhalation, oral, and iv and ip injection exposures. Furthermore, since breath concentrations reflect blood concentrations, the real-time exhaled breath data following iv injection, oral gavage, or ip injection studies provide a unique opportunity to evaluate differences in the rapid exponential emptying of the blood compartment that occurs immediately following peak exposure. Expansion of the current PBPK model to include a kinetic description of MEK metabolites 2-butanol, 3-hydroxy-2-butanone, and 2,3-butanediol will greatly enhance our understanding of the role of these metabolites in the potentiation of neurotoxicity of hexacarbons such as *n*-hexane. Interpretation of the current data by a validated PBPK model is the first step toward understanding human kinetics and, ultimately, health risks associated with MEK exposures.

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