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# Time-resolved cutaneous absorption and permeation rates of methanol in human volunteers

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**Abstract** This paper reports on an experimental study of dermal exposure to neat methanol in human volunteers for the purposes of estimating percutaneous absorption rates, permeation kinetics, baseline (pre-exposure) levels of methanol in blood, and inter- and intrasubject variability. A total of 12 volunteers (seven men and five women) were exposed to methanol via one hand for durations of 0 to 16 min in a total of 65 sessions, making this the largest controlled study of percutaneous absorption for this common solvent. In each session, 14 blood samples were collected sequentially and analyzed for methanol. These data were used to derive absorption rates and delivery kinetics using a two compartment model that accounts for elimination and pre-exposure levels. The pre-exposure methanol concentration in blood was 1.7 ± 0.9 mg $l^{-1}$, and subjects had statistically different mean concentrations. The maximum methanol concentration in blood was reached 1.9 ± 1.0 h after exposure. Delivery rates from skin into blood lagged exposure by 0.5 h, and methanol continued to enter the systemic circulation for 4 h following exposure. While in vitro studies have reported comparable lag times, the prolonged permeation or epidermal reservoir effect for such miscible solvents has not been previously measured. The mean derived absorption rate, 8.1 ± 3.7 mg $cm^{-2}$ $h^{-1}$, is compatible with that found in the other in vivo study of methanol absorption. Both in vivo absorption rate estimates considerably exceed in vitro estimates. The maximum concentration of methanol in blood following an exposure to one hand lasting ~20 min is comparable to that reached following inhalational exposures at a methanol concentration of 200 ppm, the threshold limit value-time weighted average (TLV-TWA). While variability in blood concentrations and absorption rates approached a factor of two, differences between individuals were not statistically significant. The derived absorption and permeation rates provide information regarding kinetics and absorbed dose that can help to interpret biological monitoring data and confirm mathematical models of chemical permeation.

**Key words** Biological monitoring · Exposure · Methanol · Solvent · Skin

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## Introduction

Many chemicals can penetrate the skin's diffusional barriers and enter the systemic circulation via capillaries at the dermo-epidermal junction, and a growing number of studies indicate the importance of the percutaneous exposure pathway (Mattie et al. 1994). Percutaneous exposures can be difficult to predict, although biological monitoring (BM) techniques provide useful tools for many compounds in workplace and some environmental settings, and many predictive models are available (Anderson and Keller 1984; US EPA 1992; Horton et al. 1992; Auton et al. 1994; Wilschut et al. 1995; Roy et al. 1996). However, the interpretation of BM results and modeling predictions depends upon many factors, including the kinetics of uptake, the elimination, speciation and partitioning of the chemicals in the body, the pattern of exposure, and the timing of sample collection. Measurements of absorption rates can aid the interpretation of BM data and provide information helpful in reconstructing past exposures, assessing and controlling current exposures, and predicting future exposures.

Percutaneous absorption of chemical solutes is often represented using a permeability coefficient $k_p$ (cm $h^{-1}$) describing the flux or flow of a compound across a membrane (skin), $J_{m,ss}$ (mg $cm^{-2}$ $h^{-1}$) as a steady-state diffusion process following Fick's law (Grandjean 1990; US EPA 1992)

$$J_{m,ss} = k_p \Delta C = k_{m/v} D_m \Delta C / l_m \quad (1)$$

where $\Delta C$ is the concentration differential across the skin (mg cm$^{-3}$), $k_{m/v}$ is the membrane/vehicle partition coefficient, $D_m$ is the diffusion coefficient in the membrane (cm$^2$ h$^{-1}$), and $l_m$ is the pathlength of chemical diffusion (cm). If the applied permeant concentration $C$ (mg cm$^{-3}$) is much greater than the concentration in the skin, then $\Delta C \approx C$. Pathlength $l_m$ is commonly taken as the thickness of the stratum corneum, the main barrier to permeation, while $D_m$ can be estimated using physical-chemical properties of the permeant and the membrane or, more practically, can be based on experimental absorption rates with the substitution of appropriate values for $k_{m/v}$, $\Delta C$ and $l_m$. Parameters of this model, specifically $D_m$ and $l_m$, must be recognized as bulk or averaged values that only approximately describe the complexity of chemical transport in the highly structured skin, and Fick's law applies to very specific circumstances. Nevertheless, Eq. (1) can provide reasonable approximations in many cases (Grandjean 1990).

The steady-state condition represented by Eq. (1) is reached some time after the initial contact between the permeant and the skin. The "lag time" $\tau$ (h) required to reach near steady-state conditions can be estimated (Scheuplein and Blank 1971) as:

$$\tau = l_m^2 / (6 D_m) \quad (2)$$

and has been tabulated for many compounds (US EPA 1992).

Percutaneous uptake rates and lag times are determined by skin-specific factors, e.g., skin thickness, hydration, temperature and condition, and compound-specific factors, e.g., diffusion coefficient, lipophilicity, polarity, solubility and volatility (Smith 1990; Fiserova-Bergerova et al. 1990). The fate of a compound following absorption may be affected by binding to skin tissues, metabolism in the skin, liver and elsewhere, and partitioning among the body compartments (Wester et al. 1987). A delay between dermal exposure and the maximum body concentration has been attributed to skin resistance, chemical binding, metabolism and partitioning (Fiserova-Bergerova et al. 1990; US EPA 1992; Leung and Paustenbach 1994). Experimental and modeling studies have noted kinetic features, e.g., the time lag represented in Eq. (2), and an "epidermal reservoir" in the stratum corneum for organic chemicals (Hadgraft 1979; Southwell et al. 1984; US EPA 1992; Roy et al. 1996). The time lag has led US EPA (1992) to recommend the use of Fick's second law for dynamic conditions, rather than Eq. (1) (Cleek and Bunge 1993).

Permeation rates can be measured in numerous ways (see particularly Wester and Maibach 1987; Kemppainen and Reifenrath 1990). In vitro techniques typically use excised skin placed in diffusion cells. In vivo techniques include measurements of surface disappearance after dermal application, biological responses, and the use of biological samples, e.g., measurements of radioactivity from labeled compounds or concentrations of parent compounds and metabolites. Percutaneous absorption of neat chemical liquids may not be governed by Fick's first law of steady-state diffusion, and direct in vivo skin contact measurements have been recommended (Leung and Paustenbach 1994). In vivo and in vitro measurements have shown reasonably good agreement for some hydrophilic compounds, but poorer agreement for very hydrophilic or lipophilic compounds (US EPA 1992). Unfortunately, available measurements are scarce and not standardized, and information is generally insufficient to characterize the diversity of skin sites, intersubject variability, different exposure patterns, and permeation kinetics. For ethical and practical reasons, in vivo studies rarely use human subjects, and the species interpolation required from animal data causes additional uncertainty.

## Materials and methods

### Study design and modeling

This paper reports on an experimental study where dermal exposures of methanol were administered to human volunteers. Methanol's toxicity (Kavet and Nauss 1990) and possible use as a motor fuel together suggests that dermal exposures could be widespread and significant.

To reveal permeation kinetics, the study used a series of blood samples collected before and after dermal exposures and a simple two compartment model representing the exposed skin and the rest of the body. Recent physiologically based skin models have depicted three layers of the skin, i.e., the surface layer, stratum corneum and viable tissue, which may be particularly applicable to lipophillic compounds (Auton et al. 1994). However, the one-layer model may be justified given that methanol is not lipophillic. Also, the use of complex models and indirect methods to estimate absorption is likely to result in significant uncertainties given that many model parameters are not well known.

During exposure, the absorption and permeation of the solvent in the skin occur according to Eq. (1) at rate $J_{m,ss}$ over exposed skin area $A$ (cm$^2$). At each time $t$ (min), the concentration of the solvent in exposed skin, $C_{m,t}$ (mg cm$^{-3}$), is a balance between the uptake rate, $J_{m,t}$, and the delivery rate of the solvent from exposed skin to blood and the rest of the body, $J_{b,t}$ (mg cm$^{-2}$ h$^{-1}$):

$$dC_{m,t}/dt = (J_{m,t} - J_{b,t})/(A l_m) \quad (3)$$

The rate of solvent uptake is assumed to reach steady state rapidly during the time the hand is immersed in the solvent, thus $J_{m,t} = J_{m,ss}$ during the exposure. Before and after solvent immersion, $J_{m,t} = 0$. Off-gassing, metabolism in the exposed skin, and other losses are assumed to be negligible. Strictly speaking, $J_{m,ss}$ is a steady-state rate; however, it can be viewed as an average rate over the exposure duration $t_{exp}$ (h) in the following derivation. Only solvent fluxes to and from the skin reservoir are estimated, and not the concentration in the exposed skin $C_{m,t}$, skin depth $l_m$, or volume of the local skin compartment, $A l_m$.

Once in blood, the solvent may be partitioned, diluted among body fluids, metabolized, and eliminated. Assumptions used to derive delivery rate $J_{b,t}$ from concentration measurements in blood include: (1) $J_{b,t} = 0$ prior to skin immersion; (2) $J_{b,t}$ is relatively constant in short intervals so that an average rate $J_{b,i}$ in time period $i$ can be determined; (3) mixing in general circulation and partitioning in the body are fast; and (4) elimination is first order with a known rate constant. The methanol concentration in blood is assumed to reflect the dose and body concentration since partitioning in fatty tissues for this miscible solvent is unimportant. [Methanol's $K_{ow}$ is small, ~0.17, and partition coefficients are near unity, e.g., 1.3 and 1.1 for rich and slowly perfused tissues, respectively

(Horton et al. 1992). Lipophilic compounds require different treatment to account for partitioning.) With these assumptions, the methanol concentration in the body, $C_t$ (mg cm$^{-3}$), is governed by

$$dC_t/dt = AJ_b/V - kC_t \quad (4)$$

where $V$ is the total (distribution) volume of body fluids (cm$^3$) and $k$ is the first-order elimination rate (h$^{-1}$). Flux $J_{b,t}$ is likely to differ from $J_{m,ss}$ as: (1) a lag is likely due to the time for the solvent to be transferred across the skin; (2) a $J_b$ may have separate rate limitation due to low capillary blood flows, solubility limitations, and other reasons; and (3) delivery continues after the exposure ends as solvent in the exposed skin is only gradually depleted.

Concentrations in blood were measured 12 times after the exposure started, allowing $J_{b,i}$ to be estimated in 12 time periods. In each time period, the concentration in blood can be estimated by solving Eq. (4):

$$C_t = AJ_{b,i}/(kV)[1 - \exp(-k(t - t_i)] + C_i \exp(-k(t - t_i)) + C_e \quad (5)$$

where $t_i$ is the start of time period $i$ (h), $C_i$ is the concentration increment above the endogenous level at time $t_i$ (mg cm$^{-3}$), and $C_e$ is the endogenous level of the compound (mg cm$^{-3}$). $C_i$ may represent levels due to some previous exposure. $C_e$ is estimated as the pre-exposure level using the minimum of measurements taken 10 and 15 min prior to exposure.

The area under the curve in period $i$, $AUC_i$ (mg l$^{-1}$ h), i.e., the concentration-time product, is the integral of Eq. (5):

$$AUC_i = \int_{\Delta t_i} C_t\,dt = AJ_{b,i}/(kV)\{\Delta t_i + [\exp(-k\Delta t_i) - 1]/k\} + C_i/k[1 - \exp(-k\Delta t_i)] \quad (6)$$

where $\Delta t_i$ is the duration of the period (h) and $C_e$ is considered to be zero (only concentrations above endogenous levels are of interest). Then, $J_{b,i}$ can be solved as:

$$J_{b,i} = \{AUC_i + C_i/k[\exp(-k\Delta t_i) - 1]\}\,kV/\{A[\Delta t_i + (\exp(-k\Delta t_i) - 1)/k]\} \quad (7)$$

where $AUC_i$ is calculated for each period using pairs of adjacent concentration measurements and the trapezoidal rule, $AUC_i = (C_i + C_{i+1})\Delta t_i/2$. Delivery rate $J_{b,i}$ accounts for initial and endogenous concentration levels ($C_i$ and $C_e$, respectively), elimination (at rate $k$), and dilution (into $V$). The total amount of solvent entering blood (calculated as $\sum_{i=1,\ldots,12} J_{b,i}\Delta t_i$) is equal to that entering the skin over the exposure duration $t_{exp}$ (h) (estimated as $J_{m,ss}\ t_{exp}$), so the absorption rate estimate is:

$$J_{m,ss} = \left(\sum_{i=1,\ldots,12} J_{b,i}\Delta t_i\right)/t_{exp} \quad (8)$$

Finally, permeability coefficient $K_p$ can be determined from Eq. (1). In summary, Eq. (7) uses adjacent observations from the sequence of blood samples to determine the delivery rate of methanol to blood from exposed skin for that period, and Eq. (8) integrates over all periods to derive the overall permeability coefficient in which absorption and permeability are assumed to occur at a constant rate over exposure duration $t_{exp}$. This approach is motivated by the short exposure periods and by the observed trends of methanol concentrations.

The derived absorption and delivery rates use subject-specific estimates of distribution volume $V$ based on subject weight and scaled from the average individual given by Guyton (1994) as weighing 70 kg and having $V = 40$ l of body fluids. A methanol half-life of 1.56 h (Batterman et al. 1996c) was used.

Another measure of exposure is the entire area-under-the-curve, AUC (mg l$^{-1}$ h), measured in the experiment to 7 h after exposure and defined as $AUC = \sum_{i=1,\ldots,12} AUC_i$. Given the definition of $C_i$, the AUC represents levels above the exogenous level.

### Subjects and methods

The dermal exposure protocol and sample analysis procedure have been described elsewhere (Franzblau et al. 1995; Batterman et al. 1996a, b) and only a brief description is provided here. Exposure sessions for each volunteer were scheduled at least 1 week apart. In a session, a subject's left hand to the distal wrist crease was placed in a beaker of neat analytical grade methanol (99.8% pure, EM Science, Gibbstown, N.J.) for 2, 4, 8 or 16 min. To avoid inhalation of methanol vapor, the beaker was placed inside a laboratory fume hood, and subjects placed their arm through a slit in plastic sheeting that covered the hood opening. At the end of the exposure, the hand was air dried. Blood samples were collected 15 and 10 min prior to exposure, and at 0, 15, 30, and 45 min, 1, 1.5, 2, 3, 4, 5, 6, and 7 h following the exposure. A similar protocol, but without exposure, was used as a control for each subject.

Blood samples were collected into "gray top" Vacutainer tubes (containing potassium oxalate and sodium fluoride) from the arm of the unexposed hand. Tubes were kept on ice or refrigerated at 4 °C until analyzed. Methanol concentrations were determined by splitting each blood sample into two replicates, and averaging the results of analyses of each replicate using an automated headspace sampler, gas chromatography and flame ionization detection. For blood, the detection limit was ~0.5 mg l$^{-1}$, and the precision was 3%–5%.

The hand area to the distal crease of each subject was measured by tracing the outline of the exposed hand and measuring finger and hand thickness (depth) at numerous locations. These data were then converted into area estimates by assuming simple geometric shapes for the palm and fingers. Skin conditions, e.g., roughness and presence of damage, were noted by visual examination.

Five women (ages 41–63 years) and seven men (ages 22–54 years), participated in the experiment. Not all subjects participated in every exposure, and several subjects repeated some exposures. Most subjects repeated the 8-min exposure session. Subjects were permitted to eat and drink freely during the experiment except for alcoholic beverages during the session and the preceding 24 h. None had known occupational or avocational exposure to methanol, formic acid or formaldehyde. Two subjects were smokers (males 11 and 14). All subjects were white except one who was Afro-American (male 3). Subjects were instructed not to use skin creams, moisturizers, etc., during the session. The subjects provided written informed consent using forms and protocols approved by the University of Michigan School of Public Health.

## Results

### Subject characteristics

Table 1 summarizes results of the dermal exposure experiments. The number of sessions for each exposure duration ranged from 8 (2 min duration) to 21 (8 min duration). While the subjects varied somewhat for each exposure duration, the average weight (80 ± 14 kg) and hand area (491 ± 60 cm$^2$) did not vary significantly. However, the number of male participants in the 2-min session dropped from the overall average of eight to only three, giving a sample too small to be representative. Tables 2 and 3 present additional results, showing results grouped by subject and sex, respectively. Among the 12 subjects, hand area was highly correlated with subject height ($r = 0.92$) and to a lesser degree with weight ($r = 0.40$). Also, males in the study were younger and generally had greater hand area, weight and height than females.

Several subjects had rough to very rough skin, particularly males 1 and 11. Three subjects (males 1, 12 and 13) had skin damage at finger tips, apparently due to nail-biting. After especially the longer exposures, the exposed hand was temporarily whitened in color and very dry.

**Table 1** Subject characteristics, baseline concentrations, maximum concentrations, and area under the curve (AUC), all averaged by exposure duration. Maximum concentration and AUC corrected for baseline concentration. Righthand column (*All*) shows statistics for all exposure durations ($n = 65$). Standard deviation in parentheses

| | Exposure duration | | | | | All |
|---|---|---|---|---|---|---|
| | 0 min | 2 min | 4 min | 8 min | 16 min | |
| Sample size | 12 | 8 | 13 | 21 | 11 | 65 |
| Male (%) | 58 | 38 | 77 | 62 | 64 | 62 |
| Weight (kg) | 79 (14) | 80 (16) | 82 (15) | 79 (13) | 80 (15) | 80 (14) |
| Hand area ($cm^2$) | 486 (60) | 470 (69) | 508 (60) | 492 (58) | 491 (61) | 491 (60) |
| Baseline concentration (mg $l^{-1}$) | | | | | | |
| Mean | 1.6 (0.8) | 2.1 (1.3) | 1.6 (0.8) | 1.6 (0.6) | 2.0 (1.5) | 1.7 (0.9) |
| Minimum | 0.7 | 0.5 | 0.7 | 0.7 | 0.4 | 0.4 |
| Maximum | 3.3 | 4.1 | 3.5 | 2.7 | 4.7 | 4.7 |
| Maximum concentration above baseline (mg $l^{-1}$) | | | | | | |
| Mean | 0.8 (0.6) | 2.7 (0.9) | 2.7 (1.2) | 5.9 (2.4) | 11.5 (2.3) | – |
| Minimum | −0.1 | 1.4 | 0.7 | 2.6 | 8.1 | – |
| Maximum | 2.3 | 3.7 | 5.9 | 12.5 | 16.5 | – |
| Lag time for maximum concentration (hours after exposure) | | | | | | |
| Mean | – | 2.2 (1.3) | 1.5 (0.9) | 1.9 (1.1) | 1.8 (0.8) | 1.9 (1.0) |
| Minimum | – | 0.8 | 0.5 | 0.8 | 0.8 | 0.7 |
| Maximum | – | 5.0 | 4.0 | 5.0 | 3.0 | 4.3 |
| Area-under-the-curve (mg $l^{-1}$ h) | | | | | | |
| Mean | −0.3 (2.5) | 8.8 (4.1) | 9.3 (6.6) | 20.9 (6.5) | 41.2 (11.2) | – |
| Minimum | −4.8 | 4.2 | 0.7 | 10.7 | 17.4 | – |
| Maximum | 3.7 | 14.2 | 23.0 | 35.0 | 55.3 | – |

**Table 2** Subject characteristics and study results averaged by subject. Maximum concentrations and AUC corrected for baseline. Coefficients of variation (COV) are calculated for maximum and AUC for 8-min dermal exposure, and are based on two sessions for each subject, except for subjects 5, 4 and 27 (one session each). Skin damage: *R* rough, *R+* very rough, *B* = apparent nail biting; *n* sample size

| | Subject number, males | | | | | | | Subject number, females | | | | | Mean |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 3 | 5 | 11 | 12 | 13 | 14 | 4 | 24 | 25 | 26 | 27 | |
| Age (years) | 32 | 30 | 54 | 30 | 22 | 33 | 26 | 49 | 54 | 41 | 63 | 53 | 41 |
| Weight (kg) | 87 | 103 | 70 | 80 | 74 | 86 | 63 | 66 | 70 | 79 | 63 | 105 | 79 |
| Height (cm) | 183 | 191 | 174 | 186 | 183 | 173 | 174 | 169 | 167 | 166 | 164 | 164 | 174 |
| Hand area ($cm^2$) | 514 | 600 | 522 | 532 | 531 | 502 | 511 | 422 | 440 | 407 | 447 | 409 | 486 |
| Skin condition | R+, B | R | R | R+ | B | B | – | R | – | – | R | R | – |
| Baseline concentration (mg $l^{-1}$) | | | | | | | | | | | | | |
| Mean | 1.6 | 1.7 | 2.2 | 0.9 | 0.9 | 1.0 | 1.1 | 1.9 | 2.3 | 2.7 | 2.9 | 1.9 | 1.7 |
| SD | 0.7 | 0.5 | 1.1 | 0.3 | 0.1 | 0.5 | 0.5 | 0.4 | 0.5 | 1.5 | 1.1 | 0.6 | 0.7 |
| COV (%) | 47.0 | 32.6 | 48.4 | 39.9 | 11.4 | 49.2 | 43.8 | 21.7 | 21.2 | 56.4 | 36.2 | 34.2 | 36.9 |
| *n* | 7 | 7 | 6 | 5 | 5 | 5 | 5 | 6 | 4 | 5 | 5 | 5 | 5.4 |
| Maximum concentration (mg $l^{-1}$) | | | | | | | | | | | | | |
| 0 min | 0.7 | 1.3 | 1.2 | 0.5 | 0.5 | 2.3 | 0.2 | 1.3 | 0.7 | −0.1 | 0.3 | 0.4 | 0.8 |
| 2 min | 3.7 | 3.7 | 2.9 | – | – | – | – | 3.5 | 2.9 | 1.6 | 1.4 | 2.2 | 2.7 |
| 4 min | 3.3 | 3.1 | 1.9 | 5.9 | 1.8 | 2.5 | 2.3 | 2.2 | – | – | – | 2.3 | 2.8 |
| 8 min | 9.2 | 5.4 | 3.7 | 6.0 | 4.4 | 6.5 | 7.1 | 3.1 | 8.4 | 4.4 | 3.6 | 7.7 | 5.8 |
| 16 min | 16.5 | 11.9 | 9.1 | 12.6 | 11.6 | 13.3 | 12.5 | 10.1 | – | 8.1 | 10.5 | 10.6 | 11.5 |
| AUC (mg $l^{-1}$ h) | | | | | | | | | | | | | |
| 0 min | −4.8 | 3.4 | 0.7 | 0.3 | 0.3 | 1.1 | −2.5 | 3.7 | 0.8 | −2.6 | −1.7 | −1.8 | −0.3 |
| 2 min | 14.2 | 13.3 | 13.2 | – | – | – | – | 7.1 | 7.4 | 4.6 | 4.2 | 6.4 | 8.8 |
| 4 min | 10.3 | 12.8 | 3.3 | 23.0 | 3.4 | 10.5 | 7.1 | 10.0 | – | – | – | 4.2 | 9.4 |
| 8 min | 27.8 | 24.0 | 20.6 | 24.8 | 20.8 | 21.1 | 19.5 | 11.1 | 25.3 | 16.5 | 12.8 | 21.4 | 20.5 |
| 16 min | 55.3 | 30.7 | 47.2 | 54.6 | 44.6 | 36.0 | 45.2 | 48.4 | – | 17.4 | 39.0 | 34.4 | 41.2 |

## Baseline concentrations

The two pre-exposure measurements for a subject in a particular session were generally similar. For individual sessions, baseline methanol levels averaged 1.7 ± 0.9 mg $l^{-1}$ ($n = 65$) and ranged from 0.4 to 4.7 mg $l^{-1}$ (Table 1). Average baseline levels among the 12 subjects differed significantly ($P = 0.0001$) and means ranged from 0.9 to 2.9 mg $l^{-1}$ (Table 2). The average baseline level for females (2.4 ± 0.8 mg $l^{-1}$) was significantly

**Table 3** Subject characteristics and study results averaged by exposure duration and sex. Ratio shows mean male:female ratio. Standard deviation in parentheses. Standard deviation of ratio obtained by Gaussian quadrature. *Asterisk* denotes that average and standard deviation excludes 0- and 2-min dermal exposure durations

| | | Exposure duration | | | | | Average |
|---|---|---|---|---|---|---|---|
| | | 0 min | 2 min | 4 min | 8 min | 16 min | |
| Hand area ($cm^2$) | Male | 530 (32.7) | 546 (47.6) | 535 (35.6) | 531 (32.6) | 530 (32.7) | 534 (36) |
| | Female | 425 (18.1) | 425 (18.1) | 418 (7.5) | 427 (18.2) | 421 (18.5) | 423 (16) |
| | Ratio | 1.25 (0.09) | 1.28 (0.12) | 1.28 (0.09) | 1.24 (0.09) | 1.26 (0.10) | 1.26 (0.10) |
| Weight (kg) | Male | 80 (13.0) | 87 (16.1) | 82 (13.4) | 81 (12.7) | 80 (13.0) | 82.2 (13.6) |
| | Female | 76 (16.8) | 76 (16.8) | 79 (22.3) | 74 (13.7) | 78 (18.9) | 76.8 (17.7) |
| | Ratio | 1.05 (0.29) | 1.14 (0.33) | 1.05 (0.34) | 1.09 (0.26) | 1.03 (0.30) | 1.07 (0.30) |
| Baseline concentration ($mg\ l^{-1}$) | Male | 1.4 (0.9) | 1.1 (0.5) | 1.5 (0.9) | 1.4 (0.5) | 1.3 (0.9) | 1.3 (0.8) |
| | Female | 2.0 (0.4) | 2.8 (1.2) | 1.9 (0.5) | 1.8 (0.5) | 3.4 (1.3) | 2.4 (0.8) |
| | Ratio | 0.69 (0.48) | 0.38 (0.25) | 0.74 (0.50) | 0.78 (0.37) | 0.37 (0.29) | 0.59 (0.38) |
| Maximum concentration ($mg\ l^{-1}$) | Male | 1.0 (0.7) | 3.4 (0.4) | 2.9 (1.4) | 6.2 (2.4) | 12.5 (2.2) | – |
| | Female | 0.5 (0.5) | 2.3 (0.9) | 2.2 (0.1) | 5.5 (2.5) | 9.8 (1.2) | – |
| | Ratio | 1.80 (2.22) | 1.48 (0.59) | 1.30 (0.61) | 1.14 (0.69) | 1.27 (0.27) | 1.24* (0.52) |
| AUC ($mg\ l^{-1}$ h) | Male | −0.2 (2.7) | 13.6 (0.5) | 9.7 (7.3) | 22.8 (5.0) | 44.8 (9.0) | – |
| | Female | −0.3 (2.6) | 5.9 (1.5) | 8.1 (3.7) | 17.7 (7.6) | 34.8 (13.0) | – |
| | Ratio | 0.67 (9.74) | 2.29 (0.58) | 1.20 (1.06) | 1.29 (0.62) | 1.29 (0.55) | 1.26* (0.74) |

higher than that for males ($1.3 \pm 0.8\ mg\ l^{-1}$, $P < 0.0001$, Table 3). Overall, baseline line measurements were quite variable with a coefficient of variation (COV) of 55%. This variability may be attributed to both "individual" or intersubject variability, and to "session" or intrasubject variability. The average COV among subjects was 37%. The remainder, a roughly comparable amount, was attributed to intrasubject variability. Both sources of variability are important if small differences in methanol levels are to be distinguished.

## Maximum concentrations

Maximum concentrations reported are the peak methanol level in blood following the exposure, corrected for the baseline level (which is subtracted). Tables 1–3 list maxima overall and averaged by subject and sex. Figure 1 plots maximum concentrations versus exposure duration, showing a strong linear relationship ($r = 0.89$). Moderate scatter is seen, especially for the 8-min exposure duration where the largest number (all 12) of subjects was tested. However, differences in means of the 8-min maxima among subjects were not statistically significant ($P = 0.19$ in a one-factor ANOVA). Tests for intersubject differences using all exposure durations simultaneously also showed no effect of subject ($P = 0.17$ in a two-factor ANOVA). Based on the 8-min exposures, the average intra-subject COV was 31%, compared to the total (intra- plus intersubject) variability of 41%.

While intersubject differences in maximum concentrations were not statistically significant, average male-to-female ratios were fairly constant for the longer exposure durations, and maximum concentrations for males averaged 24% higher than for females (Table 3).

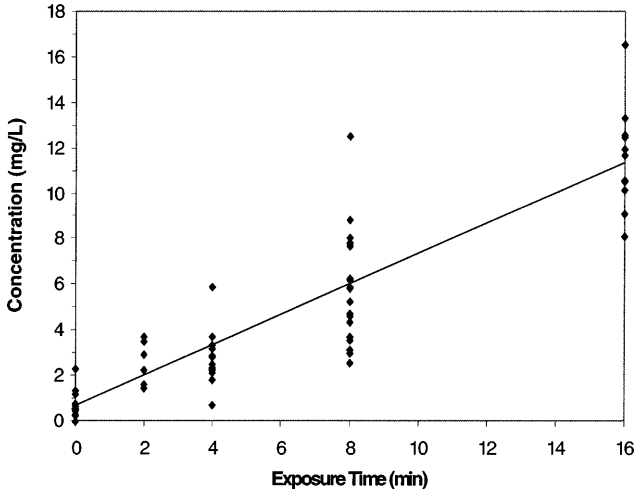


**Fig. 1** Maximum methanol concentrations in blood, corrected for baseline, versus duration of neat dermal exposures to one hand. Trend line: $Y = 0.668X + 0.660$, $R^2 = 0.79$

This statistic excludes 0- and 2-min exposure results, since concentration increases above baseline levels were small and peaks were not consistently detected in these experiments. Peak concentrations for any exposure duration were variable, e.g., the ranges for 8- and 16-min exposures were 2.6–12.5 and 8.1–16.5 $mg\ l^{-1}$, respectively. Baseline variability of a few milligrams per liter cannot account for these differences.

Maximum concentrations occurred an average of $1.9 \pm 1.0$ h after the end of the exposure (Table 1). For individual sessions, this time had considerable variability, especially for the 2-min exposures. Fig. 2 shows that methanol concentrations in blood increased to near peak levels ~1 h following exposure, had a broad and flat peak at 1.9 h, then decreased due to the clearance of

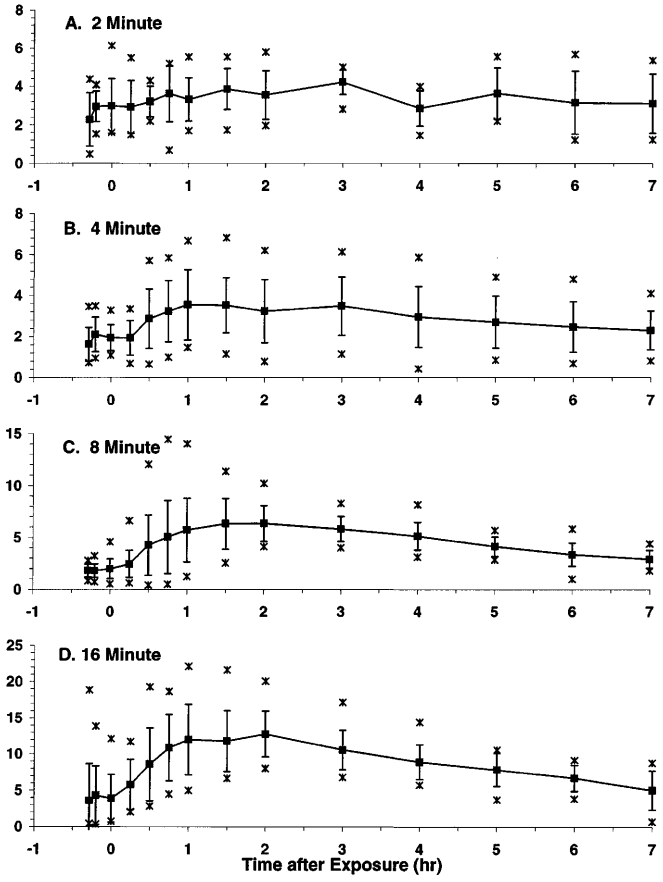


**Fig. 2** Methanol concentrations in blood (mg $l^{-1}$) before and following neat dermal exposures of 2-, 4-, 8- and 16-min duration. *Line* indicates mean; *error bars* show standard deviation; *points* indicate extrema

methanol. This pattern is especially clear for 8- and 16-min exposures.

Effects of body weight and exposed skin area on maximum concentrations were investigated in several analyses. If maxima and exposure durations are linearly related, as indicated by Fig. 1, then the maximum concentration divided by the corresponding exposure duration allows the comparison of data collected at different exposure durations. The linear correlation coefficients of this quotient to exposed skin area and body weight were 0.12 and 0.19, respectively. These small coefficients explain a negligible fraction of the observed variance. Maxima had yet lower correlation to an exposed skin area/body weight quotient to which doses, if all else is constant, should be proportional. Various multiple regression models designed to identify possible interactions showed inconsistent or weak relationships. To avoid errors due to the linearity assumption, analysis was then restricted to the 8-min data. Nevertheless, results defied easy characterization. For example, concentration maxima tended to increase with body weight ($r = 0.46$) and decrease with hand area ($r = -0.07$); the opposite was expected. This analysis may indicate the importance of inter- and intrasubject variability (e.g., skin differences between subjects and skin condition), that maxima may not be representative, and/or the presence of confounding among the variables. Some confounding seems likely given the limited number of subjects and the correlation among hand area, age, sex, and weight.

## Area-under-the-curve

Statistics of the AUC are presented in Tables 1–3. Figure 3 plots AUC versus exposure duration, showing high correlation ($r = 0.89$). Concentration maxima and AUCs were highly correlated ($r = 0.935, n = 65$). Based on the 8-min data, the average intrasubject COV was 26% and the total (intra- plus intersubject) COV was 31%. These COVs are slightly lower than comparable statistics for the maximum. Like the maximum concentrations, intersubject differences in mean AUCs were not statistically significant for the 8-min exposure ($P = 0.53$) or for all data ($P = 0.16$) in one- and two-factor ANOVAs, respectively. Using the 8-min data, the correlation coefficient between the AUC and hand area was 0.55, in line with expectations (unlike concentration maxima), but still rather low. As Ravis (1990) has stated, for the reason that the AUC represents a cumulative measurement, it is superior to single concentration measurements like the maximum. However, the results indicate that a number of factors influence uptake, and we now apply the model presented earlier.

## Permeation and delivery rates

Delivery rates $J_{b,i}$ were estimated for each measurement interval and session to derive the trends shown in Fig. 4. Methanol delivery into blood began during or immediately after exposure and reached a maximum rate ~0.5 h after the exposure. Over the next several hours, delivery

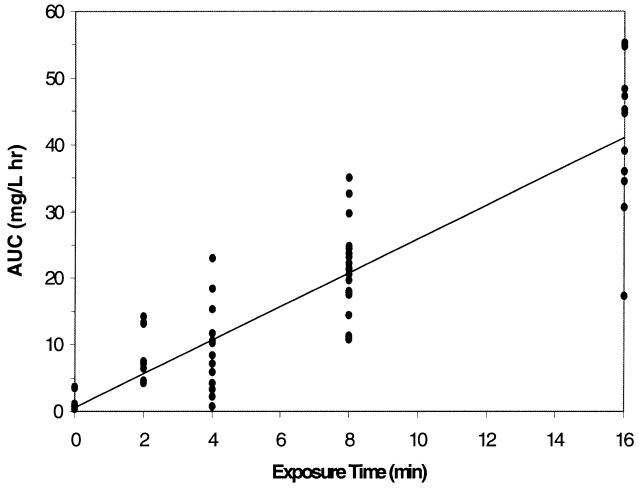


**Fig. 3** Area-under-the-curve (concentration–time product), corrected for baseline, versus duration of the exposure to one hand. Trend line: $Y = 2.54X + 0.533$, $R^2 = 0.80$

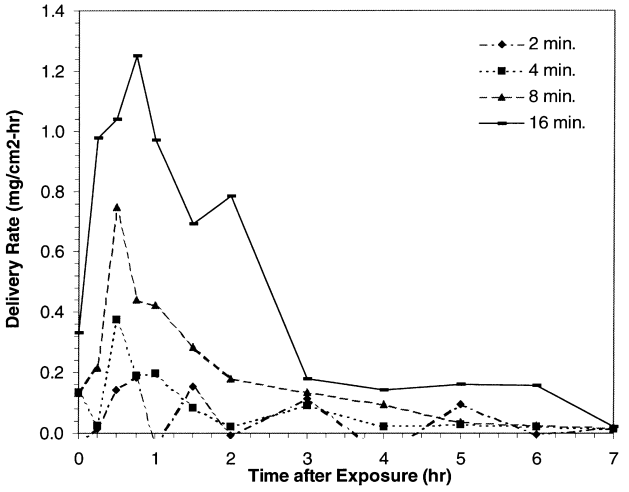


**Fig. 4** Derived delivery rates of methanol versus time after exposure for 2-, 4-, 8- and 16-min exposure durations

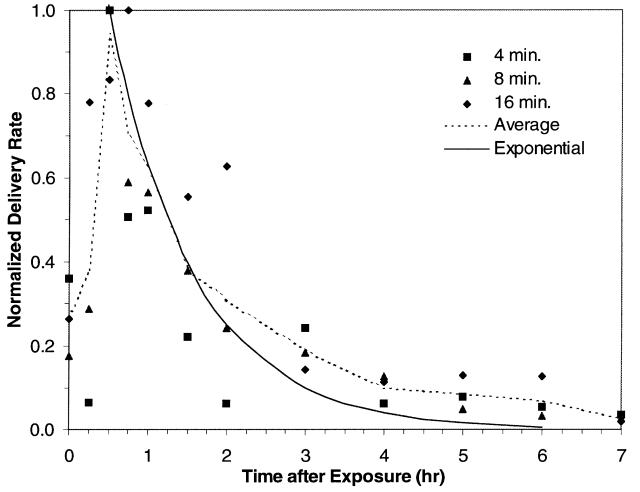


**Fig. 5** Normalized delivery rates (shown as points), average trend, and exponential model fit to 4- to 16-min data. Exponential model has a 0.75 h half-life. Normalized to maximum rate for each duration, as shown in Table 4

rates gradually decreased. While the 2-and 4-min experiments showed a degree of scatter, trends were similar. The maximum delivery rates increased with exposure duration and reached 1.25 mg $cm^{-2}$ $h^{-1}$ in the 16-min experiments (Table 4).

To further illustrate transient behavior, trend lines in Fig. 4 were scaled to their corresponding maximum (Table 4) and plotted in Fig. 5. Trends of the scaled delivery rates (points) and the average (line) were similar and showed no effect of exposure duration. The decrease 0.5 h after exposure was fit to an exponential model with a half-life of 0.75 h (continuous line in Fig. 5). This model and the data indicate that delivery of methanol into blood continued for ~4 h after the exposure ceased.

Typically, permeation is expressed as the average uptake rate into skin from a solvent reservoir over the duration of the exposure, rather than as a possibly slow and prolonged delivery rate through skin and into blood. Equation (8) was used to obtain the steady-state absorption rate consistent with this terminology and Eq. (1). The derived absorption rate averaged 8.1 ± 3.7 mg $cm^{-2}$ $h^{-1}$ and was consistent across exposure durations. The variability of the rate, calculated as the standard deviation across sessions at each exposure duration (Table 4), includes inter- and intrasubject variability.

Table 4 also lists the total methanol uptake for the "average" subject using the experimental estimate and two literature estimates. The experimental estimate uses the derived absorption rate and the average exposed skin area. The first literature estimate is based on an in vitro study by Southwell et al. (1984) which used eight tests of unsupported, elderly, Caucasian, midline abdominal skin in a glass diffusion cell held at 30 °C where an average absorption rate of 1.27 mg $cm^{-2}$ $h^{-1}$ was found (converted from the permeation rate reported). The second literature estimate is based on an in vivo study by Dutkiewicz et al. (1980) which used 22 tests of three subjects where methanol was applied in a closed cell to forearm skin for 15 to 60 min. The average absorption rate measured was 11.7 mg $cm^{-2}$ $h^{-1}$, close to 10 times Southwell's in vitro rate. The uptake based on the derived absorption rates is between the two literature estimates; the best-estimate rate (8.1 mg $cm^{-2}$ $h^{-1}$) is close to that of Dukiewicz et al. (1980). Finally, for demonstration purposes only, Table 4 shows a crude uptake

**Table 4** Derived delivery and absorption rates, averaged by exposure duration and sex. Total uptake estimated for "average" subject (80 kg, 491 $cm^2$ exposed skin area) calculated using experimental results and two literature values

| Parameter | Exposure duration (min) | | | | Average |
|---|---|---|---|---|---|
| | 2 min | 4 min | 8 min | 16 min | |
| Maximum delivery rate (mg $cm^{-2}$ $h^{-1}$) | 0.18 | 0.38 | 0.75 | 1.25 | – |
| Absorption rate (mg $cm^{-2}$ $h^{-1}$) | | | | | |
| Average | 8.71 | 6.93 | 7.74 | 8.94 | 8.08 |
| SD | (4.70) | (4.97) | (2.80) | (2.29) | (3.69) |
| Total absorption (mg) | | | | | |
| Using absorption rate | 143 | 227 | 507 | 1170 | – |
| Southwell et al. (1993) | 21 | 41 | 83 | 166 | – |
| Dukiewicz et al. (1984) | 188 | 376 | 753 | 1506 | – |
| Using Maximum Concentration[a] | 129 | 129 | 279 | 543 | – |

[a] Total mass of methanol in body (mg) based on maximum concentration and distribution volume

measure based on the maximum concentration in blood multiplied by the body volume. As this calculation does not account for elimination and kinetics, the true uptake is considerably underestimated. Thus, such estimates should not be used to estimate dose.

### Lag time estimates

The lag time necessary to reach the maximum permeation rate can be interpreted using Eqs. (1 and 2). The thickness of the stratum corneum on the hand varies widely, from 400 μm on the palm to a 49 μm on the back of the hand (Scheuplein and Blank 1971). (Note that these thicknesses considerably exceed those at most other skin sites, which range from 10 to 40 μm.) By substituting the average permeation rate (8.1 $cm^{-2}$ $h^{-1}$) and a lag time $\tau$ of 30 min in Eqs. (1) and (2), the estimated effective pathlength $l_m$ is 307 μm. Alternatively, lag times may be bracketed for $l_m$ ranging from 400 to 49 μm (for the palm and back of the hand, respectively), giving 5 min $< \tau <$ 40 min. These estimates ignore effects of the viable epidermis and the ''tortuous'' diffusion path in the stratum corneum. Acknowledging their approximate nature, the observed lag times appear reasonable.

## Discussion

### Significance of dermal exposures

The biological exposure index (BEI) for urinary methanol is 15 mg $l^{-1}$ (ACGIH 1994), a level found, on average, after several hours of inhalational exposure at the methanol threshold limit value (TLV), 200 ppm (Franzblau et al. 1995). Because blood-to-urine partitioning of methanol is near unity, methanol concentrations in blood are similar to those in urine, although urinary levels lag by ~2 h (Batterman et al. 1996b). Neglecting lags and partitioning, the longer (16 min) dermal exposures in this study yielded concentrations of methanol in blood that approached the methanol BEI, and the dose to one individual (male 1 with the most severe skin damage) exceeded the BEI. Extrapolating our results, an exposure to one hand lasting 18–21 min (depending on whether or not baseline is included) would reach, on average, the 15 mg $l^{-1}$ BEI. Thus, this study offers good evidence that brief skin contact to solvents can cause significant exposures. Indeed, the literature contains several case reports of severe percutaneous uptake and toxicity of methanol (Lazariew 1954; Downie et al. 1992).

### Comparison to literature estimates

The average derived absorption rate (8.1 ± 3.7 mg $cm^{-2}$ $h^{-1}$) is compatible with that found in the other known in vivo study (11.5 mg $cm^{-2}$ $h^{-1}$; Dutkiewicz et al. 1980). This study used exposure durations from 15 to 60 min, a forearm site, and only three subjects. Some effect of exposure duration was noted, and 15-min experiments yielded a lower permeation rate (8.8 mg $cm^{-2}$ $h^{-1}$) very close to our results. Several factors may account for differences between the studies. Percutaneous absorption is significantly affected by the site of application (Maibach et al. 1971), and large differences may be attributable to differences between hand and forearm sites. Also, as discussed below, the variability of skin appears to control intra- and intersubject uptake. Dutkiewicz et al. (1980) did not specify subject or skin characteristics. Still, results are remarkably similar considering the different measurement approaches used, i.e., Dutkiewicz et al. (1980) quantified absorption by measuring the disappearance of methanol from the skin surface; rates here are based on methanol entering and measured in blood. The technique used by Dutkiewicz et al. has been criticized as rates of absorption by systemic circulation and uptake by the stratum corneum may be combined (US EPA 1992).

Results can also be compared with those in two in vitro studies. In addition to the study of Southwell et al. (1984) which found a $K_p$ = 0.0016 cm $h^{-1}$ (absorption rate = 1.27 mg $cm^{-2}$ $h^{-1}$), Scheuplein and Blank (1973) also used human abdominal tissue and determined $K_p$ = 0.0005 cm $h^{-1}$ (absorption rate = 0.4 mg $cm^{-2}$ $h^{-1}$). It should be noted that Scheuplein and Blank used a dilute (0.1 M) aqueous methanol solution (the other studies used neat methanol). The varied in vitro estimates may be explained, in part, by differences between uptake rates from dilute aqueous and neat solutions (Leung and Paustenbach 1994). Still, Southwell's $K_p$ value is recommended by US EPA in an interim guidance document for the purpose of estimating dermal exposures from environmental pollutants (US EPA 1992). Our data show that absorption rates are 6 times higher for exposures to hands; Dutkiewicz estimated rates 7 to 9 times higher for the forearm. The consistency of the in vivo results suggests that the guidance document requires revision.

### Use and interpretation of derived absorption and permeation rates

The derived permeation and absorption rates account for endogenous methanol production, previous exposure, elimination, and transport through the exposed skin. Results show a lag of ~30 min before the peak methanol permeation rate is reached, and a ~4 h period following exposure of continued methanol delivery into blood, presumably from the exposed skin acting as a reservoir of methanol. The lag and reservoir effects were consistent in all exposure sessions, although trends were less clear with the short (2 and 4 min) exposures as methanol concentrations in blood did not rise much above baseline levels. The similarity between the (~0.5 h)

lag to reach maximum permeation rates and the post-maximum delivery decay rate (0.75 h half-life) may indicate the same controlling process, probably diffusive transport across the stratum corneum and the viable epidermis. Estimated permeation rates and lag times are consistent with this explanation. However, skin on the hand is very diverse, e.g., the great variation in the thickness of the stratum corneum between the palm and other areas has been noted. Such differences suggest that mechanistic modeling may require disaggregation by skin site, e.g., several sets of parameters for various regions of the hand. While evaluations at more uniform and better characterized skin sites might simplify analysis, the hand is one of the most likely sites of dermal exposure.

While the "epidermal reservoir" is generally believed to be active for lipophilic compounds (Hadgraft 1979), our results suggest a similar mechanism for methanol, which is hydrophillic. In a related study, the persistence of high methanol fluxes from exposed skin to air led to the same suggestion, a reservoir in exposed skin, i.e., cells, interstitial spaces of the stratum corneum, or other structures in the dermis (Batterman et al. 1996b). If unaccounted for, the reservoir effect can bias estimates of clearance rates. For example, the apparent elimination half-life based on Fig. 2d is ~4 h, over twice the true rate.

If the clearance rate is slow and the permeation through skin is rapid for a compound, then the timing of BM measurements is not critical. Given an appropriate BM measurement, the absorbed dose and, if exposure characteristics are known, permeation and absorption rates can be estimated. This is only approximately true for methanol. The trend of methanol concentrations in blood showed a broad and relatively flat peak 1–3 h following exposure due to an approximate balance between permeation and elimination. The interpretations of BM data become difficult for compounds with clearance times similar to or less than permeation lag times. Calculated lag times vary over a large range, from minutes (for acetaldehyde, ethleneimine, *m*-xylene) to days (for chlordane, DDT, dieldrin, endrin, heptachlor; US EPA 1992). For methanol, in vitro experiments show lag times of ~0.4 h for methanol (Southwell et al. 1984); a mechanistic model indicates that ~0.5 h is required to reach steady-state permeation conditions for an acetone solute (Shatkin and Brown 1991); and our data show a lag time of ~0.5 h for methanol permeation and ~0.75 h reservoir half-life. Without accounting for lags and clearance, the total chemical uptake estimated using biological monitoring will be underestimated.

In practice, few occupational or environmental studies will have the luxury of collecting blood or other biological samples at short intervals following exposure, and it is unlikely that pre-exposure levels will be checked. Additionally, dermal exposures may occur at several skin sites and at several times, and may be combined with vapor inhalation or possibly gastrointestinal absorption. Pharmacokinetic models may help to compensate for limitations of BM measurements related to clearance, permeation, and time of sampling vis-à-vis time of exposure. The advantage of the suggested method is its ability to derive kinetics and the dose using simple models that require few parameters. The method is applicable to other compounds if the distribution of the compound in the body and the elimination rate are known.

## Sensitivity of derived absorption estimates

The accuracy of the delivery rate estimate for a time period $J_{b,i}$ for an individual rests on the accuracy of the concentration measurements that define $AUC_i$, and estimates of endogeneous methanol levels, fluid volume and elimination rates for that individual. While variability in these terms can lead to uncertainty, trends obtained in individual sessions were consistent. Reliability increases when deriving absorption rate $J_{m,ss}$ as all of the data are used, and further when averaging across replicate sessions and individuals.

All of the absorption rates reported depend on three common parameters, namely, the clearance rate, the dilution volume (including partitioning effects), and the area of exposed skin. To examine the sensitivity to these parameters, Eqs. (7) and (8) can be manipulated or an analysis can be made using experimental data. The latter approach is easier to interpret and the following gives results using the 8-min exposures where the sample size was the largest. As expected, the estimated absorption rate increases as the clearance half-life decreases, e.g., for (hypothetical) half-lives of 4, 3, 2, 1, and 0.5 h, the derived absorption rates are 3.6, 4.4, 6.2, 11.6, and 22.2 mg $cm^{-2}$ $h^{-1}$, respectively. (All other parameters are held at their estimated values, i.e., AUC, hand area, volume, etc., use subject-specific estimates for the 8-min data set.) The relative sensitivity in the vicinity of the nominal study parameters is −0.5, i.e., a 1% increase in half-life decreases the derived absorption rate by 0.5%, indicating low sensitivity to clearance rates. Increasing distribution volume $V$ by 10% yields an average absorption rate of 8.51 (from the nominal 7.7) mg $cm^{-2}$ $h^{-1}$ and a relative sensitivity of 1.0. Thus, results are proportional and moderately sensitive to $V$. Finally, increasing skin area $A$ by 10% decreases the average absorption rate to 7.0 mg $cm^{-2}$ $h^{-1}$, giving a relative sensitivity of −1.0. These results again show moderate sensitivity and the expected inverse proportionality to $A$.

Overall, results show only modest sensitivity to the methanol elimination rate, probably the most uncertain parameter in the study. Recent estimates of elimination rates for methanol are confined to a small range (1.5–2 h half-life) (Batterman et al. 1996c). This small range combined with the low sensitivity indicate that its uncertainty has no serious effect on results. Sensitivity analyses can be of significant value for other compounds where some or many parameters are uncertain, and thus it can be crucial to estimate possible errors.

## Variability

This study of 12 individuals in 65 exposure sessions represents the largest controlled study of percutaneous methanol exposure in the literature. As such, it offers useful information regarding the variability of pre- and post-exposure levels. Statistically significant differences in pre-exposure or baseline methanol levels in blood were found between individuals, and females had higher levels than males (2.4 vs 1.3 mg $l^{-1}$). The methanol BEI appropriately includes the "B" notation indicating that the compound is "usually present in a significant amounts in biological specimens collected from subjects who have not been occupationally exposed" (ACGIH 1994). (The methanol BEI also specifies the notation Ns, indicating that the determinant is non-specific and observed after exposure to some other chemicals, but not the notation Sq, which would suggest that it is a semi-quantitative index of exposure and that quantitative interpretation of the measurement is ambiguous.) Because sex, age, weight, hand area, and other factors were correlated among the subjects, intersubject differences found here should be downplayed. In any event, baseline concentrations were well below levels believed to be of toxicological significance and the occupational guideline.

After exposure, the methanol concentrations in blood were highly variable. Differences between subjects were not statistically meaningful and no clear relationship of dose to the exposed skin area, subject weight or other factor was found. This variability, lack of relationship to weight and area, and association with a qualitative examination of skin condition together suggest that skin characteristics affecting absorption, e.g., hydration, condition, and temperature, are the major biological determinants affecting uptake. Further, these characteristics may have varied enough over periods of weeks to months (the study duration) to alter an individual's uptake and to account for some of the intrasubject variation. Indeed, the texture, moisture, etc., among the subject's hands varied considerably, and hands were somewhat to considerably dryer and rougher following exposure. Subjects with the most severe pre-existing damage to the skin tended to have the highest methanol uptake. Damage and changes to the skin, caused by occupation or disease which increases hydration and temperature and reduces evaporative loss, have been noted to increase absorption rates (Treffel et al. 1992).

The observed variability is not surprising. The in vitro tests of Southwell et al. (1984) show interspecimen variation of 79% for methanol, higher than that found for the other four compounds studied (34%–48%). The same study found similar variation in lag times. While the abdominal samples used appeared less variable than samples taken from other anatomical sites, the authors stated that skin changes due to excision, storage and manipulations of specimens may have caused their results to reflect greater variation than in vivo studies.

Dutkiewicz et al. (1980) reported that the duration of the exposure was another source of variation in methanol absorption rates. The highest rate was found for an exposure duration of 30–35 min; rates at 15 and 60 min were reduced by 25%–35% from the maximum. While no mechanism was postulated, the exposure duration of the highest rate corresponds to the (0.5 h) lag time found here and by Southwell et al. (1984). An exposure duration similar to the lag time may result in solvent just saturating the stratum corneum and the shallow epidermis, at which time transport to blood becomes limited by capillary blood flow. In this study, derived absorption rates for 2–16 min exposures were consistent, although variability increased for short exposures, mainly due to uncertainties in the blood measurement errors and baseline estimates. Since all exposure durations were shorter than the lag time, no such effect, if it exists, appears active in our results. Given the increasingly recognized need to avoid or limit percutaneous exposures, studies using short dermal exposures may be the most appropriate.

## Conclusion

The study has demonstrated the derivation of absorption and delivery rates from a sequence of blood measurements following exposures to neat methanol. Although different methods were used, the estimated absorption rate is comparable to the other in vivo study and considerably greater than in vitro estimates in the literature. While very simple models are used, the derived rates are based on first principles and reveal kinetics that include lags and reservoir effects. As elimination processes and endogenous levels are incorporated, the derived rates can yield correction factors useful in biological monitoring. While the variability in baseline levels and post-exposure responses is sizable, concentrations in blood increase linearly with the duration of the exposure, at least on average and for relatively short exposures.

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