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Dermatopharmacokinetics and Pharmacodynamics: *In Vivo* Analysis of Common Paint Product Solvents

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LIST OF ABBERVIATIONS

ASGDI	Atmospheric sampling glow-discharge ionization
cm	Centimeter
GC	Gas chromatography
hr	Hour
IP	Intraperitoneal
IV	Intravenous
k_a	First-order absorption rate constant for IP exposure
k_{as}	First-order absorption rate constant for oral exposure
K_{fo}	First-order metabolic constant
kg	Kilogram
K_m	Metabolic constant for affinity
K_p	Permeability coefficient (cm/hr)
L	Liter
MEK	Methyl ethyl ketone
mg	Milligram
min	Minute
ml	Milliliter
MS/MS	Mass spectrometer
n	Number
PBPK	Physiologically based pharmacokinetic
ppb	Parts-per-billion
ppm	Parts-per-million
S.D.	Standard deviation
V_{max}	Metabolic constant for capacity

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ABSTRACT

Exposure assessment is an important component in estimating health risk for individuals exposed to chemicals. Regulatory agencies have established standards for allowable occupational exposures, primarily via the inhalation pathway. In contrast, very little data is available to provide agencies sufficient guidance to establish permissible dermal exposure levels. Part of this shortfall lies in the fact that measurement of the amount of chemical absorbed through the skin is both experimentally difficult and time-consuming. In the research described here an innovative methodology was utilized to non-invasively evaluate dermal absorption by continually analyzing exhaled breath. Because breath concentrations can be used to reflect blood concentrations, constant analysis of exhaled breath provides an opportunity to evaluate differences in the rapidly changing blood compartment that occurs immediately following peak exposure. Animal studies were conducted to collect time-course data on the dermal absorption of two common solvents – toluene and methyl ethyl ketone. Both of these solvents are components of various paint and adhesive products, and may be frequently encountered in the occupational setting and by the consumer. Studies were conducted to expose animals to these compounds to provide an understanding of the impact of exposure matrix on dermal absorption. The exhaled breath kinetic data collected from each exposed animal was subsequently evaluated using an established mathematical model to determine the rate of dermal absorption. The studies indicate that the aqueous compounds are rapidly absorbed through the skin of a rat with a permeability coefficient of 0.074 $\pm$ 0.005 cm/hr for toluene. For methyl ethyl ketone, dermal absorption occurs in an apparent biphasic rate – exhaled breath data suggest an initial rapid rate of appearance in systemic blood, followed by a slow, sustained rate. The underlying factors driving this observed biphasic dermal absorption remain to be determined. Additionally, the dermal absorption of toluene from an enamel paint matrix is essentially identical to the dermal absorption of toluene from an aqueous matrix when normalized to the toluene exposure concentration. In both cases, a permeability coefficient of 0.07 cm/hr adequately described the data, although toluene concentrations differed significantly (25 mg/ml for enamel paint versus 0.5 mg/ml for the aqueous matrix). To evaluate the impact of paint constituents on the dermal bioavailability, additional dermal exposures were conducted using reformulated enamel paint, wherein the titanium dioxide (particulate) and xylene co-solvent were replaced by toluene. The PBPK model simulations of the exhaled breath data from these exposures required a permeability coefficient roughly half the value from the intact paint (0.032 cm/hr), although the toluene concentration was more than 12 times greater than in the original paint. These data highlight the impacts both concentration and matrix components within the exposure matrix have on dermal permeability. Similar results were observed for dermal exposures to toluene in lacquer thinner-based matrices.

SIGNIFICANT FINDINGS

The overall objective of this research project was to evaluate the percutaneous absorption of compounds commonly encountered in paint products (toluene and methyl ethyl ketone). The studies conducted in rats have demonstrated that the dermal absorption of toluene in an aqueous matrix occurs rapidly, yet the extent of absorption was substantially less than previous estimates based on human studies. In contrast, dermal studies conducted using aqueous methyl ethyl ketone was absorbed to a much greater degree than previously determined. Additionally, the studies conducted here indicate that toluene, in paint matrices available to the public, are absorbed through the skin of a rat with a permeability coefficient nearly identical to that observed for the dermal absorption of toluene in an aqueous matrix. Comparisons suggest that the matrix impacts toluene dermal absorption to a lesser degree than concentration within the matrix.

USEFULNESS OF FINDINGS

The work described here has resulted in the development of a physiologically based pharmacokinetic model capable of describing the absorption, tissue distribution, metabolism and elimination of methyl ethyl ketone in F344 rats. This model incorporates oral, intravenous, inhalation, and intraperitoneal routes of administration. The U.S. EPA has recently requested a copy of this published model to aid in the development of a reference concentration (RfC) for methyl ethyl ketone. In addition, studies conducted to evaluate the dermal absorption of aqueous toluene in F344 rats has provided a rodent-human comparison to toluene dermal absorption (Thrall et al. 2002). This cross-species evaluation contributes to the basic understanding of dermal bioavailability and can be used by risk assessors to improve occupational exposure standards and health risk assessments. Further, the data from the evaluations conducted here will aid in establishing dermal absorption guidelines that mimic actual occupational exposure situations to chemicals.

SCIENTIFIC REPORT

Background

Paint products (paints, coatings, varnishes, shellacs, enamels, and related products such as thinners and strippers) represent a unique challenge in occupational hazard evaluation and exposure assessment because of the complexity of the product formulations and the number of potential routes of exposure. These paint products can be water-, solvent-, or oil-based, thus making vehicle influence highly variable. Dermal permeability, and thus bioavailability, will differ substantially depending upon which type of paint product one is exposed to, and painters are usually exposed to more than one kind of product. The research in this proposal will focus on toluene and methyl ethyl ketone (MEK), two organic solvents frequently encountered in various paint products, particularly in the screen-printing industry (White et al. 1995) as representatives of chemical classes to describe dermal exposure contributions to total exposure. A theoretical estimation model predicts that both of these compounds have a significant potential for dermal absorption (Fiserova-Bergerova et al. 1990).

Toluene is a ubiquitous chemical that is commonly used for its solvent properties in industry and manufacturing (Ikeda et al. 1984; Ikeda and Kasahara 1986) and is a component of many paint products. Because of its widespread use, there is considerable potential for both occupational and non-occupational exposure. In man, high level toluene exposures produce incoordination, ataxia, unconsciousness, and death; lower, acute exposures lead to dizziness, exhilaration and confusion (Benignus 1981). Once in the body, toluene can be exhaled unchanged, or metabolized in the liver to benzoic acid, which is then conjugated with glycine to form hippuric acid, and is excreted in urine.

Methyl ethyl ketone (MEK) is an industrial chemical used mainly as a component of solvent mixtures for application of a wide variety of coatings (Yoshikawa et al. 1995). The notable acute effects of occupational exposure to MEK are similar to those reported for other organic solvents, and include neuronal depression and other dysfunctions (Bang 1984). MEK does not appear to be neurotoxic by itself, but rather to potentiate neurotoxicity of other hexacarbons, including n-hexane (Altenkirch et al. 1977), 2,5-hexanedione (Ralston et al. 1985), and n-butyl ketone (Saida et al. 1976). Ketones, such as MEK are readily absorbed through the intact skin, and are usually rapidly excreted in the expired air (International Labour Office, 1983). A human dermal vapor study by Brooke et al. (1998) showed that MEK uptake via the skin contributes to 3-3.5% of total body burden. Major MEK metabolites include 2-butanol, 3-hydroxy-2-butanol and 2,3-butanediol (DiVincenzo et al., 1976).

The overall objective of this research project is to provide a fundamental understanding of the influence of various types of paint product formulations on the dermal bioavailability of these commonly encountered solvents, MEK and toluene. By

systematically comparing the impact of paint product components on the bioavailability of these solvents in comparison to bioavailability to aqueous compound, this research will establish a means to extrapolate to other relevant solvents. To achieve the proposed objective, the initial Aim will focus on structural modification of an existing physiologically based pharmacokinetic (PBPK) model for toluene to include a skin compartment. This Aim will also involve *in vitro* studies to develop blood to air and tissue to blood partition coefficients and metabolic rate constants (K_m and V_{max}) for MEK. This data will be used to develop a PBPK model to describe MEK uptake and disposition in the rat. The resulting models will subsequently be used, in Aim 2, to determine the skin permeability constant, K_p for toluene and MEK in an aqueous media using F344 rats. This Aim will serve as a benchmark to compare permeability of toluene and MEK under different paint product formulations explored in Aim 3. The paint products, an aerosol spray paint, enamel paint, a polyurethane paint, and a lacquer thinner, will be evaluated in a step-wise fashion to pinpoint the component and/or components that impact solvent bioavailability in comparison to aqueous compound. In summary, the research objectives are:

1. **To describe dermal absorption of toluene and MEK using PBPK models in order to determine skin permeability constants (K_p).**

2. **To evaluate the kinetics and dermal bioavailability of aqueous toluene and MEK using F344 rats.**

3. **To describe, in a step-wise manner, the influence of formulation on the percutaneous absorption of toluene and MEK in four diverse paint products using F344 rats.**

The experimental procedures, methodology, results, discussion and conclusions for each of the specific aims will be provided in detail in the appropriate sections below.

Aim 1: Modification of an existing toluene PBPK model and development of a MEK PBPK model for determination of skin permeability constants (K_p) in F344 rats.

MEK PBPK MODEL DEVELOPMENT

The structure of the rat PBPK model was similar to that used to describe styrene kinetics in rats (Ramsey and 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 et al. (1986). Absorption of MEK following IP injection or oral gavage was described as a first-order process with a rate constant (hr^{-1}) of k_a or k_{as}, for IP or oral exposures, respectively. For *in vivo* kinetic

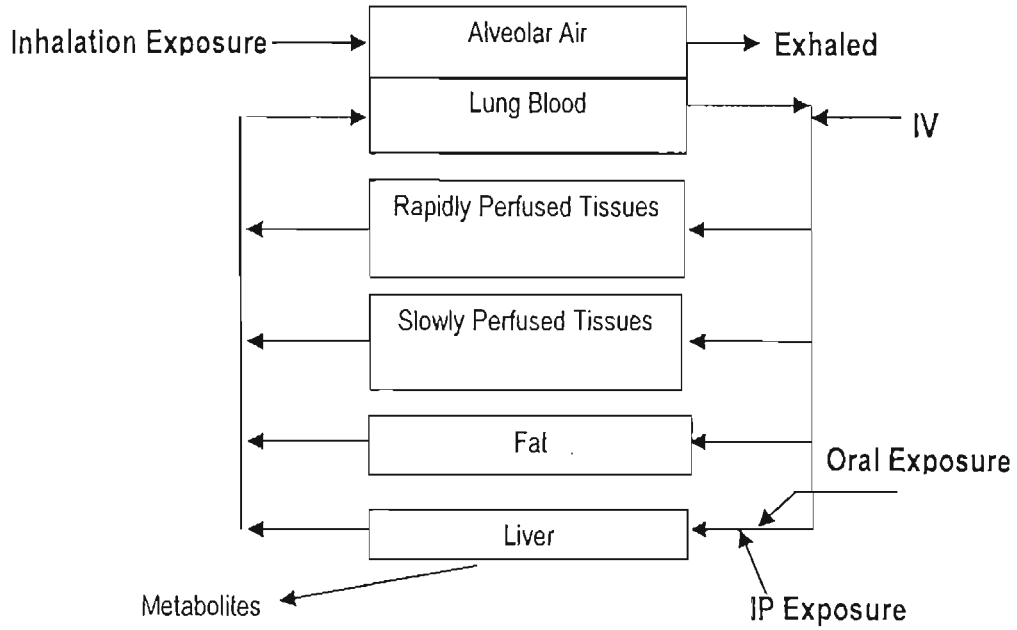

Figure 1: Schematic diagram of the PBPK model for MEK.

studies using the off-gassing chamber, the changing concentration of MEK in the off-gassing chamber was described in terms of input from the exhaled breath and removal from the chamber, either by rebreathing or to the MS/MS system for analysis.

To develop and validate the rat PBPK model, partition coefficients were developed as described below. 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[a]

Parameter	Rat
Body weight (kg)	0.25
Cardiac output (L/hr)	5.4
Alveolar ventilation (L/hr)	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] Thrall et al. (2000)

Development of MEK Partition Coefficients

To develop a PBPK model for MEK, substrate to air partition coefficients were experimentally determined for rat blood, epididymal fat, thigh muscle, and liver using an *in vitro* vial equilibration technique as described by Sato and Nakajima (1979) and Gargas et al. (1989). Briefly, this method involves harvesting tissues and heparinized blood from naïve male F344 rats. Weighed samples of blood, saline, tissues homogenized in saline (1:3) and empty reference vials were incubated with MEK in a 37°C shaker for 1 and 3 hr. Headspace concentrations of MEK were analyzed by gas chromatography (GC) using a Hewlett-Packard model 6890 system (Avondale, PA).

Results

The blood to air partition coefficient of 138 $\pm$ 15 compared well with the rodent value of 139 $\pm$ 6 reported by Beliveau and Krishnan (2000) and with the human value of 125 $\pm$ 10 reported by Fiserova-Bergerova and Diaz (1986). 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 and Diaz, 1986). A comparison of the partition coefficient values determined in this study with literature values is provided in Table 2.

Table 2: Substrate to Air Partition Coefficients for MEK (mean ± S.D.)

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

[a] Current data
[b] 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)

Development of metabolic rate constants for MEK

Metabolic rate constants (K_m and V_{max}) were determined using a gas uptake technique 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 ¼ -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%/hr. The chamber

atmosphere was recirculated using a Bellows (model MB-41, Metal Bellows Corp., Los Angeles, CA) stainless-steel metal pump at 120 L/hr. 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 oxygen when an audible 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-inches 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 hr thereafter. Atmospheric concentrations of MEK in the chamber were determined every 0.083 hr by gas chromatography using a Hewlett-Packard model 5890 Series II system.

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 ½-hr prior to gas uptake exposure as described previously by Gargas et al. (1986).

Results

Closed, recirculating chamber exposures of naïve rats were conducted with initial exposure concentrations ranging from approximately 100 to 2000 ppb (Figure 2). An optimal fit of the 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 with 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 predictions, and was 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/hr/kg, and K_{fo} (first-order) of 4.1 hr^{-1} (Table 3).

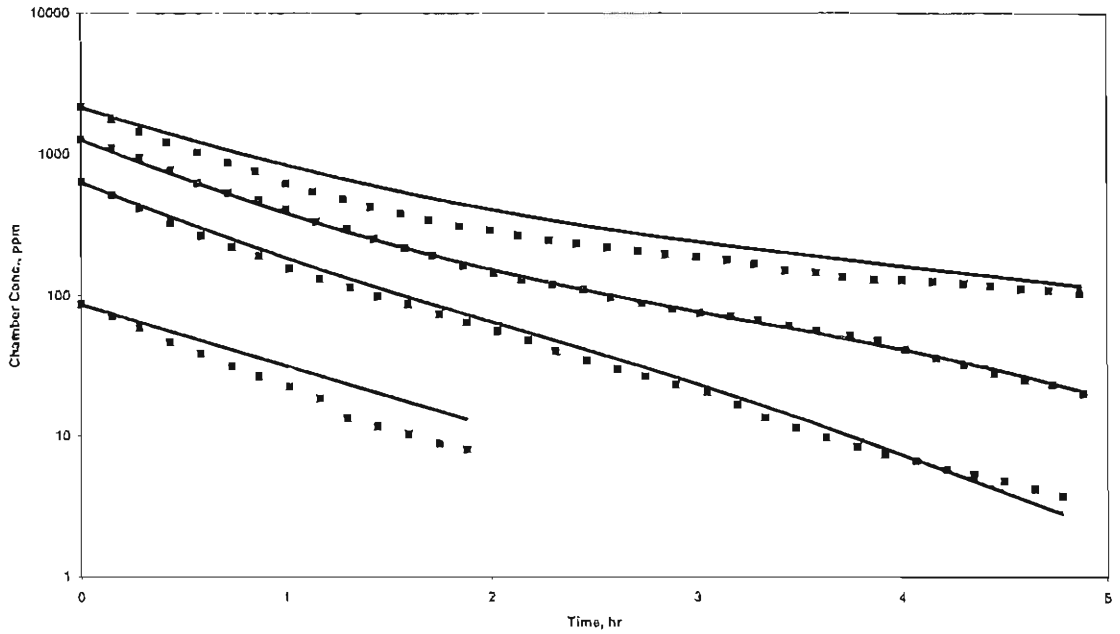

Figure 2: Uptake of MEK from a closed, recirculating atmosphere by three naïve F344 male rats per exposure. The initial chamber concentrations were 87, 560, 1265, or 2121 ppm. The smooth curves were generated by the PBPK model using the constants given in Tables 1 and 2.

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 naïve animals (Table 3).

Table 3: *In Vivo* Metabolic Rate Constants

Metabolic Rate Constants	
V_{max} (mg/hr/kg body weight)	5.44
K_m (mg/L)	0.63
K_m (mg/L) – pyrazole treated animals	30.3
K_{fo} (hr^{-1})	4.1

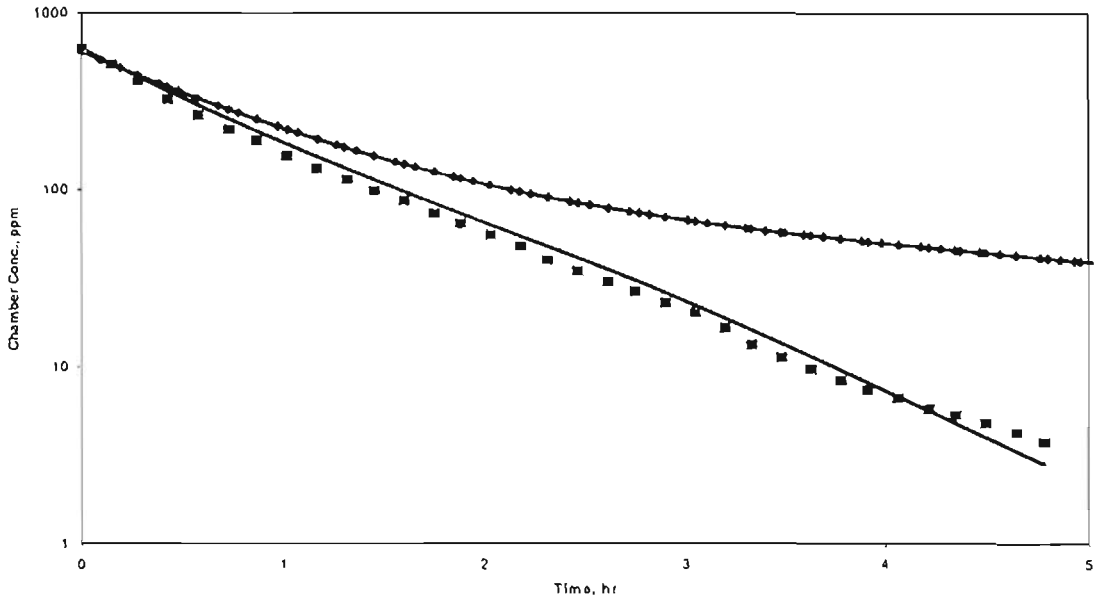

Figure 3: A comparison of MEK uptake from a closed, recirculating atmosphere at 560 ppm in pyrazole-pretreated (◆) and naïve rats (■). The smooth curve for the pyrazole-pretreated rats was generated by the PBPK model using the kinetic constants given in Table 3.

In Vivo Model Evaluation Studies

Separate groups of naïve animals received a single intravenous (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 continually monitored for up to 6 hrs post-exposure, 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 12 L/hr. A Teledyne Discovery II ion-trap mass spectrometer (MS/MS) equipped with an atmospheric sampling glow-discharge ionizations (ASGDI) source sampled directly from the off-gassing chamber approximately every 1.6 second. 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.

Results

A series of animals were exposed to aqueous MEK at 25 mg/kg by IV injection and the MEK concentration in exhaled breath continually monitored for approximately 3 hrs 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 hrs post-exposure (Figure 4, points). The PBPK model, incorporating partition

coefficient and metabolic parameters determined as described in prior sections 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/hr) provided a much better fit between the PBPK model-predicted and experimentally observed exhaled breath data (Figure 4, line). No reduction in alveolar ventilation was necessary for any exhaled breath data sets from any exposure routes other than the IV route.

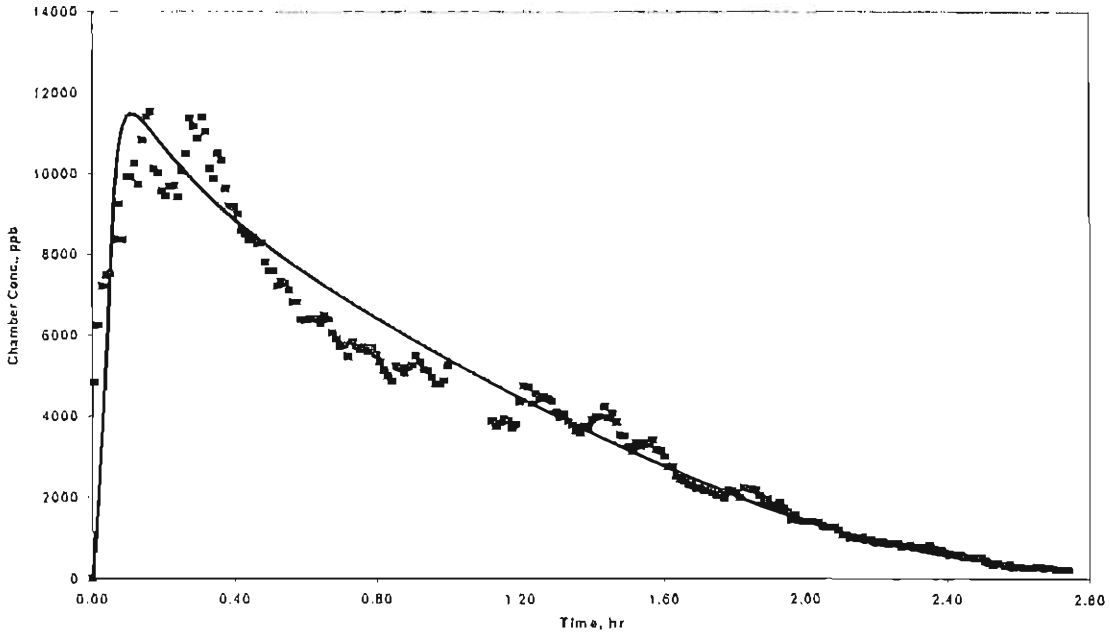

Figure 4: PBPK model prediction of the chamber concentration of MEK exhaled (ppb) from a rat receiving an IV injection of 25 mg/kg aqueous MEK via a jugular vein cannula (solid line) compared to the measured data from this study (points).

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. 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 animal per exposure route was used to estimate the oral and 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 just over one-hour post dosing and slowly decreased thereafter (Figure 5). The IP absorption constant (k_a) was estimated by the PBPK model to be 0.91 hr^{-1} and the optimized absorption coefficient fit all IP exposure data sets from n=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 hrs the animals were monitored.

Following oral gavage doses, MEK was quickly and completely absorbed (Figure 6). Peak exhaled breath concentrations were achieved within one hr post-exposure, and decreased slowly over the next three hours. The absorption rate constant (k_{as}) for oral exposure was estimated by the PBPK model to be 1.9 hr^{-1} and provided a good fit to all n=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 hrs the animals were monitored post exposure.

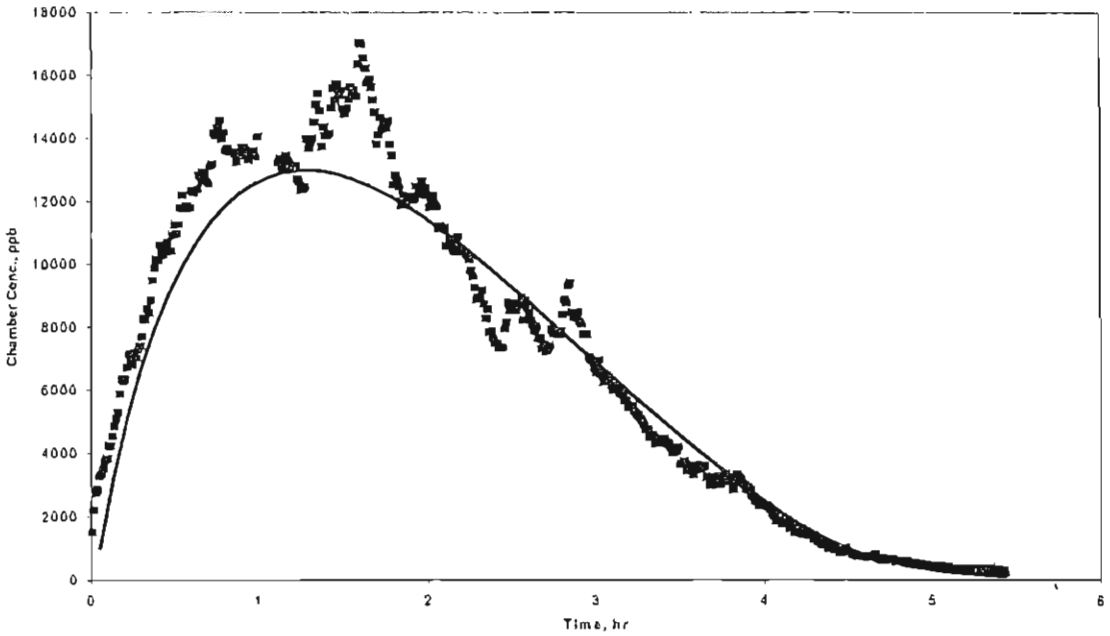

Figure 5: PBPK model prediction of the chamber concentration of MEK exhaled (ppb) from a rat receiving a single IP dose of 50 mg/kg aqueous MEK (solid line) compared to the measured data from this study (points).

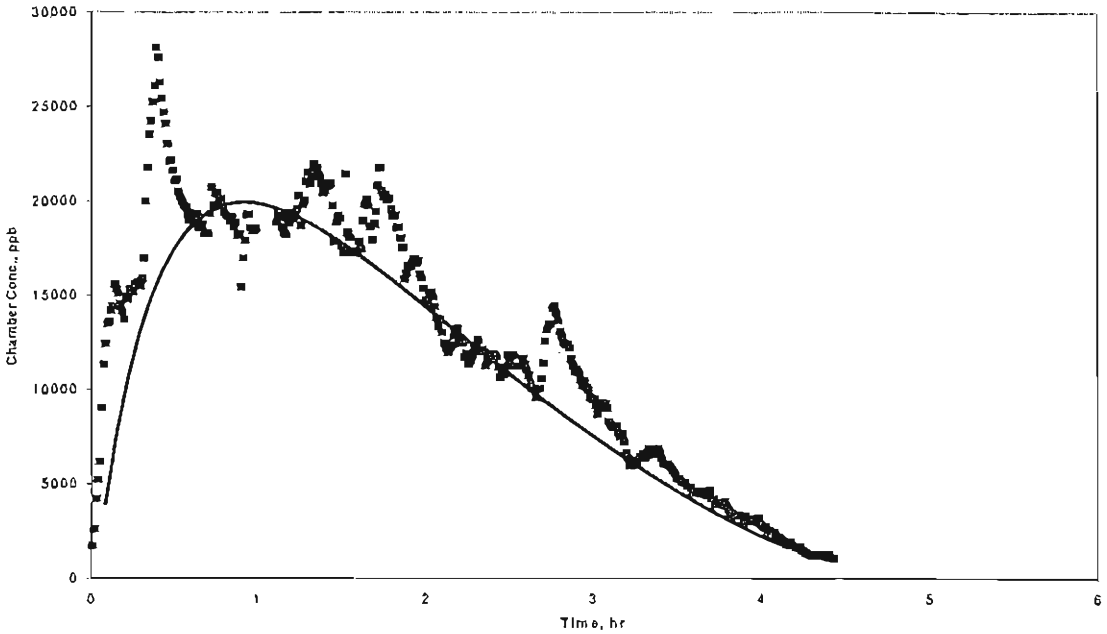

Figure 6: PBPK model prediction of the chamber concentration of MEK exhaled (ppb) from a rat receiving a single oral gavage dose of 50 mg/kg aqueous MEK (solid line) compared to the measured data from this study (points).

Conclusions (MEK PBPK Model Development)

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, both in terms of relative tissue solubility and metabolism. In some cases, such as partition coefficient values, the data generated here was found to directly coincide with prior reports. In other cases, key data was 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 that 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 5 times compared to the naïve animals. Previous investigators have established that, in rodents, MEK is metabolized reductively by alcohol dehydrogenase to 2-butanol and oxidatively to 3-hydroxy-2-butanone, presumably by cytochrome P450-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 demonstrates that MEK is rapidly absorbed following either oral or IP administration, with peak exhaled breath concentrations occurring approximately 1 hr following exposure. In contrast, Dietz et al. (1981) reported peak blood concentrations of MEK at 4 hrs following oral exposure to 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 compare with the Dietz et al. (1981) data. 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.

Aim 2: Evaluate the *in vivo* kinetics and dermal bioavailability of aqueous toluene and MEK using F344 rats.

DERMAL PBPK MODEL FOR TOLUENE

For dermal exposures, the rate of change of the compound in the skin compartment is related to the rate of penetration through the skin (the flux) and the rate of delivery due to blood flow and arterial concentration (the perfusion).

The toluene PBPK dermal model was adapted from Tardif et al. (1993) and modified by the addition of a skin compartment. Anatomical compartments in the model were used to describe the distribution of toluene into the rapidly perfused, slowly perfused, fat, liver, and skin compartments. The skin compartment in the model represented exposed skin; non-exposed skin was lumped into the slowly perfused compartment. Total skin, with a volume of 10% of the body weight, is assumed to receive 5% of the cardiac output. The exposed skin volume and blood flow rate were calculated as described by Jepson and McDougal (1997). For toluene, metabolism has been shown to occur primarily in the liver, and to be independent of the route of exposure (Cohr & Stokholm, 1979). Although metabolism at the site of entry is considered possible, this loss is assumed to be insignificant in comparison to liver metabolism; thus metabolism was described as occurring in the liver. Model parameters are given in Table 4.

Table 4: Toluene PBPK Model Parameters

Parameter	Rat
Body weight (kg)	0.23-0.41
Cardiac output (L/hr)	5.4
Alveolar ventilation (L/hr)	5.4
Blood flow (% cardiac output)	
Liver	25
Fat	4
Rapidly perfused	51
Slowly perfused	15
Total skin	5
Tissue volume (% body weight)	
Liver	4
Fat	8
Rapidly perfused	5
Slowly perfused	64
Total skin	10
Metabolic constants	
V_{max} (mg/kg/hr)	4.68
K_m (mg/L)	0.55
Partition coefficients	
Saline:air	1.2
Blood:air	18.0
Liver:air	83.5
Fat:air	1021
Muscle:air	27.7
Skin:air	43.0

Dermal exposures were conducted as described previously (Thrall et al., 2000) with modifications. In brief, animals were prepared for application of the dermal patch the day prior to experimentation by lightly clipper shaving the hair on the lower back under gentle restraint. The aqueous exposure patch consisted of a 2.5-cm inner diameter

hand-blown glass cell (O.Z. Glass Co., Pinole, CA) with a needle hole opening in the top to allow addition of the dosing solution. The cell was attached to the shaved area on the lower back of the animal using a cyanoacrylate adhesive and allowed to dry overnight. On the day of exposure, approximately 2 ml aqueous toluene was added to the exposure cell by passing a 23-gauge blunt-tip needle on a gas-tight syringe through the needle hole, which was then sealed using silicone. Actual dosing volume was determined by weighing the syringe before and after dosing. The surface area of skin exposed was 4.9 cm^2.

Animals were exposed dermally to aqueous toluene at 1 of 2 target concentrations of 0.5 mg/ml (0.05%; n=3) or approximately half that value at 0.25 mg/ml (0.025%; n=3). Dermal dosing solutions were prepared fresh on the day of the experiment in a small volume with shaking to ensure the solution was well mixed. Target concentrations were selected to stay below the solubility limit of toluene (0.07%) and still achieve measurable toluene levels in the exhaled breath of the animal exposed. To quantitate total absorbed dose, a weighed aliquot was collected from the original dosing solution and from the remaining solution at the end of the exposure. These samples were analyzed by a GC headspace method using a Hewlett-Packard model 5890 Series II (Avondale, PA).

The real-time breath monitoring system utilized during the animal studies is identical to that described previously. The animals were individually placed in the small glass off-gassing chambers immediately following dermal applications. Animals were awake and could move freely while in the off-gassing chamber. Certified pure breathing air was supplied to the animal through the lid of the off-gassing chamber at a calibrated rate of approximately 12 L/hr. The MS/MS system continually withdrew air samples from the off-gassing chamber through a port in the lid at the same rate of approximately 12 L/hr to provide a new data point every 1.6 second. The concentration of toluene in the chamber was used to represent exhalation from the animal using PBPK model equations as described by Gargas (1990).

At the end of the monitoring period, animals were humanely sacrificed and returned to the off-gassing chamber for several minutes to verify that chamber concentration reflected toluene eliminated via the exhaled breath, and not leakage from the exposure patch system.

Results

Animals were exposed dermally to aqueous toluene at a 0.5 or 0.2 mg/ml target concentration. The actual dosing concentrations were verified for each individual animal by GC analysis of the original dosing solution. Actual dosing concentrations were found to range at the lower exposure from 0.19-0.20 mg/ml (1.75 $\pm$ 0.32 mg/kg) and from 0.42-0.51 mg/ml (4.14 $\pm$ 0.38 mg/kg) at the higher exposure (Table 5).

Table 5: Rat Dermal Exposures (Average ± S.D. of n=3 Individual Data Sets)

Exposure (mg/kg)	Percent dose absorbed	K_p (cm/hr)
1.75 ± 0.32	45 ± 4	0.076 ± 0.004
4.14 ± 0.38	42 ± 18	0.070 ± 0.004

A representative exhaled breath profile from an animal treated dermally with a 2-ml volume of the 0.51 mg/ml aqueous toluene dose is given in Figure 7. The exhaled breath data, reflected as toluene chamber concentration, clearly shows an initial absorption phase, followed by a slower elimination phase. Exposures at this level resulted in a peak exhaled breath concentration of approximately 500 ppb, which was achieved within 1 hr after application of the dermal dose.

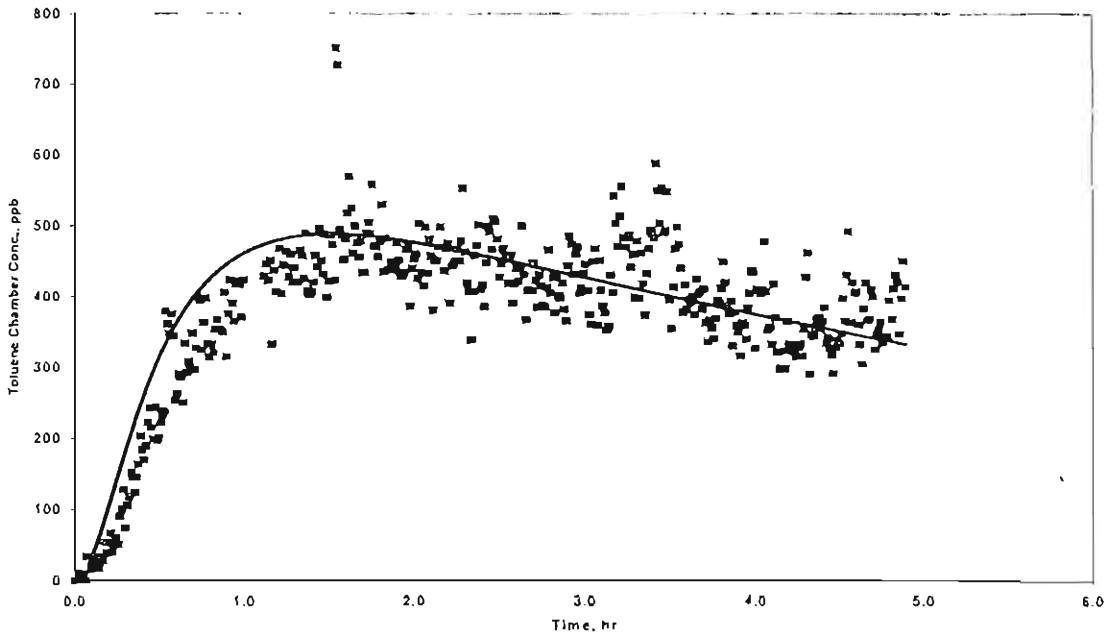

Figure 7: PBPK model prediction (line) and exhaled breath data, reflected as chamber concentration (points) for a rat exposed to a 2.08-ml volume of 0.51 mg/ml (4.41 mg/kg) aqueous toluene over a 4.91-cm^2 area of the back.

A similar exhaled breath profile was observed in animals treated with the lower toluene exposure dose level. In comparison to the higher dose level, exposures at this level resulted in a peak exhaled breath concentration of approximately 250 ppb, which was again reached within 1 hr after application of the dermal dose.

The toluene PBPK model, modified by the addition of a skin compartment, was used to estimate the permeability coefficient (K_p) for dermal absorption of aqueous toluene for each individual rat. This was done by requiring the PBPK model to determine the rate constant (in cm/hr) needed to match the achieved exhaled breath data. The estimated

K_p values ranged from 0.076 ± 0.004 cm/hr for the lower exposure dose level to 0.070 ± 0.004 cm/hr for the higher exposure dose (Table 5). Regardless of exposure level, an over-all average (n=6) indicates that 43.8 ± 9.6% of the toluene was absorbed during the 5 hr the animals were monitoring. A comparison of the PBPK model estimates of the concentration of toluene remaining at the end of exposure and the measured values showed good agreement. Chamber monitoring for toluene concentrations following sacrifice of the animals revealed that no leakage of the exposure system occurred.

Conclusions (Dermal Model Development for Toluene)

The studies conducted here indicate that toluene, in an aqueous matrix, is rapidly absorbed through the skin of a rat. Although the current studies were conducted at aqueous toluene concentrations well above the current drinking water standards, the calculated permeability coefficient should be applicable to lower concentrations.

A single permeability constant for absorption of aqueous toluene in the rat, calculated from the exhaled breath data using the PBPK model, was found to be 0.074 ± 0.005 cm/hr. Although a comparative rodent value for aqueous toluene was not located in the literature, the rat in vivo K_p for toluene vapor exposures was reported to be substantially higher at 0.72 cm/hr (McDougal et al., 1990). Similar relationships are reported by Jepson and McDougal (1997) for aqueous versus vapor absorption dibromomethane and bromochloromethane. Numerous investigators have also shown that the dermal absorption of a variety of compounds is greater in rats than in humans (Bronaugh, 1998; Jepson and McDougal, 1997; McDougal et al., 1990; U.S. EPA, 1992). The U.S. EPA (1992) human K_p value for aqueous toluene was estimated to be 1 cm/hr based on flux data from Dutkiewicz and Tyras (1968). Given that the K_p value for aqueous toluene exposures in F344 rats determined here is lower than the human estimated value, a reevaluation of human dermal absorption may be warranted.

DERMAL PBPK MODEL FOR MEK

A series of studies were conducted to evaluate the dermal absorption of aqueous MEK in F344 rats. Animals were exposed to MEK at various concentrations ranging from 0.025 to 0.5% using the glass patch system and analyzing exhaled breath concentrations as described for toluene. The absorption of MEK from an aqueous matrix appears to occur in an apparent biphasic rate; exhaled breath data suggest an initial rapid rate of appearance in systemic blood, followed by a slow, sustained rate, as illustrated in Figure 8.

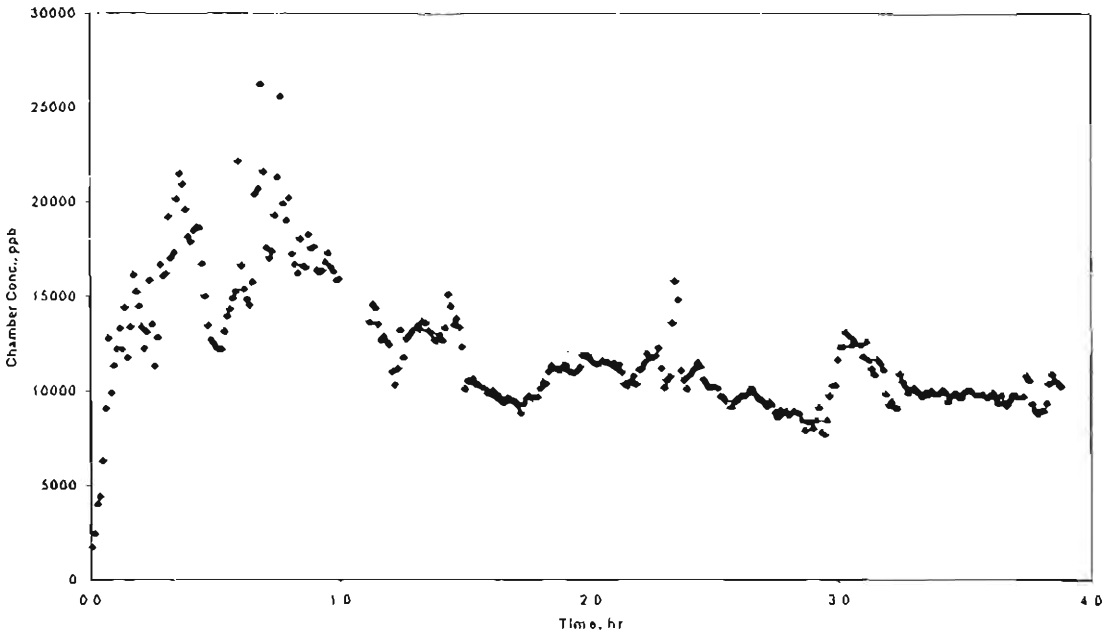

Figure 8: Dermal absorption of aqueous MEK in F344 male rats.

Close evaluation of the limited literature on MEK dermal studies in humans suggests that these same biphasic absorption phenomena occur in man (Munies and Wurster, 1965). However, the predicted permeability coefficient based on the exhaled breath data determined here is contradictory to the US EPA (1992) default human permeability coefficient value for aqueous MEK of 0.0001 cm/hr based on *in vitro* data obtained using abdominal skin. The underlying factors driving this observed biphasic dermal absorption remains to be determined.

Aim 3: Determine the impact of paint product formulation on the dermal absorption of toluene and MEK using F344 rats

The dermal bioavailability of toluene was assessed in paint products based on characterized percent composition of organic and inorganic compounds from similar type compounds, as shown in Table 6. The paint products were mixed by hand and tested for uniformity by taking 3 aliquots from different areas of the paint product mix. Toluene concentrations within the reconstituted paint product were assaying for in these aliquots using headspace gas chromatography analysis. Paint product ingredients were applied to the rat skin as an amount relating to the initial percent composition in the complete product.

Table 6: Percent Composition of Paint Products

	Enamel Paint		Lacquer Thinner	
Compound	Commercial	Reformulated	Commercial	Reformulated
Aliphatic hydrocarbons	47	47	---	---
Ethylbenzene	12	12	3	3
Xylene	20	0	---	---
Toluene	3	41	51	0.05
Titanium dioxide	18	0	---	---
Methyl ethyl ketone	---	---	8	8
Acetone	---	---	12	12
Ethyl acetate	---	---	5	5
Methanol	---	---	21	73

Dermal exposures to solvent-enhanced paint products using F344 rats

Male F344 rats were prepared for dermal studies as described for aqueous toluene studies. Expired breath from the rats was monitored using the ion-trap mass spectrometer, as described previously. After obtaining the breath samples, animals were sacrificed and placed back in the off-gassing chamber for a short period of time to ensure that measured chamber concentrations are attributable to exhalation and not a leaking patch system. Remaining test solution and rinses from washing the dermal cell were analyzed for concentration using headspace gas chromatography.

Results

Table 7: Analyzed toluene concentrations in dosing solutions ($\pm$ S.D.)

Dosing Solution	Toluene Concentration (mg/ml)	Number of Exposures
Commercial enamel paint	25.7 $\pm$ 2.3	6
Reformulated paint	323 $\pm$ 2.9	3
Commercial lacquer thinner	79.7 $\pm$ 2.4	5
Reformulated lacquer thinner	0.4 $\pm$ 0.01	4

Animals were exposed to toluene concentrations ranging from 0.4-323 mg/ml (Table 7).

Due to difficulties with patch adhesion integrity, exposures were conducted using commercial lacquer thinner diluted 1:5 in methanol.

The exhaled breath profiles observed in animals treated with the commercial lacquer thinner product compared with the aqueous toluene exposures differed substantially. For example, Figure 9 illustrates the exhaled breath data, reflected as toluene chamber concentrations normalized to the amount of toluene administered per kg body weight (ppb/mg/kg), from animals treated with toluene in lacquer thinner (commercial and reformulated) compared to the aqueous matrix. Peak exhaled breath concentrations were found to range from 250 ppb/mg/kg in the low-toluene reformulated lacquer thinner to roughly 25 ppb/mg/kg in the commercial lacquer thinner. The toluene dermal PBPK model was used to simulate the dermal exposure and estimate the exhaled breath concentrations. A permeability coefficient (K_p) value of 0.39 cm/hr, consistent with a rapid rate of absorption, was found to adequately describe the exhaled breath data.

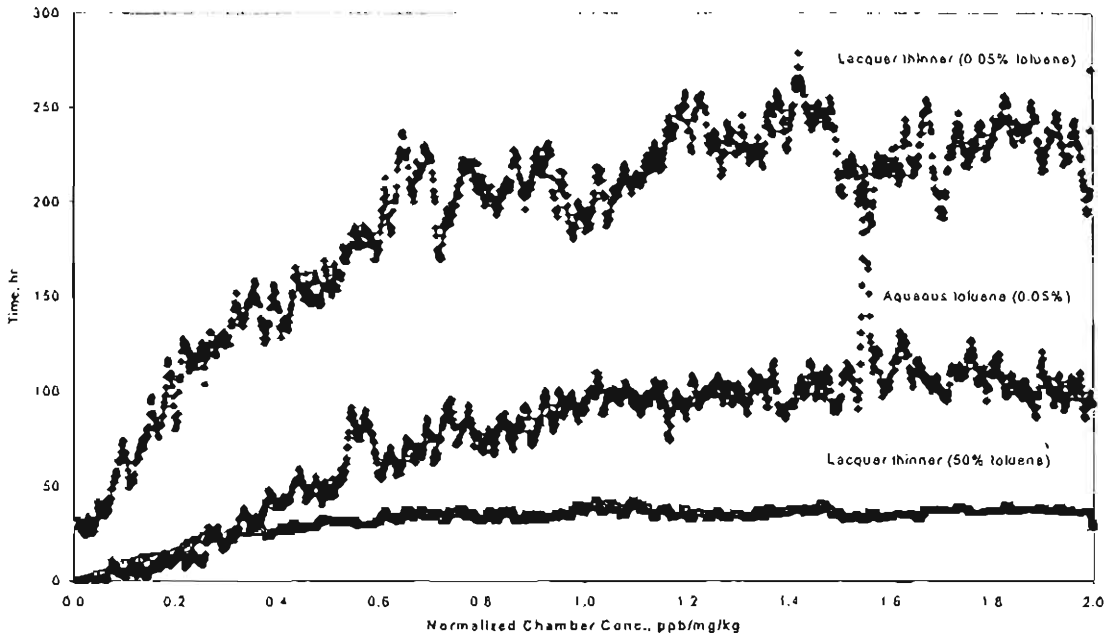

Figure 9: Comparison of exhaled breath profiles, in ppb/mg/kg, for rats treated dermally with a 2-ml volume of reformulated lacquer thinner containing 0.05% toluene, 0.05% aqueous toluene, and lacquer thinner containing 50% toluene.

In comparison, the exhaled breath profiles from animals treated dermally with the commercial enamel paint resulted in peak concentrations of approximately 30 ppm (30,000 ppb) achieved within 1-hr after application of the dermal dose. The dermal PBPK model for toluene was used to estimate permeability coefficient (K_p) for each exposure matrix. The data indicates that the dermal absorption of toluene from an enamel paint matrix is essentially identical to the dermal absorption of toluene from an aqueous matrix when normalized to the toluene exposure concentration (in mg/kg). In both cases, a permeability coefficient of 0.07 cm/hr adequately described the data (Figure 10), although toluene concentrations differed significantly (25 mg/ml for enamel

paint versus 0.5 mg/ml for the aqueous matrix). To evaluate the impact of paint constituents on the dermal bioavailability, additional dermal exposures were conducted using reformulated enamel paint, wherein the titanium dioxide (particulate) and xylene co-solvent were replaced by toluene. In contrast to the observations with the commercial paint product, peak exhaled breath concentrations for the reformulated paint were not observed within 2-hr after application of the dermal dose. The PBPK model simulations of the exhaled breath data from these exposures required a permeability coefficient roughly half the value from the intact paint (0.032 cm/hr), although the toluene concentration was more than 12 times greater than in the original paint (Figure 11). These data highlight the impact concentration within the exposure matrix has on dermal permeability.

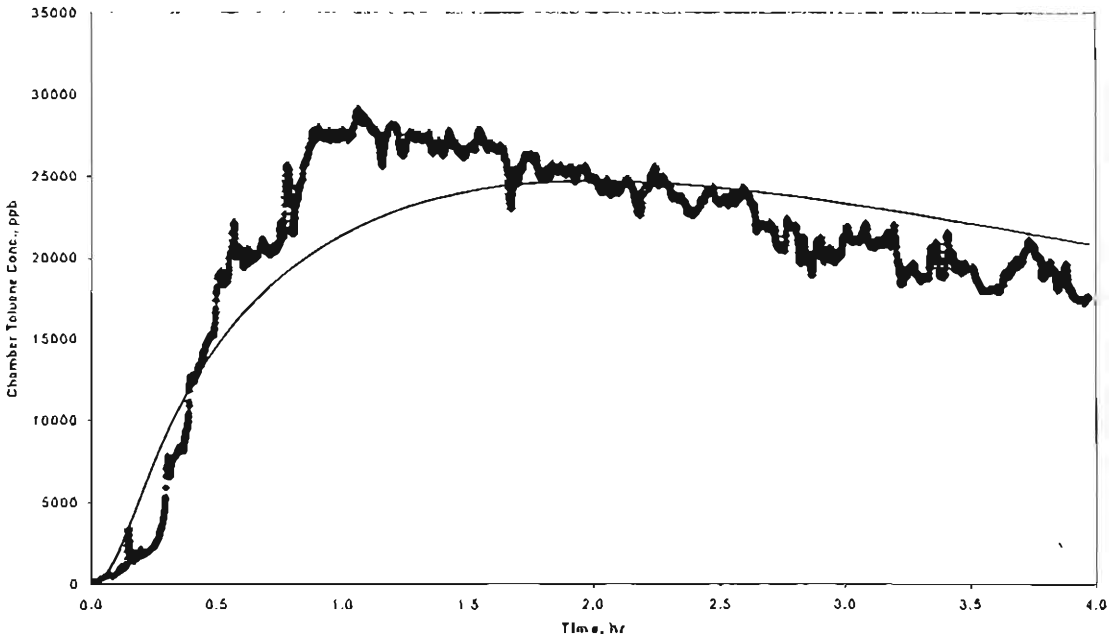

Figure 10: PBPK model prediction (line) and exhaled breath data, reflected as chamber concentration (points) for a rat exposed to a 2.0-ml volume of commercial enamel paint over a 2.27-cm^2 area of the back.

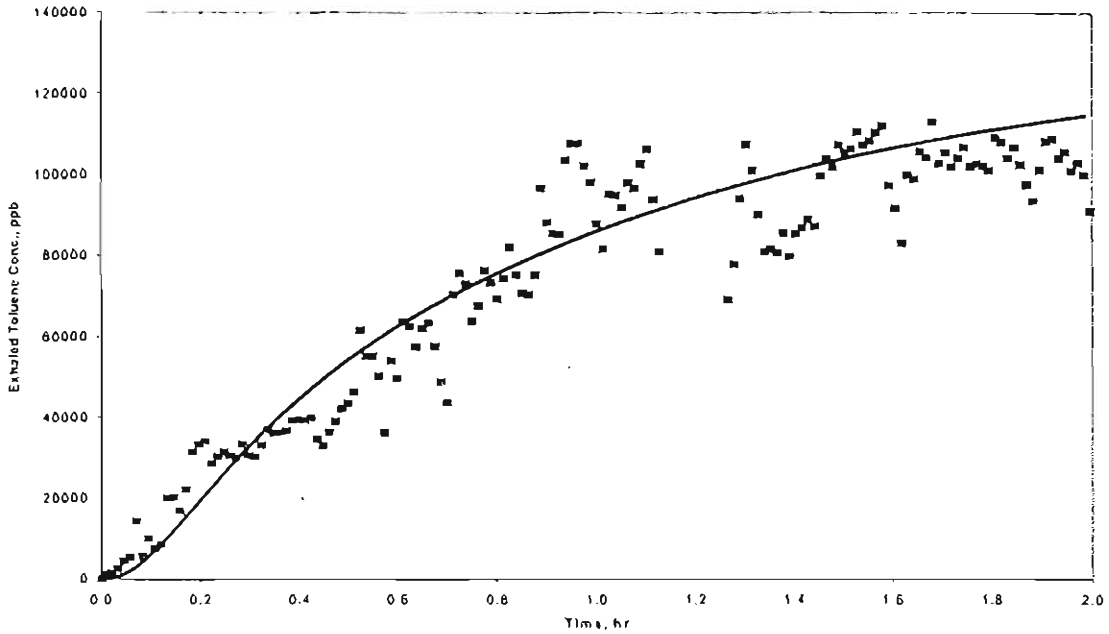

Figure 11: PBPK model prediction (line) and exhaled breath data, reflected as chamber concentration (points) for a rat exposed to 1.95-ml volume of 325 mg/ml (1746 mg/kg) toluene in reformulated paint over a 2.27-cm^2 area of the back.

Conclusion (Dermal absorption of toluene from paint products)

The studies conducted here indicate that toluene, in matrices available to the public, are absorbed through the skin of a rat with a permeability coefficient nearly identical to that observed for the dermal absorption of toluene in an aqueous matrix. The permeability coefficient estimated using the toluene dermal PBPK model for an aqueous exposure of 0.074 cm/hr (Thrall and Woodstock, 2002) is consistent with the value of 0.073 cm/hr for toluene in the commercial paint product. On the other hand, simulation of the dermal exposure to toluene in a reformulated paint product required a permeability coefficient roughly half the value from the intact paint (0.032 cm/hr) although the toluene concentration was more than 12 times greater. These comparisons suggest that either particular constituents (ie, xylene and titanium dioxide) within the matrix play an important role in modulating dermal absorption of toluene, or that the permeability of toluene is influenced by the exposure concentration. Further studies are required to examine these differences.

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PUBLICATIONS: PRESENT AND ANTICIPATED FUTURE

Thrall, K.D., and Woodstock, A.D. (2002). Evaluation of the dermal absorption of aqueous toluene in F344 rats using real-time breath analysis and physiologically based pharmacokinetic modeling. *Journal of Toxicology and Environmental Health, Part A.* 65:2087-2100.

Thrall, K.D., Soelberg, J.J., Weitz, K.K., and Woodstock, A.D. (2002). Development of a physiologically based pharmacokinetic model for methyl ethyl ketone in rats. *Journal of Toxicology and Environmental Health, Part A* 65:881-896.

Thrall, K.D., Kania, M.R., and Woodstock, A.D. Dermal absorption of toluene from enamel paint in F344 rats. *Journal of Toxicology and Environmental Health, Part A* (in preparation).

Thrall, K.D., Kania, M.R., and Woodstock, A.D. Evaluation of the dermal absorption of toluene from a complex lacquer thinner matrix using F344 rats. *Journal of Toxicology and Environmental Health, Part A.* (in preparation)

Thrall, K.D., Weitz, K.K., and Woodstock, A.D. Evaluation of the dermal absorption of common solvents. *To be presented at the 4th Biannual NORA Symposium NORA 2003: Working Partnerships – Research to Practice, Crystal City, VA, June 23-24, 2003.*

Woodstock, A.D., and Thrall, K.D. (2003). Evaluation of dermal absorption of aqueous toluene in F344 rats using real-time breath analysis and physiologically based pharmacokinetic modeling. *Presented at the 42nd Annual Meeting of the Society of Toxicology, Salt Lake City, UT, March 9-13, 2003.*

Kania, M.R., Woodstock, A.D., and Thrall, K.D. (2003). Dermal absorption of toluene from enamel paint in F344 rats. *Presented at the 42nd Annual Meeting of the Society of Toxicology, Salt Lake City, UT, March 9-13, 2003.*

Woodstock, A.D., and Thrall, K.D. (2002). Determination of the dermal absorption of methyl ethyl ketone in F344 rats using real-time breath analysis and PBPK modeling. *Presented at the Annual American Industrial Hygiene Conference and Exposition, San Diego, CA, June 1-6, 2002.*

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Thrall, K.D., Soelberg, J.J., Weitz, K.K., and Woodstock, A.D. (2002). Development of a PBPK model for methyl ethyl ketone in F344 rats. *Presented at the 41st Annual Meeting of the Society of Toxicology, Nashville, TN, March 17-21, 2002.*

Woodstock, A.D., and Thrall, K.D. (2002). Evaluation of the dermal absorption of methyl ethyl ketone in F344 rats using real-time breath analysis and PBPK modeling. *Presented at the 41st Annual Meeting of the Society of Toxicology, Nashville, TN, March 17-21, 2002.*

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Centers for Disease Control
and Prevention (CDC)

Memorandum

Date: October 28, 2003

From: Michael J. Galvin, Ph.D., Program Official MJG
Office of Extramural Programs, NIOSH, E-74

Subject: Final Report Submitted for Entry into NTIS for Grant 5 R01 OH003658-03.

To: William D. Bennett
Data Systems Team, Information Resources Branch, EID, NIOSH, P03/C18

The attached final report has been received from the principal investigator on the subject NIOSH grant. If this document is forwarded to the National Technical Information Service, please let us know when a document number is known so that we can inform anyone who inquires about this final report.

Any publications that are included with this report are highlighted on the list below.

Attachment
cc: Sherri Diana, EID, P03/C13

List of Publications

Thrall KD, Woodstock AD: Evaluation of the Dermal Absorption of Aqueous Toluene in F344 Rats Using Real-Time Breath Analysis and Physiologically Based Pharmacokinetic Modeling. Journal of Toxicology and Environmental Health, Part A 65:2087-2100, 2002

Thrall KD, Soelberg JJ, Weitz KK, Woodstock AD: Development of A Physiologically Based Pharmacokinetic Model for Methyl Ethyl Ketone in F344 Rats. Journal of Toxicology and Environmental Health, Part A 65:881-896, 2002

Title:	Dermatopharmacokinetics and Pharmacodynamics: In Vivo Analysis of Common Paint Product Solvents
Investigator:	Karla D. Thrall, Ph.D.
Affiliation:	Battelle Memorial Institute
City & State:	WA
Telephone:	(509) 376-6115
Award Number:	5 R01 OH003658-03
Start & End Date:	3/1/2001–2/28/2003
Total Project Cost:	$601,586
Program Area:	Allergic and Irritant Dermatitis
Key Words:	dermatitis

Final Report Abstract:
Exposure assessment is an important component in estimating health risk for individuals exposed to chemicals. Regulatory agencies have established standards for allowable occupational exposures, primarily via the inhalation pathway. In contrast, very little data is available to provide agencies sufficient guidance to establish permissible dermal exposure levels. Part of this shortfall lies in the fact that measurement of the amount of chemical absorbed through the skin is both experimentally difficult and time-consuming. In the research described here an innovative methodology was utilized to non-invasively evaluate dermal absorption by continually analyzing exhaled breath. Because breath concentrations can be used to reflect blood concentrations, constant analysis of exhaled breath provides an opportunity to evaluate differences in the rapidly changing blood compartment that occurs immediately following peak exposure. Animal studies were conducted to collect time-course data on the dermal absorption of two common solvents - toluene and methyl ethyl ketone. Both of these solvents are components of various paint and adhesive products, and may be frequently encountered in the occupational setting and by the consumer. Studies were conducted to expose animals to these compounds to provide an understanding of the impact of exposure matrix on dermal absorption. The exhaled breath kinetic data collected from each exposed animal was subsequently evaluated using an established mathematical model to determine the rate of dermal absorption. The studies indicate that the aqueous compounds are rapidly absorbed through the skin of a rat with a permeability coefficient of 0.074 ± 0.005 cm/hr for toluene. For methyl ethyl ketone, dermal absorption occurs in an apparent biphasic rate - exhaled breath data suggest an initial rapid rate of appearance in systemic blood, followed by a slow, sustained rate. The underlying factors driving this observed biphasic dermal absorption remain to be determined. Additionally, the dermal absorption of toluene from an enamel paint matrix is essentially identical to the dermal absorption of toluene from an aqueous matrix when normalized to the toluene exposure concentration. In both cases, a permeability coefficient of 0.07 cm/hr adequately described the data, although toluene concentrations differed significantly (25 mg/ml for enamel paint versus 0.5 mg/ml for the aqueous matrix). To evaluate the impact of paint constituents on the dermal bioavailability, additional dermal exposures were conducted using reformulated enamel paint, wherein the titanium dioxide (particulate) and xylene co-solvent were replaced by toluene. The PBPK model simulations of the exhaled breath data from these exposures required a permeability coefficient roughly half the value from the intact paint

(0.032 cm/hr), although the toluene concentration was more than 12 times greater than in the original paint. These data highlight the impacts both concentration and matrix components within the exposure matrix have on dermal permeability. Similar results were observed for dermal exposures to toluene in lacquer thinner-based matrices.

Publications:

Thrall KD, Soelberg JJ, Weitz KK, Woodstock AD: Development of A Physiologically Based Pharmacokinetic Model for Methyl Ethyl Ketone in F344 Rats. Journal of Toxicology and Environmental Health, Part A 65:881-896, 2002

Thrall KD, Woodstock AD: Evaluation of the Dermal Absorption of Aqueous Toluene in F344 Rats Using Real-Time Breath Analysis and Physiologically Based Pharmacokinetic Modeling. Journal of Toxicology and Environmental Health, Part A 65:2087-2100, 2002