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Breath Monitoring of Inhalation and Dermal Methanol Exposure

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A fundamental assumption of monitoring breath for a toxicant is that the concentration of the toxicant in breath is proportional to the concentration in blood. The present study was designed, in part, to assess the conditions under which measurement of methanol in breath would be useful for estimating the blood concentration of methanol following inhalation or dermal exposures to methanol. Paid volunteer subjects underwent controlled inhalation exposure to methanol vapor at various concentrations for 8 hours, or dermal exposures (without inhalation exposure) to methanol for varying periods of time. Blood and end-expiratory air were analyzed for methanol from samples obtained prior to exposures, and at various times during and after exposures. The results demonstrate that blood and breath concentrations of methanol are disproportional for varying periods of time during and following cessation of methanol exposure, depending on the route of exposure (dermal versus inhalation). In settings where there might be opportunities for combined inhalation and dermal exposure to methanol, it would be necessary to wait at least 2 hours to collect breath specimens following cessation of methanol exposure. This prolonged waiting period might serve to decrease the attractiveness of measurement of methanol in breath as a strategy for monitoring occupational methanol exposure. FRANZBLAU, A.; BATTERMAN, S.; D'ARCY, J.B.; SARGENT, N.E.; GROSS, K.B.; SCHRECK, R.M.: BREATH MONITORING OF INHALATION AND DERMAL METHANOL EXPOSURE. APPL. OCCUP. ENVIRON. HYG. 10(10):833–839; 1995.

Methanol is widely used in industrial applications primarily as a chemical intermediate. Such use has limited potential for large-scale human exposure because the processes involved are usually closed and the number of workers is relatively small.(1) The opportunity for human exposure may increase substantially in the future if methanol succeeds as an alternate automotive fuel or fuel additive.(1–3) Acute toxic effects of methanol exposure, primarily via ingestion, are well described.(4) However, human health effects of chronic, low level exposure are largely unknown. There have been no human epidemiologic studies focused on the effects of chronic low level methanol exposure, and results of animal studies are difficult to extrapolate to humans because of significant differences in the metabolism and toxicity of methanol in most animal models.(5–7)

An essential step in the design and implementation of an investigation of health effects of methanol is to measure or estimate exposure accurately. Absorption of methanol can occur via the lungs, the gastrointestinal tract, or percutaneous exposure,(8) and so availability of a method for biological monitoring, or a biologic exposure index, would be valuable since monitoring of methanol concentration in air alone may underestimate the absorbed dose. A number of studies have reported measurements of methanol in the breath of exposed subjects.(8–12) Breath monitoring has a number of potential advantages as a method of biological monitoring. In particular, breath sampling and measurement of methanol in breath can be simple, rapid, accurate, and noninvasive.

A fundamental assumption of monitoring breath for a toxicant is that the concentration of the toxicant in breath is proportional to the concentration in blood, that is, measurement of the concentration in one medium allows for accurate estimation of the concentration in the other via use of the blood:air partition coefficient. Previous studies involving measurement of methanol in breath have not explicitly confirmed this assumption. The present study was designed, in part, to assess the conditions under which measurement of methanol in breath would be useful for estimating the blood concentration of methanol following inhalation and dermal exposures, as might occur in an occupational setting.

Methods

Methanol Exposures

The methanol inhalation protocol consisted of 10 separate sessions for each subject. There were five different exposure levels: 0, 100, 200, 400, and 800 ppm. Subjects repeated each exposure twice: once at rest and once while performing light exercise on a bicycle ergometer so as to increase mean minute ventilation by approximately 50 percent over baseline. Except for a 15-minute interruption after 6 hours, exposures lasted 8 hours. Blood and breath samples were obtained before exposure, after 6 hours in the chamber, and after 8 hours in the chamber. Three additional breath samples were obtained at the 6- and 8-hour points by exiting the chamber and collecting samples at 5-, 10-, and 15-minute intervals.

Dermal exposure to methanol consisted of placing one hand in a large beaker of neat, analytical-grade methanol (99.8% pure; EM Science, Gibbstown, New Jersey) up to the distal wrist crease for varying periods of time (0, 2, 4, 8, and 16 minutes). The beaker was located inside a laboratory hood. To avoid methanol inhalation, the opening to the hood was covered with a large plastic sheet and subjects would insert one hand into the hood through a slit in the plastic. The hood was maintained under negative pressure relative to the room, and, in conjunction with the plastic sheet, this served to prevent inhalation of methanol. After removal from the beaker at the prescribed time, subjects' hands were allowed to air-dry while inside the hood. Blood and breath samples were obtained before exposure, at time zero (defined as when the hand was withdrawn from the beaker of methanol), and 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes following cessation of dermal exposure to methanol.

Inhalation Chamber

Human exposures to methanol vapor were conducted in a 3.7 × 3.7 × 2.7 m stainless steel Rochester-type exposure chamber with 45° tetrahedral top and bottom cones, a suspended floor and ceiling, a rest room, and an airlock for entry and exit. The chamber had a total volume of 47 m^3 and a ventilation rate of 14.2 m^3/min (18 chamber volumes/hour) using high efficiency particlate air-filtered, purified, and dehumidified air. Temperature was controlled at 22° ± 2°C. Vaporization and delivery of methanol vapor to the chamber took place in two steps. The methanol was pumped from a reservoir into the 80°C vaporization section of the generator by an explosion-proof metering pump. The vaporizer had a continuous flow of 200 L/min of filtered, compressed air, producing a methanol concentration of approximately 15,000 ppm. The diluted methanol vapor stream was metered into the inhalation chamber air flow through a mass flow controller to achieve the desired concentration.

Exposure Chamber Air Monitoring

The concentration of methanol in the chamber was monitored using a MIRAN 1-A (The Foxboro Co., Foxboro, Massachusetts) infrared analyzer equipped with a closed-loop calibrator. The MIRAN was set at a wavelength of 9.55 μm (1047 cm^{-1}), an absorbance scale of 1.0, and a path length of 17.25 m. The output was recorded continuously using a Kiethley data acquisition card (Kiethley model 575; LABTECH, Taunton, Massachusetts) and analyzed with LABTECH notebook software. Calibration was performed using direct injection of methanol liquid into the calibration loop. The limit of detection was approximately 1 ppm, and the coefficient of variation for calibration of the instrument was 3 percent.

No measurements of methanol distribution within the chamber were made during these studies. However, in earlier studies using ozone in the same chamber, the concentration distribution on a 4-ft grid at floor level, breathing zone height (5 ft), and ceiling level (8 ft) did not vary by more than 5 percent from the concentration measured simultaneously at the inlet valve just below the the top of the chamber.(13) From these data with a very reactive gas at 0.4 ppm we are confident that the concentration of methanol vapor did not vary by more than 5 percent of the measured value at any location within the chamber during these studies.

Breath Sampling and Analysis

Subjects were instructed to perform normal tidal breathing, and at the end of a tidal expiration to hold their breath for a timed period of 10 seconds. Breath was then exhaled via a mouthpiece into a breath collection system. The system consisted of a T-fitting, a 500-ml trapping volume bag, and a 500-ml aluminized Mylar sample bag (Quintron Instrument Co., Milwaukee, Wisconsin). The sample bag was fitted with a one-way filling valve and a Luer-lok fitting for drawing gas samples. After normal tidal exhalation and breath holding for 10 seconds, the first 500 ml of exhaled air was captured in the trapping bag, which, when filled, triggered the opening of the one-way valve on the sampling bag. The last 200 to 500 ml of exhaled air, constituting the end tidal sample, was thereby collected for analysis. Nearly all breath samples were analyzed within 1 day, or 2 days at most, for methanol and carbon dioxide via Fourier transform infrared (FTIR).(9) Measurement of carbon dioxide provided an independent criterion for determining that each breath sample represented alveolar air.

After warming the gas collection bags for ~2 minutes, breath samples were introduced into a previously evacuated 5-m "White" cell (Infrared Associates) mounted atop a Bomem MB-100a FTIR spectrometer (Montreal, Canada) equipped with a mercury–cadmium–telluride nitrogen-cooled detector. To avoid sample condensation, cell pressure was maintained at 500 mmHg using a vacuum regulator. Infrared spectra were collected at 2 cm^{-1} resolution using 32 scans, and analyzed in SpectraCalc (Galactic Industries, Salem, New Hampshire) using an ordinary least-squares fitting procedure with multiple spectral regions and linear baseline corrections. Reference spectra (standards) were analyzed on the same instrument using 2 percent carbon dioxide in nitrogen (Scotts Specialty Gases, Troy, Michigan) and 50 ppm methanol in nitrogen. Limits of detection were ~0.5 ppm for methanol and ~0.2 percent for carbon dioxide, and precisions exceeded 2 percent.

Tests of stability and recovery of methanol stored in breath sampling bags indicated negligible losses due to adsorption, diffusion, leaks, etc., over periods of at least 2 days. The integrity of the breath analysis system, constructed of inert materials (Teflon, glass, stainless steel, etc.) to minimize adsorption effects, was periodically verified by measuring the concentration in breath sampling bags filled with chamber air. This system provided reliable results over the range of concentrations reported here.

Blood Sampling and Analysis

Blood samples were collected into "gray top" Vacutainer® tubes (containing potassium oxalate and sodium fluoride). During dermal methanol experiments, blood samples were obtained from the arm of the unexposed hand. Tubes were kept on wet ice or refrigerated at 4°C until analyzed. All analyses were performed within 7 days of sampling. Methanol concentration in blood was determined using head space gas chromatography and flame ionization detection(9) as follows: Using an autopipetter, 0.5 ml blood and 20 μL isopropanol standard [1000 mg/L, high performance liquid chromatography (HPLC)-grade] were placed into a clean, previously labeled 20-ml vial. The vial was sealed with a butyl-rubber septum-equipped crimp cap and then loaded onto the carousel of a Tekmar 7050/7000 (Cincinnati, Ohio) automated head space sampler. After a 30-minute incubation at 60°C and 2 minutes of mixing, 1 ml of the head space was injected into a

TABLE 1. Demographic Characteristics of Study Subjects

Subject	Age	Sex	Race	Current smoker	Protocol*
1	49	Female	White	Yes	D & I
2	55	Male	White	Yes	D & I
3	33	Male	White	No	D & I
4	31	Male	African-American	No	D & I
5	30	Male	White	Yes	D
6	22	Male	White	No	D
7	33	Male	White	No	D
8	26	Male	White	Yes	D

*D = dermal experimental protocol; I = inhalation experimental protocol.

2 m × 0.125 inch packed column containing 5 percent Carbowax 20M 60/80 mesh Carbopack B (Supelco Inc., Supelco Park, Bellefonte, Pennsylvania) of a Varian 3700 gas chromatograph (GC) (Mountain View, California). The column was operated isothermally at 90°C. The GC detector output was collected on a PC-based data acquisition system and processed for baseline correction and peak integration. Two replicates of each blood sample were analyzed. Five-point calibration curves were performed daily. Standards were prepared using HPLC-grade methanol, distilled water, and the isopropanol standard. Each carousel included two blanks and five quality control (QC) standards. Acceptable analyses achieved QC accuracies and precisions better than 10 and 5 percent, respectively. The limit of detection was below ~0.5 mg/L and the coefficient of variation for calibration was typically 3 to 5 percent.

Human Subjects

The demographic characteristics of subjects are listed in Table 1. Four persons completed the inhalation experiment and eight subjects completed the dermal exposure experiment. The four subjects who completed the inhalation study were among the eight who completed the dermal exposure protocol (see Table 1). Subjects were permitted to eat and drink freely during the experiment, even while in the exposure chamber, with the caveat that they had to abstain from alcoholic (ethanol-containing) beverages during experimental sessions and during the 24-hour period preceding each experimental session. If they were smokers they could not smoke cigarettes during experimental sessions. None of the subjects had known occupational or avocational exposure to methanol, formic acid, or formaldehyde.

All subjects provided written informed consent. The consent forms and research protocols had been approved by the Human Subjects Review Committees of the University of Michigan School of Public Health and the General Motors Research & Development Center.

Results

The mean results of breath and blood measurements of four subjects while sedentary with inhalation exposure to 400 ppm of methanol are shown in Figure 1. Following 6 and 8 hours of exposure, blood and breath methanol concentrations were increased significantly over pre-exposure values. The concentrations of methanol in blood and breath after 6 hours were slightly less than the levels achieved after the full 8-hour exposure session, although these differences were not significant. The mean concentrations of methanol in breath collected after 6 and 8 hours of exposure (72 and 77 ppm, respectively), obtained while still breathing an atmosphere with 400 ppm of methanol, were markedly higher than what would be predicted based on the measured concentration of methanol in blood samples obtained at the same times (3 to 6 ppm; see Table 2). Following 6 and 8 hours of inhalation exposure, the mean concentration of methanol in breath dropped by almost an order of magnitude after breathing uncontaminated air for only 5 minutes. The breath concentration of methanol fell slightly further with continued inspiration of clean air, and it appeared to level off after 10 or 15 minutes. It should also be noted that despite the sharp decline in the concentration of methanol in breath seen with breathing clean air for 15 minutes after 6 hours of exposure, the breath concentration of methanol rose back up to the previous high range after reentering the exposure chamber for just under 2 hours. This pattern of blood and breath results is similar regardless of the level of (nonzero) inhalation methanol exposure, or whether subjects were sedentary or performing light exercise (data not shown).

The data graphed in Figure 1 are summarized in Table 2, along with estimates of breath methanol calculated using measured blood methanol concentrations and published blood:air partition coefficients for methanol at 37°C.(14,15) Since the half-life of methanol in blood has been estimated to be approximately 3 hours,(16) the predicted breath concentrations of methanol were determined assuming that the blood concentrations of methanol remained constant during these 15-minute intervals. The actual breath measurements appear to approach predicted values asymptotically using the higher blood:air methanol partition coefficient ($\lambda = 2874$). The retention fractions were 82 and 81 percent after 6 and 8 hours, respectively.

The mean results of blood and breath measurements for 8 subjects following 16 minutes of dermal methanol exposure to one hand are shown in Figure 2. The methanol concentration in breath peaks 15 minutes following cessation of dermal exposure. The decline in breath concentrations appears to be a two-phase process, with a rapid early phase between 15 and 30 minutes after cessation of exposure, followed by a slower phase beyond 30 minutes after cessation of exposure. In contrast, the methanol concentration in blood increases for 45 minutes following cessation of exposure, and then remains relatively constant between 1 and 2 hours following cessation of exposure. The blood concentration of methanol declines only after more than 2 hours following cessation of dermal exposure. This pattern of results is similar regardless of the duration of dermal exposure (data not shown).

The data graphed in Figure 2 are listed in Table 3, along with predictions of breath methanol calculated using the actual blood methanol. Once again, the measured breath methanol concentrations more closely correspond to values predicted using the higher partition coefficient ($\lambda = 2874$) for samples collected 2 or more hours following cessation of exposure.

By comparing the measured blood concentrations of methanol in Tables 2 and 3, one can appreciate that 16 minutes of exposure of one hand (approximately 440 cm^2 of skin surface,

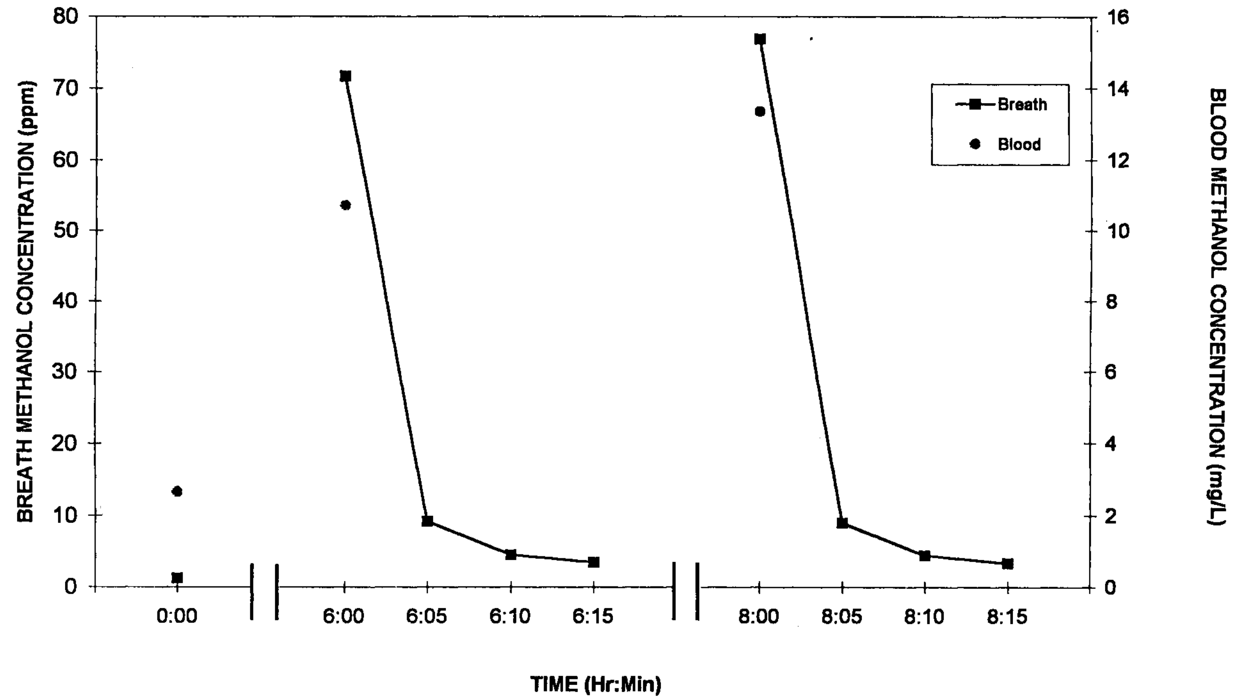

FIGURE 1. Blood and breath methanol concentrations of four subjects with inhalation exposure to methanol at 400 ppm.

or less than 3 percent of the total body surface area of a typical adult) to methanol yields a peak blood concentration of methanol which is about the same as the peak blood concentration achieved with inhalation exposure of 400 ppm for almost 8 hours. Another way of characterizing the contribution of dermal exposure to the overall absorbed dose is that exposure of one hand to methanol for 8 minutes yields a peak blood concentration that is approximately the same as that achieved following inhalation exposure at the threshold limit value (TLV) for methanol, which is 200 ppm(17) (data not shown). Thus, relatively brief dermal exposure of even a small percentage of the total skin surface area will result in a substantial absorbed dose relative to the maximal permissible dose (i.e., the dose absorbed with inhalation exposure at the TLV). These results underscore the importance of accounting for both dermal and inhalation routes of methanol absorption.

Discussion

Several previous studies have reported results of breath concentrations of methanol in relation to inhalation exposure. While Šedivec *et al.*(11) and Baumann and Angerer(10) included measurement of methanol in breath, these investigators did not measure methanol in blood, so their data cannot be used to address a key issue of the present report, which is to determine the conditions under which breath methanol measurements accurately reflect the blood methanol concentration. Also, the

TABLE 2. Inhalation Exposure to Methanol at 400 ppm (Without Exercise) With Four Subjects

	Methanol in Blood			Methanol in Breath				
	Concentration (mg/L)			Measured Concentration (ppm)				
Time (Hours)	Mean (Range)	Stand. Dev.	Number of Subjects	Mean (Range)	Stand. Dev.	Number of Subjects	Predicted Concentration (λ = 1626)	Predicted Concentration (λ = 2874)
Pre-exposure	2.65 (0.7–4.6)	1.8	4	1.3 (0.0–3.0)	1.3	4	1.2	0.7
6:00	11.1 (4.8–16.9)	6.1	4	71.7 (58.9–95.5)	16.9	4	5.2	3.0
6:05	11.1	6.1	4	9.2 (6.1–10.4)	2.0	4	5.2	3.0
6:10	11.1	6.1	4	4.5 (3.0–6.1)	1.3	4	5.2	3.0
6:15	11.1	6.1	4	3.5 (2.5–4.9)	1.0	4	5.2	3.0
8:00	13.4 (7.2–18.3)	4.8	4	76.9 (58.0–106.5)	20.8	4	6.3	3.6
8:05	13.4	4.8	4	8.9 (6.7–12.1)	2.3	4	6.3	3.6
8:10	13.4	4.8	4	4.4 (0.7–7.6)	2.9	4	6.3	3.6
8:15	13.4	4.8	4	3.3 (0.1–5.4)	2.3	4	6.3	3.6

λ = blood:air partition coefficient for methanol at 37°C (see text).

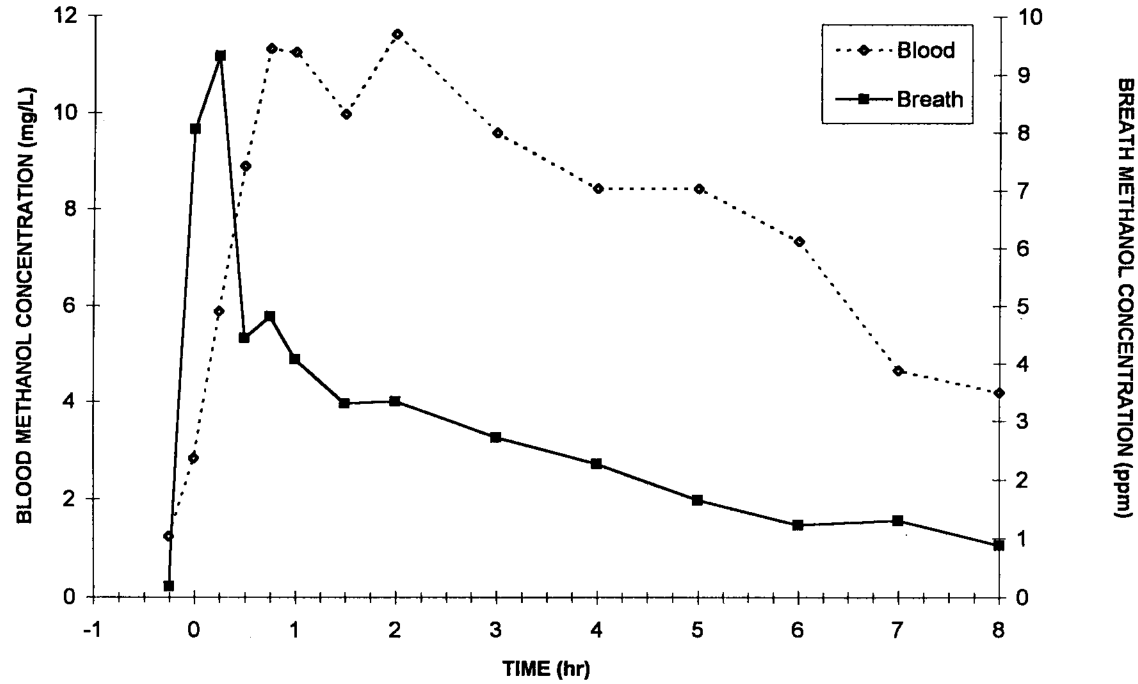

FIGURE 2. Blood and breath methanol concentrations of eight subjects following 16 minutes of dermal exposure.

timing of breath sampling in relation to exposures was not stated precisely in these reports, making it difficult to assess the temporal pattern of the concentration of breath methanol in relation to airborne exposures, particularly after the cessation of exposures.

Benoit *et al.*[12] also did not include measurement of methanol in blood, but the breath concentration of methanol was measured frequently, both during and after cessation of exposure, thus permitting comparison to our breath sampling results. In particular, their data demonstrate a very rapid increase and plateau in the concentration of methanol in breath while breathing contaminated atmospheres, and also a rapid decline of methanol concentration in breath following cessation of exposures, which closely resembles our results. The rapid

TABLE 3. Dermal Exposure to Methanol for 16 Minutes with Eight Subjects

	Methanol in Blood			**Methanol in Breath**				
	Concentration (mg/L)			**Measured Concentration (ppm)**				
Time (Hours)	**Mean (Range)**	**Stand. Dev.**	**Number of Subjects**	**Mean (Range)**	**Stand. Dev.**	**Number of Subjects**	**Predicted Concentration ($\lambda = 1626$)**	**Predicted Concentration ($\lambda = 2874$)**
Pre-exposure	1.2 (0.4–2.3)	0.7	8	0.2 (0.0–0.8)	0.3	8	0.6	0.3
0:00	2.8 (0.7–6.2)	2.2	7	8.1 (0.8–24.2)	8.7	8	1.3	0.8
0:15	5.9 (2.1–10.7)	3.4	8	9.3 (2.4–18.4)	5.7	8	2.8	1.6
0:30	8.9 (2.8–14.7)	3.9	8	4.4 (0.7–8.0)	2.3	8	4.2	2.4
0:45	11.3 (4.5–17.5)	4.1	8	4.8 (1.0–7.3)	2.0	8	5.3	3.0
1:00	11.3 (5.0–18.8)	4.4	7	4.1 (1.3–7.9)	2.2	8	5.3	3.0
1:30	10.0 (6.6–14.6)	3.0	7	3.3 (1.3–4.7)	1.2	8	4.7	2.7
2:00	11.6 (8.0–16.1)	2.5	8	3.3 (2.0–4.3)	1.0	8	5.5	3.1
3:00	9.6 (6.8–12.5)	2.0	8	2.7 (2.0–4.2)	0.8	8	4.5	2.5
4:00	8.4 (6.1–10.7)	2.0	8	2.3 (1.7–4.3)	0.9	8	4.0	2.2
5:00	8.4 (3.7–15.9)	3.6	8	1.7 (0.0–2.6)	0.9	7	4.0	2.2
6:00	7.3 (3.9–14.2)	3.2	8	1.2 (0.3–1.9)	0.5	8	3.5	2.0
7:00	4.7 (0.7–8.8)	2.7	8	1.3 (0.7–2.5)	0.6	8	2.2	1.2
8:00	4.2 (0.5–9.4)	3.2	7	0.9 (0.5–1.8)	0.4	8	2.0	1.1

λ = blood:air partition coefficient for methanol at 37°C (see text).

decline of methanol in breath following cessation of exposure was attributed to rapid pulmonary elimination of methanol "from the blood stream."

In a previous report, we presented methanol concentrations of blood and breath samples obtained simultaneously from four subjects before, during, and after cessation of exposure to 200 ppm of methanol for 6 hours.(9) The pattern of rapid increase and decrease in the concentration of breath methanol following initiation and cessation of exposure is consistent with the results of Benoit *et al.*(12) and the present report. However, in this earlier study only one postexposure measurement was obtained 1 hour after cessation of exposure, and so these earlier results do not demonstrate the very rapid decline in the first few minutes after stopping exposures.

Previous studies of inhalation exposure to methanol report measurements of methanol in breath samples obtained while subjects were still breathing methanol-contaminated air.(9,11,12) While our results demonstrate that such measurements appear to have no relationship to the blood concentration of methanol, such measurements are useful for calculating a retention fraction, and, in conjunction with ventilation rate and atmospheric concentration of methanol, permit estimation of the total absorbed dose. Previously published retention fractions for inhalation exposure to methanol have included 54.9 percent,(11) 72 percent,(12) and 73 percent.(9)

The measured breath concentrations of methanol are highly dependent on the timing of sample collection in relation to inhalation exposure. In particular, the breath concentration only reflects the blood concentration if breath sampling is delayed until after subjects have ceased inhalation methanol exposure for at least 10 or 15 minutes. Measured concentration in breath sampled while subjects were breathing methanol-contaminated air far exceeded the levels predicted using published partition coefficients. The explanation of why the breath concentration of methanol is so sensitive to the concentration of methanol in inspired air is probably related to adsorption and desorption of methanol in mucus lining the respiratory tree, and not rapid pulmonary uptake or elimination of methanol from the blood stream, as suggested by Benoit *et al.*(12) An *in vitro* study employing freshly isolated rabbit tracheae demonstrated that the percentage of vapor retained following a single passage through the tracheal segment was closely related to the water solubility of the substances being tested.(18) Methanol demonstrated the highest retention fraction (68%) of the 18 substances tested, and the tracheal retention fractions of the test compounds could be (roughly) rank-ordered based on water solubility. Therefore, when inhaling a methanol-contaminated atmosphere, a fraction of inhaled methanol is adsorbed onto mucus lining the respiratory tree, and, conversely, the excess methanol in airway mucus (i.e., that which is above the mean concentration in body water or blood) is desorbed when exhaling.

There are at least two reasons why rapid pulmonary clearance of methanol from the blood is probably not a significant contributing factor to the dramatic fall in breath methanol concentration following inhalation exposure. First, the half-life of methanol in blood is approximately 3 hours,(16) and this half-life is not compatible with a decline of breath methanol by a factor of 10 within 5 minutes. Second, pulmonary elimination of methanol accounts for less than 5 percent of the total absorbed dose (metabolic elimination is the fate of over 90% of the absorbed dose(16)). Thus, the contribution of pulmonary elimination of methanol from blood is too small to explain such a dramatic decline in the breath concentration of methanol.

One previous study has presented results related to human dermal methanol exposure,(8) but the investigators only measured methanol in expired air and urine, and not in blood. Their data, based on exposure of one hand of two test subjects for 20 minutes, reveal that the maximum pulmonary excretion of methanol occurred 30 minutes after termination of skin exposure. However, breath samples were not collected until after 30 minutes postexposure, and so these data cannot identify the early peak and subsequent rapid decline shown by our results, which included samples obtained at 0 and 15 minutes following termination of dermal exposures.

The present data demonstrate that the temporal patterns of blood and breath methanol concentrations following dermal exposure are clearly different. The early peak in breath methanol is probably related to a first pass effect. Methanol absorbed in the exposed hand is initially transported to the central circulation (and lungs) before being distributed to the rest of the body. Since absorbed methanol is believed to distribute evenly to all body water,(19) the concentration of methanol in venous blood returning from the exposed limb shortly following dermal exposure (and before the methanol has had an opportunity to distribute evenly to all body water) would be much higher than the mean equilibrium whole-body concentration. Therefore, the early breath measurements reflect higher blood methanol concentrations in the central circulation, and the simultaneous blood measurements (obtained contralaterally from the exposed arm) reflect the lower mean methanol concentrations in the entire water compartment.

The continued increase in blood methanol concentration for up to 45 minutes following cessation of dermal methanol exposure probably reflects the kinetics of methanol absorption through soft tissue (i.e., the hand in this experiment). Methanol that passes into and through the skin does not immediately enter the circulation and distribute to all body water. Rather, the soft tissues (more precisely, the local tissue water) at the site of absorption act as a local compartment, and only slowly release methanol as blood circulates through these tissues and redistributes the methanol to the entire water compartment. The measured blood methanol concentrations shown in Table 3 indicate that significant redistribution of methanol from the site of absorption continues for up to 2 hours following dermal exposure. In all of our dermal experiments the exposed skin area was the same hand for each subject, but the duration of exposure varied from 0 to 16 minutes. Yet the temporal patterns of blood and breath measurements were similar. It is not clear how a change in the exposed skin area or location, or longer durations of exposure, might alter the kinetics we observed.

As noted above, published blood:air partition coefficients for methanol vary considerably.(14,15) Our data suggest that the higher estimate of Pezzagno *et al.*(15) is more useful for estimating blood concentration from breath measurements, or vice versa.

It should also be reiterated that the dermal route of absorption can be a major, if not dominant, exposure pathway for methanol (compare results in Tables 2 and 3). These findings are consistent with previously published experimental results(8) and recent clinical descriptions.(20)

Conclusions

With purely inhalation exposure to methanol, measurement of methanol in breath will only be useful for estimating the blood concentration of methanol if breath is sampled after subjects have inspired uncontaminated air for at least 10 or 15 minutes. This delay is necessary to allow for desorption of methanol from the mucus lining airways. Since 15 minutes is short relative to the half-life of methanol in blood (approximately 3 hours), this delay should not result in significant loss of information, and a delay of 15 minutes should not be logistically difficult in terms of asking exposed workers to stay after a work shift to collect a breath specimen. However, if there is opportunity for dermal exposure (whether or not there is opportunity for inhalation exposure), then breath sampling must be delayed for at least 2 hours before measurement of methanol in breath can be used to estimate accurately the methanol concentration in blood. While it is theoretically possible to use such a delayed breath measurement to estimate the blood concentration of methanol, such a delay might be difficult logistically, since arranging for exposed workers to remain on site for 2 hours after a shift can be problematic.

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