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Dermatopharmacokinetics: *In Vivo* Analysis of Solvents

Submitted To:

Dr. Bridgette E. Garrett, Program Officer
NIOSH
1600 Clifton Road, D-74
Atlanta, GA 30333
Work phone: (404) 498-2508
e-mail address: bgarrette@cdc.gov

Submitted By:

Battelle, Pacific Northwest Division

Principal Investigator:
Karla D. Thrall, Ph.D., D.A.B.T.
ph: 509-376-6115
fax: 509-376-9064
e-mail: karla.thrall@pnl.gov

Address:
Chemical Dosimetry Group
Battelle, Pacific Northwest Division
902 Battelle Blvd.
P.O. Box 999, MS P7-59
Richland, WA 99352

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LIST OF ABBERVIATIONS

ASGDI	Atmospheric sampling glow-discharge ionization
cm	Centimeter
g	Gram
hr	Hour
IP	Intraperitoneal
IV	Intravenous
kg	Kilogram
K_m	Metabolic constant for affinity
K_p	Permeability coefficient (cm/hr)
L	Liter
MEK	Methyl ethyl ketone
MnBK	Methyl n-butyl ketone
mg	Milligram
min	Minute
ml	Milliliter
MS/MS	Mass spectrometer
M/Z	Mass to charge ratio
n	Number
PBPK	Physiologically based pharmacokinetic
ppb	Parts-per-billion
S.D.	Standard deviation
V_{max}	Metabolic constant for capacity

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ABSTRACT

Dermal exposures and subsequent percutanous absorption of solvents and other chemicals can be a critical exposure route in occupational settings. However, in silico predictive methods do not generally provide an accurate estimate of absorption when compared to dermal studies which have demonstrated that dermal exposures can be a significant contributor to total absorbed dose. Physiologically based pharmacokinetic (PBPK) models allow both the estimation of internal dose from a dermal exposure and the calculation of equivalent dose levels across dosing routes, since many chemicals have more significant oral or IV data sets. Dermal exposures to both lipophilic and hydrophilic chemicals were conducted in F344 rats with uptake measured via exhaled breath to allow detection of rapid concentration changes. Exposures were conducted by placing a set amount of test compound, either neat or in an aqueous formulation, into a sealed chamber secured to the back of the animal and monitoring exhaled breath concentrations from the animal in a gas uptake chamber for approximately three hours. Exposures were conducted for acetone, ethyl benzene, styrene, methyl ethyl ketone, and methyl n-butyl ketone (MnBK). Exposures were conducted with neat test material, in aqueous vehicle, or under both neat and aqueous conditions, depending on the solubility of the individual test compound. Total dermal absorption was found to be greatest for styrene, followed by ethylbenzene > MnBK > MEK > acetone. A PBPK model for MnBK was developed by conducting experimental studies to determine blood and tissue partition coefficient values and by conducting gas uptake studies for derivation of metabolic parameters. Additional exposures (oral and intraperitoneal) were conducted as the basis for constructing a PBPK model for MnBK. The approach of coupling mathematical models with a non-invasive rapidly monitoring methodology is critical for calculating estimates of dermal absorption. However, the dermal patch system utilized here was found to be inadequate for maintaining patch integrity and lacked sufficient volume for solvent vapors. Thus, permeability coefficient values were not possible to calculate.

SIGNIFICANT FINDINGS

The overall objective of this research project was to evaluate the percutaneous absorption of compounds commonly encountered in the occupational setting as solvents (acetone, methyl ethyl ketone, methy n-butyl ketone, styrene, and ethylbenzene). The studies conducted in rats have demonstrated that the dermal absorption of all aqueous solvents appears to occur rapidly, although leaky exposure chambers and detection limited precluded the determination of dermal permeability coefficients. A physiologically based pharmacokinetic model to describe the absorption, tissue distribution and metabolism of MnBK was developed.

USEFULNESS OF FINDINGS

The work described here has resulted in the development of a physiologically based pharmacokinetic model to describe the absorption, tissue distribution and metabolism of MnBK in F344 rats. The model incorporates oral, inhalation, and intraperitoneal routes of administration. When published, the MnBK model and supporting data will contribute to the basic understanding of the solvent and can be used by risk assessors to improve health risk assessments. Further, the data from the evaluations conducted here will aid in establishing understanding dermal absorption of solvents under conditions that mimic actual occupational exposure situations.

SCIENTIFIC REPORT

Background

Exposure assessment is an important component in estimating health risk for individuals exposed to chemicals (EPA, 1996). To date, regulatory agencies have set standards for allowable occupational chemical exposures via inhalation. Very little guidance has been published regarding permissible levels for dermal exposures. However, a recent study of workers in the auto body repair industry (Daniell et al. 1992) indicates that dermal exposures to solvent mixtures may make a major contribution to the total absorbed dose. Given this, traditional industrial hygiene air monitoring may substantially underestimate the dose of solvent uptake. The American Conference of Governmental Industrial Hygienists (ACGIH) is concerned about dermal chemical exposures, and have assigned a "skin notation" to chemicals with a potential for dermal absorption or dermal toxicity (Guy and Potts 1993).

There are a number of factors that are likely to influence the extent of dermal absorption, including surface area of the exposed skin, and physicochemical properties of the chemical itself and/or the vehicle (which may alter skin structure, change diffusion, enhance penetration, etc). Generally, skin uptake has been considered for solids and liquids, but the potential for uptake from vapors and gases has received comparatively little attention (Brooke et al. 1998). Currently, laboratory studies are the primary source of data that are used to assess potential dermal absorption in various scenarios. However, current methods of estimating absorption in these studies need improvement (Jepson and McDougal, 1997).

From the 1950s through the 1970s, the rate of uptake of a chemical through the skin was generally estimated based on studies of humans (Paustenbach and Leung 1993). More recently, estimates of possible dermal uptake of a chemical are made using animal skin (*in vivo* or *in vitro*) or human skin *in vitro*. *In vivo,* the rate of uptake of a chemical through the skin has been estimated using radiolabeled compounds and tracking the radioactivity in blood and excreta following topical application (Paustenbach and Leung 1993). This indirect method for determining percutaneous absorption provides an estimate of the total absorbed dose, but often fails to reveal information on the uptake, distribution and clearance phases of dermal absorption kinetics. Further, since blood levels may be very low in these situations, this practice is often restricted by sensitivity limits of the assay or analysis. An additional drawback with this methodology is that the nature of the radioactivity, whether it represents the parent or metabolites, is often undefined, thus kinetic interpretation is also limited.

Recent studies have illustrated that exhaled breath presents a useful alternative to radiotracer studies by providing a non-invasive methodology for assessing bioavailability of volatile compounds (Thrall et al., 1999; Thrall and Woodstock, 2002). Breath measurements are particularly useful in studies where repeated samples

collected in real time allows for the tracking of trends. Exhaled breath continually analyzed during the rapid kinetic changes that occur during, and immediately post exposure, provides a means for comparing differences between exposures to chemicals under various conditions. Furthermore, the non-invasive nature of breath analysis improves the participation rate in controlled human exposure and environmental or occupational biomonitoring studies.

For exhaled breath measurements to be useful, they must be evaluated using some form of a kinetic model. Physiologically based pharmacokinetic (PBPK) models are particularly useful for integrating a variety of data, including breath analysis, to determine the penetration rates of chemicals through the skin. A validated PBPK model will facilitate extrapolation across different routes of exposure, from high-to-low doses, and among animal species (Andersen et al. 1993). Furthermore, an appropriately validated PBPK model, when used to reliably estimate an internal dose of a compound at a target tissue, can have a significant impact on human health risk assessments. The EPA considers PBPK modeling as the method of choice for calculating a dermal permeability coefficient (K_p) when data and model are both available (EPA 1992).

The dermal penetration rate, or flux, is an integral part of a dermal exposure risk assessment, and can be considered an index of percutaneous absorption (Fiserova-Bergerova et al. 1990). The form of the flux equation used in the PBPK model assumes that the concentration inside the skin is uniform, which is not precisely correct. Unfortunately, flux equations that take into account the concentration of the chemical in the skin with respect to distance in the skin requires the solution of partial differential equations (Jepson and McDougal 1997). Partial differential equations have parameters which cannot be directly measured, and therefore have to be fit or estimated. Thus, using a partial differential equation description forces the model to be descriptive, rather than predictive. Conversely, the simple homogeneous model, as described in this proposed research, has been shown experimentally to accurately describe the penetration of chemicals such as dibromomethane and bromochloromethane (Jepson and McDougal, 1997).

The research conducted under this grant focused on two solvents, ethylbenzene and styrene, likely to be encountered in similar occupational settings. Ethylbenzene is a volatile solvent used in the production of synthetic rubber, is a component of automotive and aviation fuels, and is a precursor to styrene (International Labour Office, 1983). Styrene is used in the manufacture of plastics and synthetic rubber (Löf et al., 1986). Workers manufacturing boats, truck parts, tubs and showers, and pipes that use reinforced plastics may be exposed to styrene. Both ethylbenzene and styrene have been shown to be absorbed dermally (Wieczorek 1985; Susten et al., 1990; Morgan et al., 1991). Dermal exposures to these compounds in an aqueous matrix will be compared to prior studies with toluene. Furthermore, exposure to toluene, ethylbenzene and styrene as vapors will provide an opportunity to realistically estimate the impact of vaporization of these frequently encountered chemicals on dermal bioavailability.

The research proposed here will also focus on studies to understand the relative contribution of lipophilic and polar absorption pathways using acetone and methyl n-butyl ketone for comparison to prior studies with methyl ethyl ketone. Methyl n-butyl ketone and acetone are both used as solvents for lacquers, ink thinners, oils, fats and waxes (ACGIH 1986; Budavari 1996).

This continuation proposal had the following Specific Aims:

1. **To compare the dermal absorption of compounds with both lipophilic and hydrophilic properties with prior studies using methyl ethyl ketone in F344 rats.**

2. **To evaluate the kinetics and dermal bioavailability of ethylbenzene and styrene in an aqueous matrix using F344 rats.**

3. **To evaluate the kinetics and dermal bioavailability of ethylbenzene, styrene, and toluene vapor using F344 rats**

During the first phase of this work, we developed a rat PBPK model to describe the interaction of methyl ethyl ketone within the body, in terms of relative tissue solubility, absorption, and elimination following oral, intraperitoneal, or inhalation exposures (Thrall et al., 2002). Additionally, our dermal bioavailability studies with aqueous methyl ethyl ketone indicated that dermal absorption occurs in a biphasic manner – with an initial rapid appearance of the compound in the exhaled breath, indicative of rapid systemic absorption, followed by a more sustained moderate permeability. Munies and Wurster (1965) reported similar observations of biphasic absorption in humans upon exposure under pre-hydrated skin conditions. Evaluation of real-time exhaled breath data collected during dermal exposures to aqueous methyl ethyl ketone indicate that a single well-stirred skin compartment PBPK model will not adequately describe the data.

Methyl ethyl ketone, acetone and methyl n-butyl ketone have both lipophilic and hydrophilic properties. According to Munies and Wurster (1965), a substance in which the partition coefficient between polar and nonpolar solvents is nearly one will have the highest dermal penetration rate. Thus, based on the partition coefficient information, methyl ethyl ketone would be predicted to have the highest permeability rate. If the biphasic appearance of methyl ethyl ketone in the exhaled breath of animals treated dermally can be explained by transit of the compound via one pathway or the other, alteration of the relative solubility (more polar acetone versus more lipophilic methyl n-butyl ketone) should alter the biphasic appearance.

Development of a PBPK model for dermal absorption

Partition Coefficients: Naïve male F344 rats were euthanized by CO_2 asphyxiation and blood drawn with a heparinized syringe from the ascending vena cava and placed in a labeled vial. Tissues (liver, fat, muscle and skin) were harvested and placed in individual vials and stored at 4°C until partition coefficients were determined. Triplicate

2 ml samples of blood, 2 ml saline, and empty reference vials were incubated with methyl n-butyl ketone in a 37°C shaker for 1 and 3 hr. The later time point was included to assure that the chemical had equilibrated between vial headspace and the liquid. The methyl n-butyl ketone chemical concentration in the headspace of the test vials and reference vials was determined by gas chromatography and the liquid to air partition coefficient calculated.

Table 1: Substrate to Air Partition Coefficients for MnBK (mean $\pm$ S.D.)

Substrate to Air	Rat	Number of samples
Blood	155 $\pm$12	10
Liver	110 $\pm$ 10	10
Fat	2034 $\pm$ 148	9
Muscle	108 $\pm$ 6	6
Skin	114 $\pm$ 24	10
Brain	110 $\pm$ 8	10
Saline	89 $\pm$ 10	20

Development of metabolic rate constants for methyl n-butyl ketone. Metabolic rate constants (K_m and V_{max}) were determined using a gas uptake technique described by Gargas et al. (1986). Briefly, rats (3/exposure) were placed in a recirculating inhalation chamber. Once the animals were acclimated to the chamber, methyl n-butyl ketone was added to the system. The disappearance of compound from the chamber, as measured by gas chromatography, was quantitated over time. The gas uptake chamber is a closed system thus the only way for methyl n-butyl ketone to escape the system is by uptake and metabolism in the animals. The non-specific loss rate for methyl n-butyl ketone was determined in an empty chamber to account for deposition of compound on the chamber components, and in an empty chamber containing 3 deceased rats to account for hair deposition. Loss (non-specific and hair deposition) was accounted for in subsequent data analyses. The series of gas uptake curves were evaluated with the PBPK model to estimate the metabolic rate constants (K_m and V_{max}).

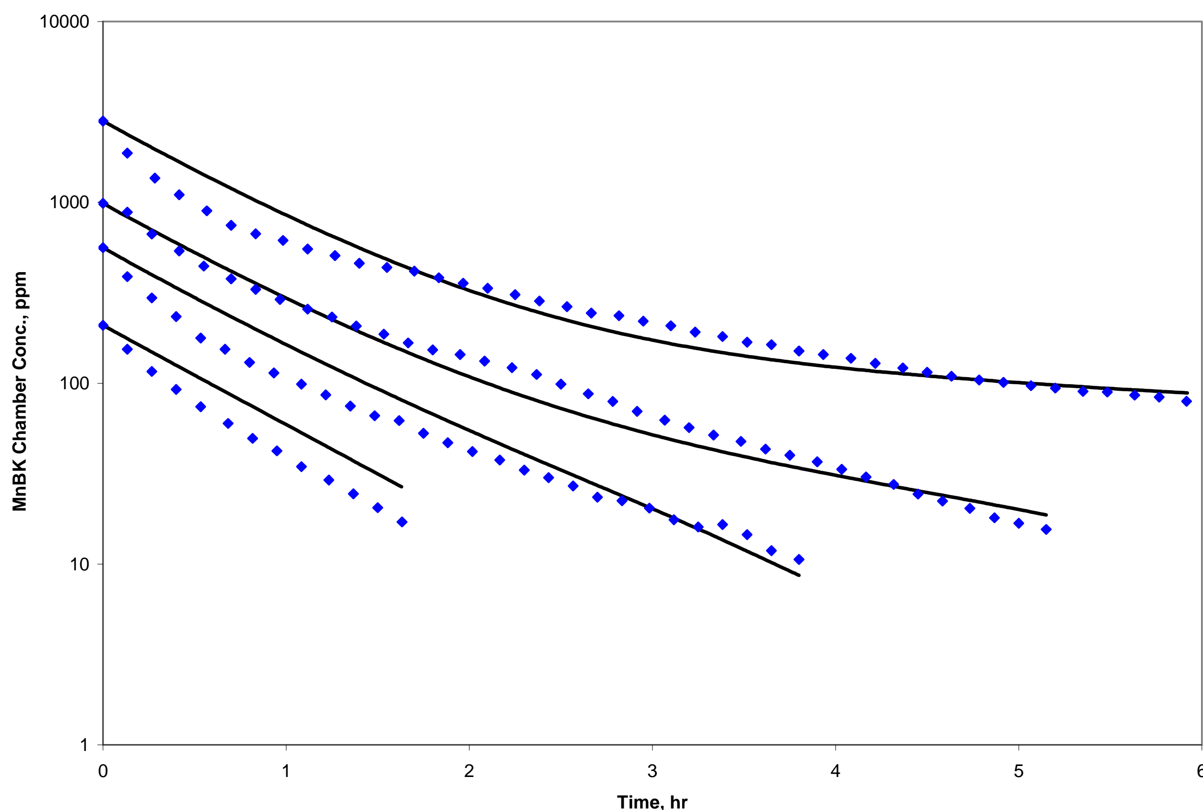

Figure 1. Uptake of MnBK from a closed, recirculating atmosphere by three naïve F344 male rats per exposure. The initial chamber concentrations were 200, 500, 1000, or 2800 ppm. The smooth curves were generated by the PBPK model.

Table 2. In vivo metabolic rate constants for MnBK

Metabolic Rate Constants	
V_{max} (mg/hr/kg body weight)	5.44
K_m (mg/L)	0.63

For IP exposures, peak exhaled breath concentrations of MnBK were observed at approximately 30 min post dosing and decreased sharply thereafter (Figure 2). The PBPK model simulations predict that nearly 100% of the injected amount of MnBK was absorbed systemically, of which most was exhaled during the 2 hrs the animals were monitored.

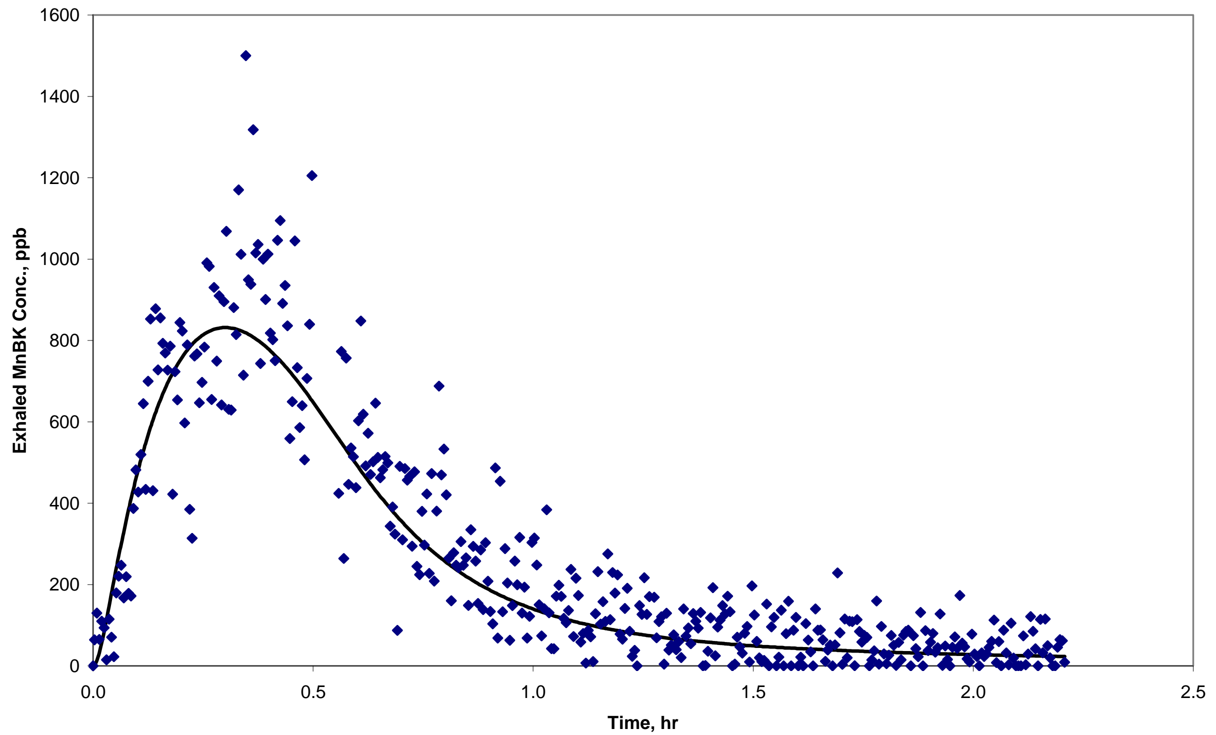

Figure 2: Chamber concentrations of MnBK, representing exhaled breath from a single F344 rat treated with MnBK by IP injection. The smooth line is the PBPK model simulation of the data.

Following oral gavage doses, MnBK was quickly and completely absorbed (Figure x). As seen with IP exposure, peak exhaled breath concentrations from oral exposures were achieved within approximately 30 min hr post-exposure, and decreased more slowly over the next several hours.

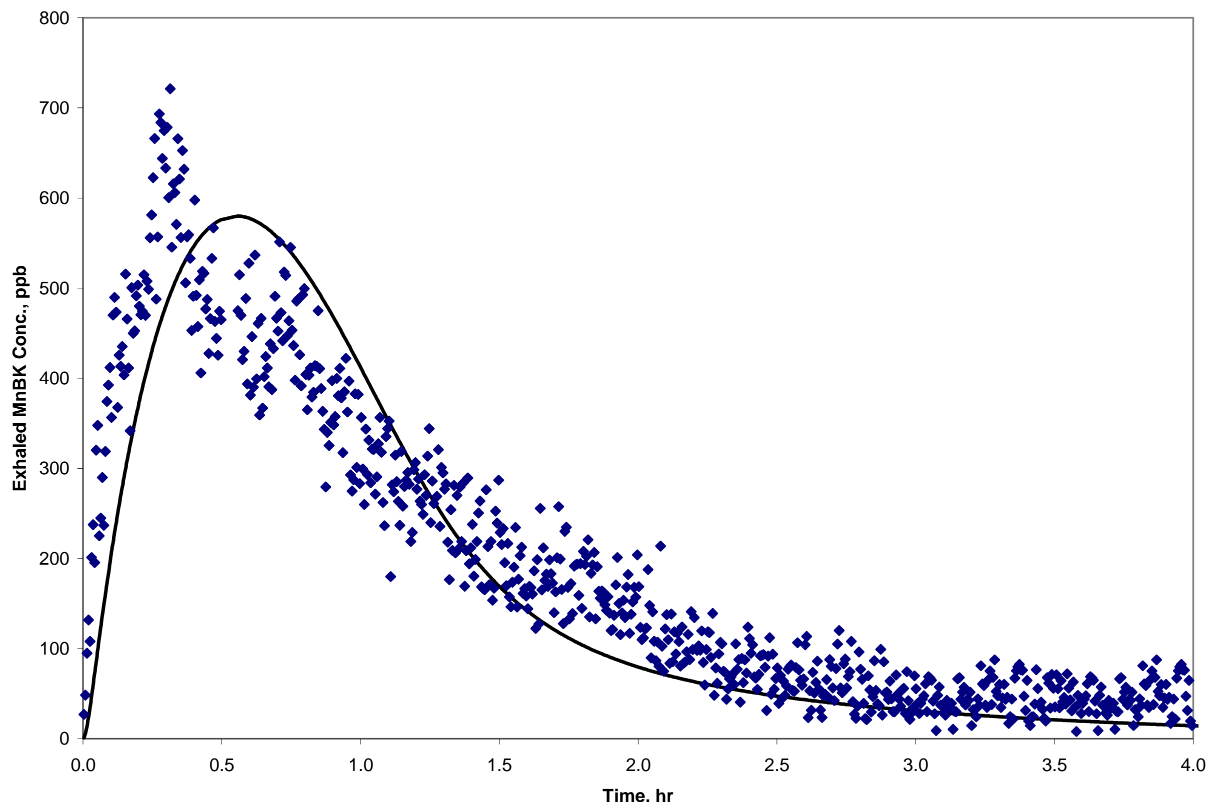

Figure 3: Chamber concentrations of MnBK, representing exhaled breath from a single F344 rat treated with MnBK by oral gavage. The smooth line is the PBPK model simulation of the data.

Dermal exposure to methyl n-butyl ketone or acetone using rats

Male F344 rats, weighing 200-220 g were obtained from Charles River Laboratories (Raleigh, NC), and allowed to acclimate for at least 5 days. The day prior to exposure, rats were anesthetized with a ketamine/xylazine mixture (58.3 mg ketamine + 8.3 mg xylazine/ml, 1.0 mg/kg). While anesthetized, the skin was lightly clipper shaved and an exposure cell attached to the clipped area using cyanoacrylate adhesive. The dermal exposure cell consisted of a 1.7-cm inner-diameter hand-blown glass cell (Northwest Technical Glass, Richland, WA) with a needle hole opening in the top to allow addition of the compound. Immediately after filling the cell, the needle hole was sealed with silicone glue and taped to prevent loss of the test compound.

Dermal exposures were initiated the day after attachment of the dermal exposure cells. Aqueous methyl n-butyl ketone or acetone (uniformly labeled ^{13}C-acetone) was added to the exposure cell and each animal individually placed in a small off-gassing chamber. ^{13}C-acetone was used to separate the heavier m/z ratio at 61 from the endogenous acetone m/z ratio at 58. Exhaled breath from the rats was monitored using the ion-trap mass spectrometer, as described below, for continual analysis during the exposure period to adequately characterize the kinetics of absorption. After obtaining the breath samples, rats were sacrificed with CO_2 and placed back in the off-gassing chamber for

a short period of time to ensure that measured chamber concentrations were attributable to exhalation, and not a leaking patch system.

Exhaled breath analysis

The exhaled breath monitoring system consisted of a small glass off-gassing chamber connected directly with a Teledyne Discovery II (LGC Inc., San Jose, CA) ion-trap mass spectrometer (MS/MS) equipped with an atmospheric sampling glow discharge ionization (ASGDI) source. The animals were individually placed in the small glass off-gassing chamber (2.2-L volume) and were awake and could move freely. Certified "Grade-D" 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 ASGDI-MS/MS system continually drew 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 seconds. The concentration of compound in the chamber was used to represent exhalation from the animal. An example for an acetone dermal exposure is given in Figure 4.

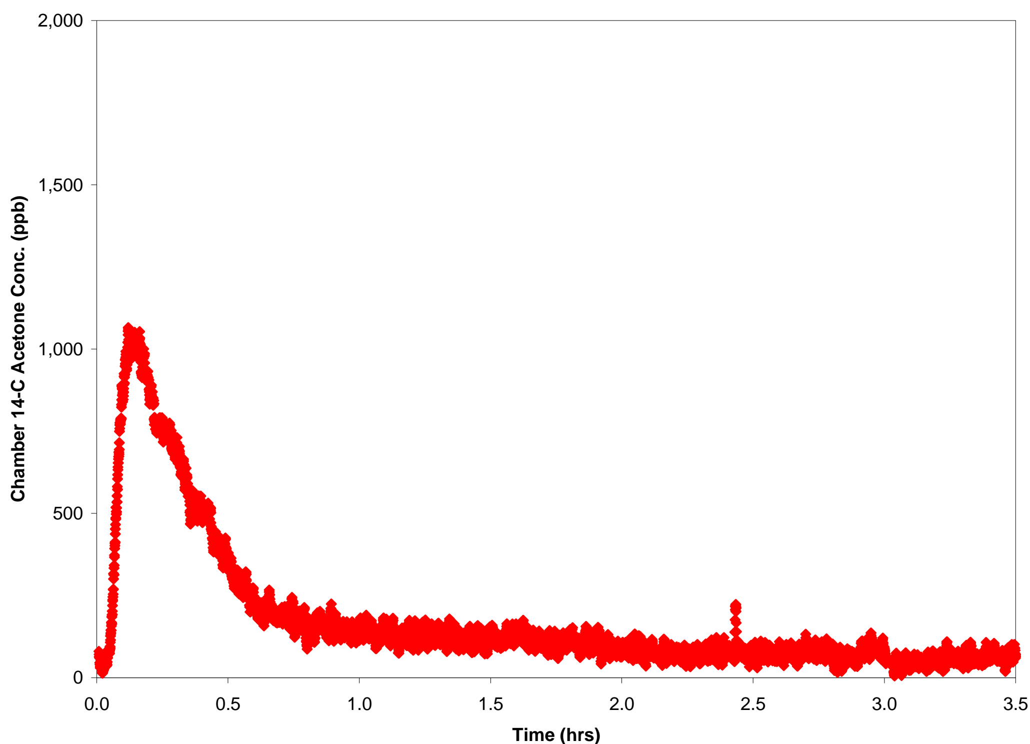

Figure 4. Chamber concentration of ^{13}C-acetone from a single animal exposed to acetone using a dermal patch system as described in the text.

Estimation of the skin permeability constant (K_p)

Based on continual measurement of the breath concentrations, the PBPK model describing the distribution, metabolism and elimination of acetone or methyl n-butyl ketone can be used to estimate the amount of chemical in the body during and after an exposure, as well as estimate the amount of compound and/or metabolite lost in the exhaled breath, urine and feces. In the current project, a separate skin compartment with transdermal flux described by a permeability-area-concentration product was added to the model to allow prediction of blood and exhaled breath concentrations based on exposure concentrations at the skin surface in a manner analogous to that described by McDougal et al. (1986). However, the variability between individual data sets of exposures was too great to allow for calculation of a single permeability constant.

Dermal exposure to aqueous ethylbenzene and styrene using rats

Male F344 rats, weighting 200-220 g were obtained from Charles River Laboratories (Raliegh, NC), and allowed to acclimate for at least 5 days. The day prior to exposure, rats were anesthetized with a ketamine/xylazine mixture (58.3 mg ketamine + 8.3 mg xylazine/ml, 1.0 mg/kg). While anesthetized, the skin was lightly clipper shaved and dermal exposure patches attached as described previously.

Dermal exposures were initiated the day after attachment of the dermal exposure cell. Aqueous samples of test material were added to each exposure cell as described previously. Six animals each were exposed to styrene or ethylbenzene. Expired breath from the animals was monitored using the ion-trap mass spectrometer, as described previously, for continual analysis during the exposure period to adequately characterize the kinetics of absorption. An example for aqueous ethylbenzene is given in Figure 5.

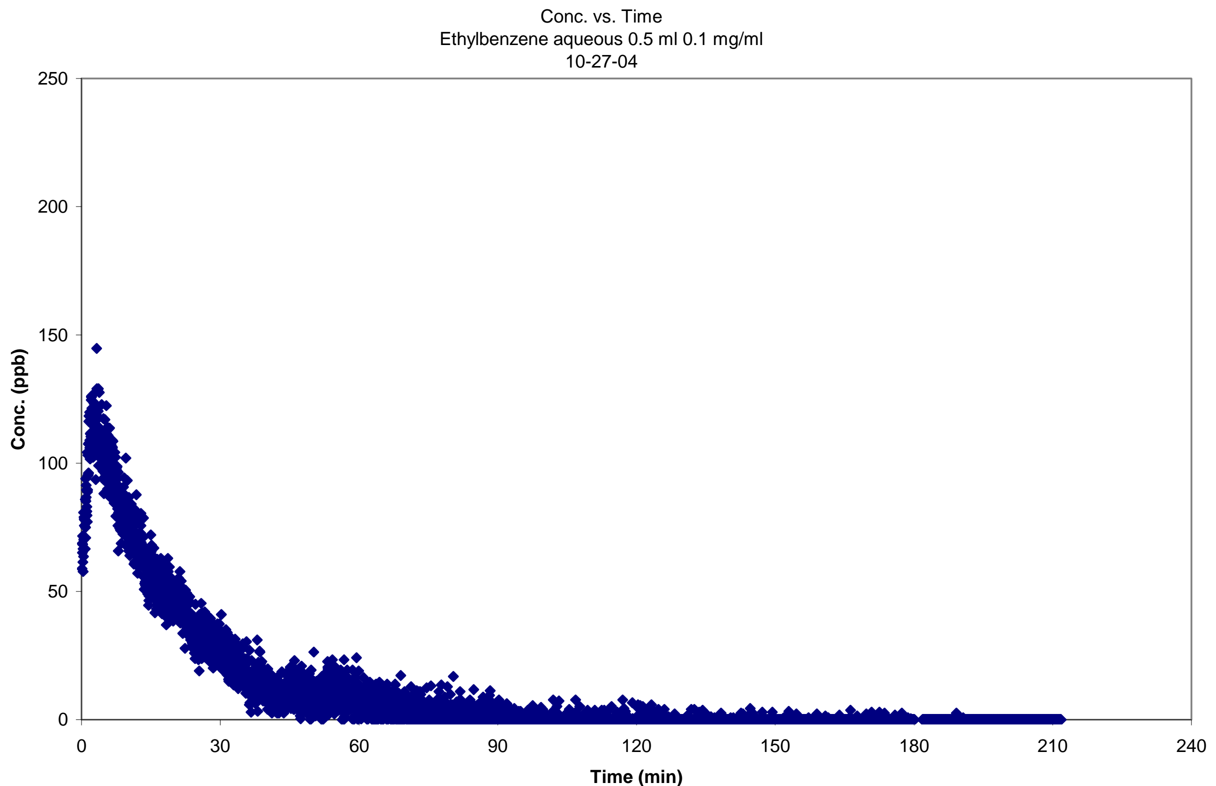

Figure 5. Chamber concentration of ethylbenzene from a single animal exposed to ethylbenzene using a dermal patch system as described.

Dermal exposure to toluene, styrene and ethylbenzene vapors using rats

Male F344 rats, weighing 200-220 g were obtained from Charles River Laboratories (Raleigh, NC), and allowed to acclimate for at least 5 days. The day prior to exposure, rats were anesthetized with a ketamine/xylazine mixture (58.3 mg ketamine + 8.3 mg xylazine/ml, 1.0 mg/kg) and an exposure cell attached as described previously.

Dermal exposures were initiated the day after attachment of the dermal exposure cells. Vaporous samples of test material were added to each exposure cell by addition of a 0.5-µl injection of neat compound into the exposure cell in a manner described under Specific Aim 1. Expired breath from the rats was monitored using the ion-trap mass spectrometer, as described previously, for continual analysis during the exposure period to adequately characterize the absorption kinetics.

Although studies were conducted using a large number of individual animals per test compound for vapor estimations, the resulting exhaled breath measurements were consistently below to detection limit for the ion-trap mass spectrometer. This is possibly due to the limited volume of headspace within the dermal patch system. An example is given for styrene, in Figure 6 below. The absence of meaningful exhaled breath data

precluded the calculation of permeability coefficients. Therefore derivation of permeability coefficients as specified in Aim 3 was not completed.

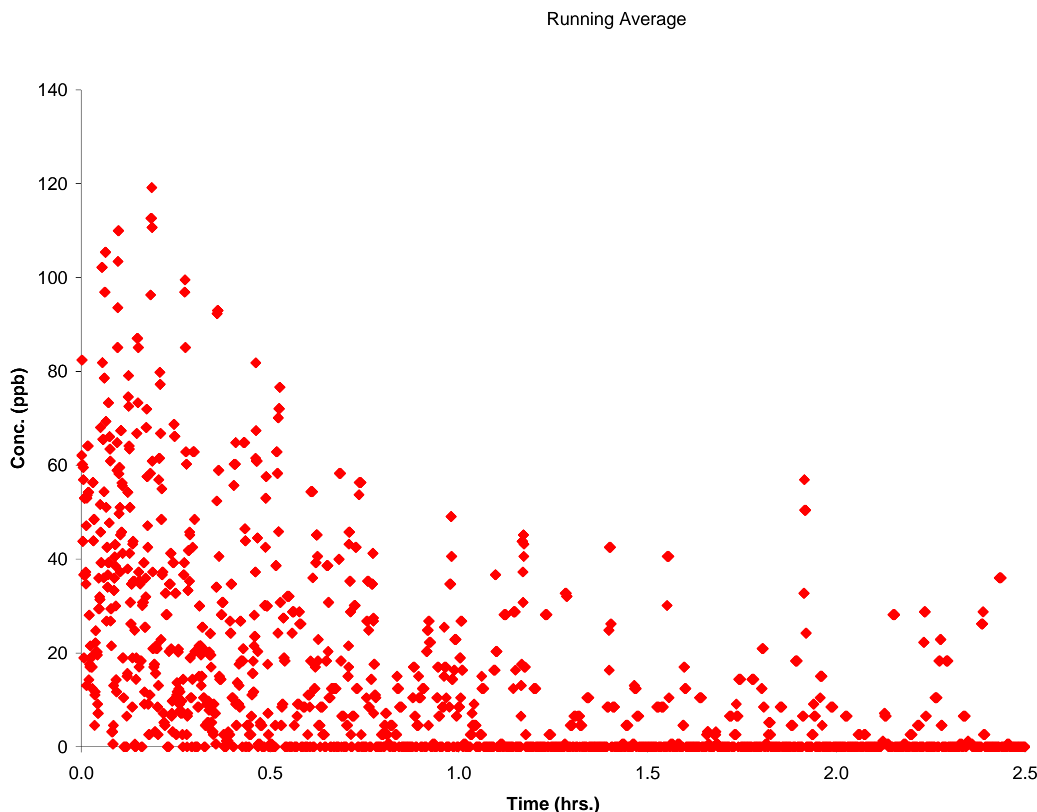

Figure 6. Chamber concentrations of styrene from a single animal exposed to styrene vapor using a dermal patch system as described.

Conclusions

Little information is available to describe the uptake, distribution, metabolism and elimination of MnBK in experimental animals or humans. However, complete development of the rat PBPK model required generation of sufficient data to mathematically describe the interaction of MnBK within the body, both in terms of relative tissue solubility and metabolism. Key data, including partition coefficients, in vivo metabolic rate constants based on gas uptake studies was not available in the literature and were determined here.

Metabolic rate constants determined from gas uptake studies reported here indicate that MnBK is metabolized in a saturable process. To better understand the kinetics of absorption and elimination of MnBK, a series of studies were conducted involing the oral or IP administration of 20 mg/kg MnBK to F344 rats followed by real-time collection and analysis of exhaled breath. The real-time exhalation data demonstrates that MnBK is rapidly absorbed following either oral or IP administration, with peak exhaled breath concentrations occurring approximately 30 min following exposure.

Although the calculation of dermal permeability coefficients was not possible under the conditions studied here, some general relationships between partition coefficients and dermal absorption are possible. For aqueous solvent solutions, the total dermal absorption was observed to be greatest with styrene, followed by ethyl benzene > MnBK > MEK > acetone. This general observed order of absorption is closely related to fat to blood partition coefficients, as shown in Table 3. In comparison to prior studies with aqueous solutions of toluene, total absorption based on partition coefficient is estimated to be greater than ethylbenzene, but less than styrene.

Table 3. Fat to blood partition coefficients

Compound	Fat:air	Blood:air	Fat:blood
Styrene	3373[a]	30[a]	112
Toluene	990[a]	16[a]	62
Ethylbenzene	1556[a]	41[a]	40
MnBK	2034[b]	155[b]	13
Acetone	78[a]	208[a]	0.37
MEK	200[a]	191[a]	1

[a] Data from Meulenberg and Vijverberg (2000)
[b] Data generated in the current project

Several experimental complications precluded the opportunity to collect sufficient numbers of acceptable data sets to allow for dermal permeability coefficients. For example, inadequate volumes of solvent vapors due to the small exposure chamber on the patch system translated into low solvent exhalation and insufficient signal for detection even though analysis used a sensitive MS/MS technique. Studies were attempted using injection of 0.5 µl of the neat test material to the exposure cell through a seal on the glass patch. Preliminary studies using a flat surface indicated that the small volume of neat material was immediately volatilized within the occluded glass cell to generate a significant vapor atmosphere. However, in practice with the patch attached to the back of the animal, the injection of neat material did not volatilize rapidly and data was variable as neat material damaged the skin surface for absorption. In addition, several of the test compounds were fairly insoluble in aqueous solutions, which limited signal detection of exhaled breath levels. On the other hand, several of the solvents were extremely efficient at dissolving the cyanoacrylate adhesive, and thus exposure systems leaked solvent directly into the chamber system. The outcome of this work suggests that a more robust exposure system should be developed to evaluate the dermal bioavailability of solvents.

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