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ORIGINAL ARTICLE

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Airborne emissions at skin surfaces: a potential biological exposure index

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Abstract Dermal exposures of methanol were administered in a clinical study designed to compare several biological indicators. Four subjects were exposed in five exposure sessions of varying length. In each session, a sequence of measurements of methanol concentrations in blood, breath, and headspace samples of air at exposed and unexposed skin were collected before and after dermal exposures. Skin headspace samples, collected in gas sampling bags, were designed to reflect equilibrium skin: air partitioning. At exposed skin, headspace samples were highly elevated for at least 8 h following exposure, indicating the presence of a methanol reservoir in skin. After exposure, methanol concentrations at exposed skin showed a rapid initial decline, then a slower first-order decrease. Methanol concentrations were clearly detectable in headspace samples at unexposed skin. Substantial transfer from exposed skin occurred due to mechanical contact and washing. When transfer was restricted, surface concentrations at unexposed skin were similar to levels in breath and were strongly correlated to methanol concentrations in blood. While results are preliminary due to the small sample sizes and several unresolved experimental issues, the simple, rapid, and noninvasive skin headspace measurements appear useful as a biological exposure indicator that clearly shows the presence and site of a dermal exposure, and measurements at unexposed skin reflect concentrations in blood.

Key words Biological monitoring · Breath sampling · Chemical analysis · Methanol · Volatile organic compounds

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Introduction

Methanol is a common solvent that has been proposed for use as an automotive fuel (Gray and Alson 1990), a use which would tremendously increase the potential for human exposure through inhalation and dermal pathways. Methanol readily passes into and through the skin, and the potentially important role of the dermal pathway for the total absorbed dose has been demonstrated (e.g., Dutkiewicz et al. 1980; Franzblau et al. 1995). An 8-min exposure of neat methanol to the area of one hand ($\approx 440\ cm^2$), for example, yields a peak blood concentration similar to that achieved from 8 h of inhalation exposure at 200 ppm (Franzblau et al. 1995), the threshold limit value (TLV) for methanol (ACGIH 1991). Exposure to methanol is readily measurable as elevated methanol concentrations in breath, blood, and urine. Such biological exposure indices (BEIs) have been used to estimate doses resulting from all exposure pathways, i.e., percutaneous absorption, inhalation, and ingestion (Murthy and Halperin 1995).

This paper presents methanol evaporation and offgassing rates through skin that were measured in a clinical study examining dermal and inhalation exposure to methanol. After administering a dermal exposure to human subjects, offgassing at exposed and unexposed skin is measured using a static headspace chamber technique in which methanol vapors accumulate and equilibrate. Chamber concentrations from skin emissions are compared to conventional BEIs, i.e., concentrations in breath and blood.

Background

Dermal exposures have been measured using procedures that include rinsing skin with solvents and analyzing the rinse solution for the chemical of concern (Roels et al. 1980), wiping skin with a solvent-impregnated pad which

is then analyzed for the chemical (Ness 1995), using an adhesive tape to remove contaminant residues for gravimetric analysis (Lepow et al. 1975), and using fluorescent tracers with video imaging to identify areas where the chemical has contacted skin (Fenske et al. 1986). To identify sites of dermal exposure, potentially contaminated clothing has been tested using headspace and extraction techniques (Ness 1995). These procedures have been used with inorganic or semivolatile contaminants, e.g., lead and pesticides. Results are often uncertain due to unknown and varying removal efficiency and unknown contact duration (EPA 1992). For vapors, absorption through skin has been investigated by a number of researchers (e.g., Tsuruta 1989).

A review of the literature showed no previous studies that estimated exposure using the flux or concentration of chemicals that permeate or evaporate from the skin and into the vapor phase. The skin headspace sampling proposed uses a chamber technique to infer exposures from this flux. Such techniques have been used in many applications to estimate emission rates and concentrations of volatile organic compounds (VOCs). As an example of a static chamber technique, VOC concentrations in liquids may be accurately estimated by measuring the concentration of the headspace gas above the liquid, since gas:liquid partition coefficients are constant in a sealed container at a specific temperature and pressure (Voice and Kolb 1993). As a second example, dynamic (flowing gas) chamber techniques may be used to quantify VOC emissions from materials placed in the chamber (ASTM 1991). In contrast to static techniques, dynamic tests measure emission rates or fluxes under nonequilibrium conditions.

Materials and methods

Dermal exposures

The dermal exposure protocol consisted of five separate sessions for each subject scheduled at least 1 week apart. Similar procedures were followed in each session, including the control. The exposure consisted of placing a subject's left hand to the distal wrist crease in a large beaker of neat analytical grade methanol (99.8% pure, EM Science, Gibbstown, N.J.). Exposure times were 0, 2, 4, 8, and 16 min. The beaker was located inside a laboratory fume hood, the opening of which was covered with plastic sheeting to prevent inhalation of methanol vapor. Subjects placed their arm through a slit in the sheeting during the exposure and the air-drying of the hand immediately afterward. Blood, breath, and skin surface air samples were collected $\approx$15 min prior to exposure and at 1, 2, 4, and 8 h following the exposure.

Sample collection and analysis

Airborne concentrations at the skin surface were measured using a static chamber technique. Each hand, the skin area tested, was placed into a contaminant-free chamber and allowed to equilibrate for 5 min, after which the headspace gas was collected for analysis. The chamber consisted of a "hand sampling bag" constructed from a 10-l Tedlar gas sampling bag equipped with a stainless steel valve/port (SKC Inc., Eighty-four, Pa.). The bag end opposite the port was sliced open and an adhesive Velcro fastener was attached to the outside of the bag. During sampling, one hand was placed into the bag, the fastener was used to seal the bag around the forearm, and air in the bag was removed by vacuum. Then, 1 l prepurified N_2 gas was metered into the bag and concentrations in the bag were allowed to stabilize for 5 min. Subjects were seated during this period. Air in the hand sampling bag was then transferred to a 0.5-l aluminized Mylar gas sampling bag (Quintron Instrument Co., Milwaukee, Wis.) using a displacement technique. After connecting the hand sampling bag to the 0.5-l bag using Teflon tubing, the 0.5-l bag was placed in an airtight chamber. This chamber was subsequently evacuated, thus drawing the air from the hand sampling bag. This technique avoided any potential contamination that might occur with the use of a pump. The Velcro enclosure was then released, and the hand withdrawn. The hand sampling bag was cleaned and dried by purging with compressed air prior to its next use. Headspace skin samples from exposed and unexposed hands of each subject were collected simultaneously using two hand sampling bags.

The gas sampling bags were analyzed for methanol and carbon dioxide (CO_2) using Fourier transform infrared (FTIR) analysis. After warming the bag for several minutes, the sample was transferred to a previously evacuated 5-m path length gas cell of a Bomen MB-100a FT-IR spectrometer (Montreal, Canada) equipped with a mercury-cadmium-telluride (MCT) nitrogen-cooled detector. All components in contact with the gas sample were stainless steel, Teflon, or deactivated glass. To avoid sample condensation, cell pressure was maintained at 500 mmHg. IR spectra were collected at 2 cm^{-1} resolution using 32 scans and fitted using an ordinary least-squares procedure. Reference spectra (standards), e.g., 2% CO_2 in N_2 (Scotts Speciality Gases, Troy, Mich.) and 50 ppm and 1000 ppm methanol in N_2, were analyzed using the same instrument. The limit of detection (LOD) for methanol was $\approx$0.5 ppm, and the coefficient of variation (COV) was $\approx$2%.

Breath samples were collected using gas sampling bags and analyzed for methanol and CO_2 as described above. CO_2 measurements were taken to ensure that breath samples represented alveolar air (CO_2 concentration $\approx$4%). Blood samples were taken from the unexposed arm into "gray top" Vacutainer tubes which were immediately refrigerated. Methanol concentrations were determined for two replicates of each blood sample using gas chromatography and flame ionization detection. For blood, the LOD was $\approx$0.5 mg/l, and COVs were 3%–5%. Details of sampling and analytical procedures for breath and blood are given in Franzblau et al. (1995).

Study population

Four women, aged 41–63, participated in the experiment. Subjects were permitted to eat and drink freely during the experiment with the exception of alcoholic beverages during the session and the 24 h preceding it. None had known occupational or avocational exposure to methanol, formic acid, or formaldehyde, and none smoked. Subjects were instructed not to use skin creams, moisturizers, etc., during the session. During the 8-min exposure session, subjects were instructed to minimize contact between their right and left hands, and not to wash their hands. Only three subjects participated in this last session. The subjects provided written informed consent using forms and protocols approved by the University of Michigan School of Public Health.

Results

Table 1 summarizes the data collected during the dermal exposure experiments. Means and standard deviations are based on measurements from the four

Table 1 Summary of data collected during the four dermal exposure sessions. Average and standard deviations for four subjects

Exposure time (min)	Time after exposure (hs): Preexposure Mean	Preexposure St.dev.	1 Mean	1 St.dev.	2 Mean	2 St.dev.	4 Mean	4 St.dev.	8 Mean	8 St.dev.
Methanol concentrations in blood (mg/l)										
0	2.2	0.5	1.9	0.5	1.7	0.4	1.6	0.5	2.2	0.6
2	2.7	0.8	4.0	1.1	4.4	1.2	3.0	0.9	3.2	1.2
4	7.9	4.6	8.4	2.9	8.4	2.5	7.2	3.4	5.7	2.6
8	1.7	0.5	7.0	2.5	7.3	0.3	5.1	1.9	1.9	0.2
16	5.7	4.4	13.3	6.1	15.1	3.4	9.9	3.2	5.3	1.8
Methanol concentrations in breath (ppm)										
0	0.0	0.0	0.1	0.3	0.0	0.0	0.2	0.3	0.0	0.0
2	0.2	0.4	0.5	0.9	0.5	0.7	0.4	0.7	0.4	0.5
4	0.3	0.2	1.7	0.6	1.1	0.6	0.8	0.3	0.4	0.5
8	0.2	0.3	1.8	0.6	1.2	0.4	0.2	0.4	0.0	0.0
16	0.4	0.9	3.4	1.1	2.7	0.8	1.5	0.4	0.4	0.5
Methanol concentrations at unexposed hand (ppm)										
0	0.7	0.1	0.9	0.2	0.8	0.0	0.7	0.1	0.7	1.0
2	0.8	0.2	9.4	11.8	1.8	2.6	0.1	0.3	0.0	0.0
4	0.0	0.0	29.6	37.4	7.9	1.9	1.7	0.8	0.0	0.0
8	0.6	0.2	1.5	0.4	1.3	0.2	0.8	0.3	0.7	0.1
16	0.0	0.0	21.2	14.8	28.1	37.1	3.6	2.3	0.6	1.3
Methanol concentrations at exposed hand (ppm)										
0	0.3	0.4	0.7	0.1	0.8	0.5	0.3	0.4	0.7	0.5
2	1.0	0.8	620	238	179	94	36	34	20.6	27.1
4	0.5	0.7	2840	3820	285	226	70	59	6.0	0.0
8	0.4	0.4	1428	334	401	114	50	33	0.7	0.1
16	0.0	0.0	14100	11300	356	213	105	140	8.6	15.6
Carbon dioxide concentrations in breath (percent)										
0	4.5	0.5	4.3	0.5	4.4	0.5	4.3	0.7	2.7	2.0
2	4.0	1.4	4.4	1.3	4.3	1.2	4.3	1.2	4.2	0.7
4	4.6	0.6	4.9	0.8	4.1	0.9	3.8	0.8	4.0	1.2
8	3.8	0.2	4.3	0.6	4.3	0.4	4.1	0.5	4.3	0.4
16	4.2	1.0	4.9	1.0	4.3	0.6	4.4	0.8	4.0	1.4
Carbon dioxide concentrations at unexposed hand (percent)										
0	0.30	0.07	0.33	0.03	0.25	0.04	0.28	0.09	0.28	0.04
2	0.28	0.04	0.25	0.05	0.24	0.03	0.26	0.04	0.29	0.01
4	0.28	0.06	0.27	0.06	0.25	0.03	0.29	0.02	0.27	0.05
8	0.24	0.03	0.22	0.00	0.26	0.02	0.25	0.01	0.26	0.02
16	0.23	0.02	0.22	0.02	0.25	0.07	0.22	0.01	0.25	0.04

subjects. Trends and other statistics of methanol concentrations are discussed below.

Time trends

Figure 1 shows time trends of surface methanol concentrations at the exposed hand. Concentrations for individual subjects are shown as points, and the four subject mean is plotted as a curve. Methanol concentrations prior to exposure and in the control experiment (without exposure) remained below 1 ppm (Table 1). In contrast, very high concentrations were observed at the exposed hand from one to several hours following exposure, e.g., the mean concentration 1 h following the 16-min dermal exposure was 14 100 ppm. This level is well below the vapor pressure of methanol ($\approx$150 000 ppm at 25°C and $\approx$305 000 ppm at 37°C). Figure 1 uses a logarithmic scale for the concentration axis. An exponential decay resulting from a first-order loss of methanol would plot as a straight line. The decline in methanol concentrations appeared to be a two-phase process, demonstrated particularly strongly with the longest exposure (Fig. 1D). The initial decline, between 1 and 2 h following exposure, was rapid. Subsequent losses, from 2 to 8 h following exposure, appeared slower and first-order but remained faster than the published 1.5- to 3-h half-life for methanol in blood (Kavet and Nauss 1990; ACGIH 1991). The same pattern was observed for all exposure durations. Methanol concentrations at the exposed skin surface remained elevated for at least 8 h following exposure.

Figure 2 displays trends in methanol concentrations measured at the unexposed hand. Concentrations

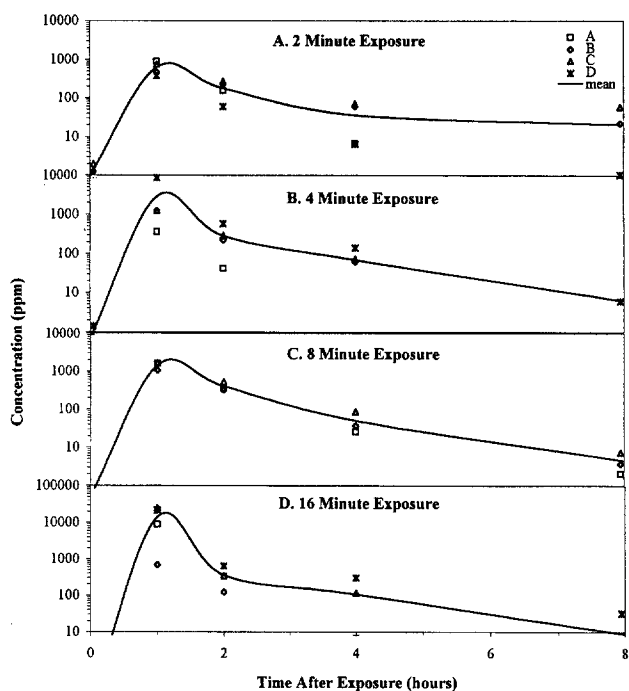

Fig. 1A–D Time trends of surface methanol concentrations measured at the exposed hand. Results of individual subjects A–D are shown as separate points; the four-subject mean is plotted as a curve

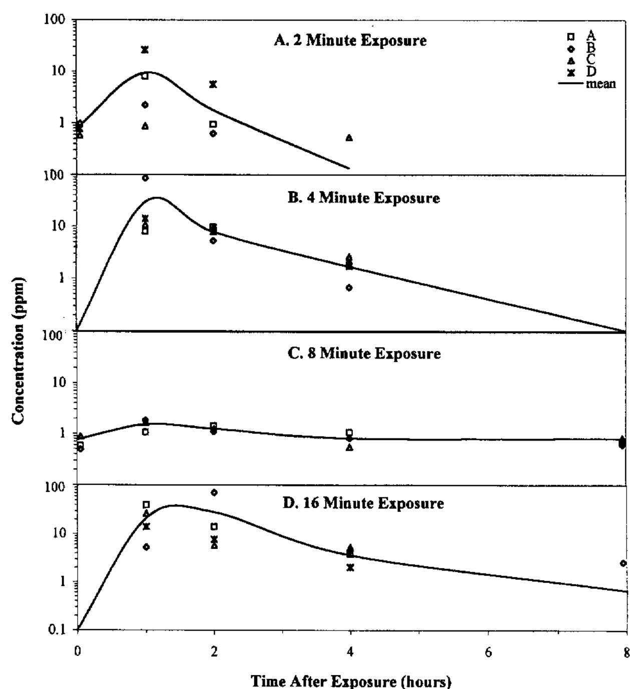

Fig. 2A–D Time trends of methanol concentrations measured at the unexposed hand. Otherwise as Fig. 1

remained below 1 ppm in the control case (Table 1). The exposure cases were classified into two groups: those with skin contact and handwashing that may promote transfer of methanol between exposed and unexposed hands (Fig. 2A, B, D), and those with minimal contact in the 8-min exposure (Fig. 2C). In the first case, concentrations remained elevated for at least 2 h following exposure, and for at least 4 h with the longer (4- and 16-min exposures. Figures 2B, C, and D show an approximately linear postexposure decline on the log-linear plot, implying a first-order clearance. As with the exposed skin, the half-life of methanol at unexposed skin in the 2-, 4-, and 16-min exposures appeared more rapid than the half-life in blood. Considerable intersubject variability was indicated. In contrast, in the 8-min exposure session where hand contact was restricted, concentrations were much lower, reaching only 1.5 ± 0.4 ppm 1 h after exposure (Table 1), and intersubject variability was less (Fig. 2C). Concentrations were similar to those in breath, e.g., 1.8 ± 0.6 ppm at 1 h in the same experiment (Table 1).

Time trends for methanol in blood are shown in Fig. 3. Subjects showed considerable variability in methanol concentrations. In cases, differences in preexposure levels were maintained throughout the session. For example, subject D maintained low methanol levels throughout the 4-min exposure session (Fig. 3B), and subject A maintained high levels throughout the 16-min session (Fig. 3D). The 16-min exposure session produced the clearest elevation in blood concentration levels, and the best reflection of the 1.5- to 3-h half-life. While methanol concentrations in the 8-min session appeared low compared to levels reached in the 4- and 16-min exposure sessions, the other sessions had considerably higher preexposure levels. Although one subject did not participate in the 8-min session, results were not significantly affected.

CO_2 concentrations in the headspace samples appeared stable throughout the experiments (Table 1). CO_2 concentrations in the skin surface samples were approximately 15 times lower than levels in breath. No significant differences in CO_2 levels were seen between exposed and unexposed skin.

Relationship among blood, breath, and skin surface measurements

Using results from the 8-min exposure session, methanol concentrations at the unexposed hand are plotted against blood concentrations in Fig. 4. Also shown is the best fit line, described by the equation $y = 0.143x + 0.247$ with a linear correlation coefficient of 0.79. For the same exposure session, methanol concentrations in breath samples are plotted against blood levels in Fig. 5. In this case, the best fit line is $y = 0.189x - 0.147$, and the linear correlation coefficient is 0.80. Thus, breath and unexposed skin methanol measurements had similar slopes and correlation coefficients to levels monitored in blood, the best measure

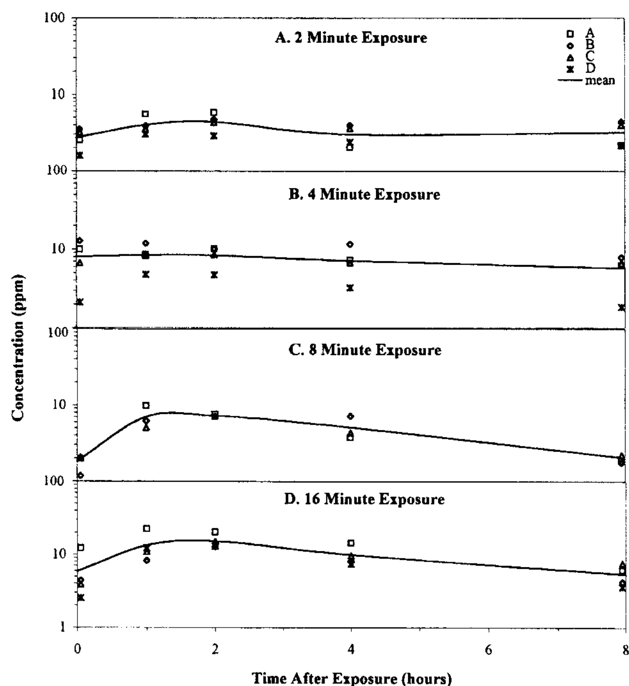

Fig. 3A–D Time trends of methanol concentrations in blood. Otherwise as Fig. 1

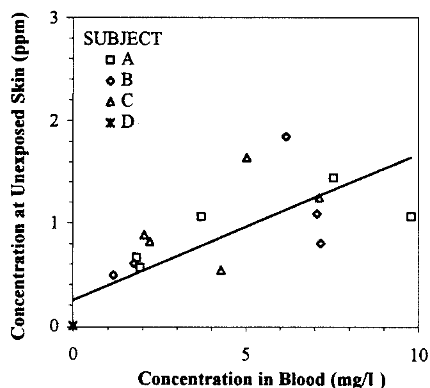

Fig. 4 Scatterplot of methanol concentrations at the unexposed hand versus concentrations in blood for the 8-min dermal session

of methanol dose. In the 16-min exposure session, where hand contact was not restricted, the best fit line ($y = 1.66x - 6.29$) was considerably different, and the correlation coefficient (0.51) was much lower.

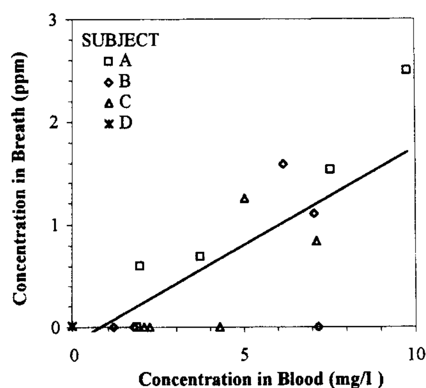

Fig. 5 Scatterplot of methanol concentrations in breath versus concentrations in blood for the 8-min dermal session

Discussion

Reservoir effect and modeling

The high methanol vapor concentrations at exposed skin indicate that skin, possibly the stratum corneum, maintains a significant reservoir of methanol for many hours. While this reservoir effect has been long known for polar and lipophilic compounds (e.g., Vickers 1963) it has not been previously reported for permeable and hydrophilic compounds like methanol. A reservoir for methanol was unexpected as diffusion through the thin stratum corneum and transport by blood in the skin was expected to be rapid. Some solvent may be sequestered once it enters fatty cells, interstitial spaces of the stratum corneum, or other structures in the dermis. Methanol in this reservoir can be transferred to other skin sites by contact, washing, or other means.

Methanol concentrations in blood following dermal exposure slowly rose to a maximum reached about 1 h after exposure and then slowly decayed. This consistent pattern, discussed in detail by Franzblau et al. (1995), may result from several mechanisms, e.g., the reservoir effect in exposed skin, a finite diffusion or permeation rate across tissue and into blood, dilution of methanol in blood and other body compartments, and the metabolism of methanol. This pattern cannot be reproduced by physiological models using a single skin compartment and partition coefficient. Results support suggestions by Raykar et al. (1988) and others that multiple compartments may be needed to represent adequately the heterogeneous stratum corneum and the delayed uptake of a solvent into blood. Multiple compartment models can also represent the pattern of methanol concentrations observed at exposed skin, i.e., a rapid initial release due to the evaporation of methanol sequestered in the reservoir, and a slower first-order diffusion process through tissue from methanol in blood.

Skin offgassing and evaporation rates

Methanol offgassing or evaporation rates are estimated and compared to the dose using results from the 16-min exposure session. The maximum methanol concentration in blood (13.3 mg/l) and the adult blood volume (≈ 5 l) indicate 66 mg of methanol in blood. Assuming

the same concentration in the ≈35 l of other body fluids, an additional 464 mg of methanol is present; thus the total dose estimate is 530 mg. (Metabolism and reservoir storage are neglected.) The 14 100 ppm concentration in the 1-l hand sampling bag at the exposed hand represents 19.5 mg or 3.6% of the dose. Assuming the measured breath concentration (3.4 ppm) applies to unexposed skin, the concentration over unexposed skin (≈1.7 m^2 area) represents 0.18 mg or 0.03% of the dose. Measurements using the static chamber technique can be converted to lower bound excretion rates by assuming a constant emission rate over the (5-min) sampling period. (If equilibrium in the chamber were reached more quickly, the emission rate would be higher.) With this assumption, the excretion rate through unexposed skin is 0.4% per hour of the dose. Note that moderate to heavy sweating rates (1–5 l per 8 h) represent 0.3%–1.6% per hour loss of body fluids. With equilibrium partitioning, methanol concentrations in water and sweat are approximately equal; thus methanol excretion rates via sweating are also ≈0.3%–1.6% per hour. The similarity of methanol offgassing and water loss rates suggests that sweat is an important excretion mechanism, as suggested by Gunderson et al. (1989) for amines. As metabolism rates exceed the offgassing estimate by two orders of magnitude, losses through skin are not an important excretion pathway for methanol.

Skin surface sampling as a biological exposure index

Methanol concentrations at both exposed and unexposed skin surfaces were readily measurable, and exposed skin maintained high concentrations for at least several hours. This suggests that skin surface sampling techniques may be used to indicate the presence and site of dermal exposure. No other procedure to assess the site of VOC dermal exposures has been identified in the literature.

To provide a quantitative BEI, skin surface concentrations should accurately reflect blood levels. Concentrations at unexposed skin may be related to blood levels using equilibrium partitioning, as assumed for concentrations in alveolar air and breath samples. Published blood:air partition coefficients for methanol at 37°C are 1626 and 2874 (Fiserova-Bergerova and Diaz 1986; Pezzagno et al. 1983). For the blood methanol level of 13.3 ± 6.1 mg/l reached 1 h after the 16-min dermal exposure, the predicted concentrations are 6.2 and 3.6 ppm. The latter is close to the 3.4 ± 1.1 ppm observed (Table 1). At equilibrium, skin headspace concentrations should reflect levels in skin and the epidermis:air partition coefficient, which is unknown. Epidermis:air and blood:air partition coefficients will differ because the lipid content of the epidermis and especially the stratum corneum exceeds that in blood. Large differences are unlikely, however, and thus similar concentrations at unexposed skin and in breath would be expected.

The concentration (21.2 ± 14.8 ppm) at unexposed skin when contact with exposed skin was permitted was much higher than breath levels. A likely explanation is transfer of methanol between the hands of each subjects. This appears to account for these observations (and perhaps much of the intersubject variability) even though the exposed hand was fully dried prior to removing it from the fume hood. Four to eight hours after the 16-min exposure, unexposed skin concentrations approached breath levels, possibly reflecting the loss of methanol that was transferred from the exposed hand. Much stronger evidence, however, was seen when hand-to-hand contact was restricted. In this case, unexposed skin and breath concentrations were similar (Table 1) and both had a moderate to high correlation with blood levels (Figs. 4, 5).

Skin headspace measurements may complement other BEIs, each of which has its own limitations. For example, methanol concentrations measured in breath, a well-accepted biomarker, may be compromised if partitioning and release of methanol in mucous membranes are unaccounted for (Franzblau et al. 1995; Kumagai and Matsunaga 1995). Skin surface measurements are rapid, sensitive, and possibly even less invasive than the collection of representative breath samples, and specialized equipment and instructions (like breath maneuvers) are not required. Greatly elevated measurements show exposed skin regions. Measurements at unexposed skin, or possibly in sweat, should reflect blood levels. In comparison to breath measurements, issues related to deadspace (nonalveolar air) and mucous membranes are avoided. To provide a quantitative measure reflecting dose, however, skin areas must be carefully selected. Because of the small sample size and single skin area tested in this pilot study, additional studies are necessary to confirm results and develop robust sampling procedures.

Skin surface sampling procedures

The skin sampling protocol was preliminary, and several problems were encountered in collecting samples in a repeatable manner. These include difficulty in sealing the hand sampling bag around the subject's arm, potentially insufficient time to reach equilibrium in the bag (see below) and sampling of slightly different skin areas each time (e.g., varying amount of wrist and arm). Additionally, more frequent measurements could help to confirm trends, and the use of dynamic chamber techniques would allow direct determination of surface fluxes. However, the static sampling technique is simple, low cost, and amenable to field use.

Several observations suggest that the 5-min period used in skin surface sampling was sufficient to reach steady-state conditions. First, considerable condensa-

tion from perspiration in the hand sampling bags was noted. If methanol dissolved in perspiration is in equilibrium with concentrations of methanol in tissue, then condensation indicates equilibrium. Second, stable CO_2 concentrations in the headspace sample suggest water and methanol vapor equilibrium. Third, if results were flux-limited, then the extent to which the four subjects varied in hand sizes, skin characteristics, and other factors that affect permeability might yield intersubject variation larger than measured. Finally, in the 8-min exposure session, headspace skin and breath measurements were very similar. While these observations suggest equilibrium was reached, tests using various bag sampling times (3, 5, and 10 min) would be desirable.

Conclusion

A method to sample headspace samples of vapors from skin has been developed. Tests using a dermal exposure of methanol showed measurable emissions through skin and the presence of a reservoir in skin, and suggested a biological exposure index which can be used to identify the site of dermal exposure and the dose. Additional studies are suggested to investigate air: skin equilibrium, permeation rates in and out of skin, mechanical transfer of methanol, the best skin sites for the measurements, and the applicability of the technique for other chemicals.

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