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Absence of Formic Acid Accumulation in Urine Following Five Days of Methanol Exposure

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Five human subjects were exposed to an atmosphere containing 200 ppm of methanol in a test chamber for 7 hours per day for 5 consecutive days (Monday through Friday). Ambient air in the chamber was monitored continuously for methanol, while urine was monitored for methanol and formic acid. Spot urine specimens were collected immediately before and immediately after exposure periods on Monday through Friday, and also on the Saturday and Sunday mornings following the week of exposure. Morning urine specimens obtained Tuesday through Saturday were collected approximately 16 hours following cessation of exposure on the preceding day. Mean urinary methanol concentrations were increased from baseline at the end of each exposure session (Monday through Friday), but had returned to baseline in samples collected 16 hours following cessation of exposure. The concentration of formic acid in morning urine specimens did not change significantly over the 7 days of this experiment. These results indicate that: 1 there is no day-to-day accumulation of formic acid in urine in conjunction with five consecutive days of near-maximal permissible airborne methanol exposure; and 2 measurement of formic acid in urine specimens collected 16 hours following cessation of exposure does not appear to reflect inhalational methanol exposure on the preceding day. **Franzblau, A.; Lee, E.W.; Schreck, R.M.; D'Arcy, J.B.; Santrock, J.; Levine, S. P.: Absence of Formic Acid Accumulation in Urine Following Five Days of Methanol Exposure. Appl. Occup. Environ. Hyg. 8(10):883-888; 1993.**

Introduction

Absorption of methanol can occur via the lungs, the gastrointestinal tract, or percutaneous exposure,[1] and so availability of a method for biological monitoring, or a biologic exposure index (BEI), would be valuable since monitoring of methanol in air alone may underestimate the absorbed dose. Attention has focused on various approaches: methanol in expired air;[1-5] methanol in blood;[2,6-8] methanol in urine;[1,4,6,7,9] formic acid in blood;[3,6,8] and formic acid in urine.[3,6,7,9] The American Conference of Governmental Industrial Hygienists (ACGIH) lists two methods for biological monitoring of occupational methanol exposure: 1) measurement of methanol in spot urine specimens collected immediately following cessation of exposure; and 2) measurement of formic acid in urine specimens collected 16 hours following cessation of exposure at the end of a typical workweek.[10]

The recommended BEI for methanol that utilizes formic acid in urine is based on a single field study.[9] In a previous report concerning the formic acid method for biological monitoring of methanol exposure, we failed to confirm that the formic acid concentration in urine collected 16 hours following cessation of exposure was related to methanol exposure, and we did not confirm that there was accumulation of formic acid in urine collected 16 hours following cessation of exposure to methanol.[11] However, this study was limited since it involved only 1 day (6 hours) of methanol exposure. Nevertheless, other investigators have also reported results which suggest that the elimination half-life of formate in urine is too short to permit day-to-day accumulation over the course of a workweek.[6]

The present study was designed to address two specific questions: 1) is there accumulation, or buildup, of formic acid in urine over the course of a typical workweek (5 days) involving daily inhalational methanol exposure; and 2) does measurement of formic acid in urine specimens collected 16 hours following cessation of exposure reflect inhalational methanol exposure on the preceding day?

Methods

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 degree 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/h) using HEPA filtered, purified and dehumidi-

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fied air from the building inhalation facility pure air system. Temperature was controlled at 22° ± 2°C and relative humidity was maintained at 50% ± 5% by rehumidification of the inlet air.

Vaporization and delivery of methanol vapors to the inhalation chambers took place in two steps. The methanol was pumped from a reservoir into the 80°C vaporization section of the generator by an explosionproof metering pump. The vaporizer had a continuous flow of 200 L/min of filtered, compressed air with a methanol concentration of approximately 15,000 ppm, which is less than the explosive range of 67,000 to 360,000 ppm. The diluted methanol vapor was metered into the inhalation chamber air flow through a mass flow controller and the vapors further diluted to achieve the desired 200 ppm concentration.

Exposure Chamber Air Monitoring

The concentration of methanol in the chamber was monitored using a MIRAN 1-A (Foxboro, South Norwalk, Connecticut) infrared analyzer equipped with a closed-loop calibrator. The MIRAN was set at an indicated wavelength of 9.55 μm (1047 cm^{-1}) using an absorbance scale of 1.0 and a path length of 17.25 m. The output was recorded continuously using a Rustrak Ranger data logger (Gulton Co., E. Greenwich, Rhode Island). Calibration was performed using direct injection of methanol liquid into the calibration loop. The limit of detection (LOD) was 1 ppm under these operating conditions, and the coefficient of variation for calibration of the instrument was 3 percent.

Urine Sampling

This experiment lasted 7 days. Methanol exposure lasting 7 hours per day occurred during the first 5 days (Monday through Friday); no exposure occurred during the last two days. Spot urine specimens were collected from each subject immediately before exposure and immediately after exposure on Monday through Friday. In addition, morning urine samples were collected on the Saturday and Sunday following the 5 days of exposure. All morning urine specimens were collected at approximately the same hour each day (7:45 A.M. ± 15 minutes). Because of the well-known impact of ethanol on metabolism and kinetics of methanol,[12] subjects were instructed to refrain from consumption of alcoholic beverages (i.e., beverages containing ethanol) beginning the day prior to the first day of the experiment until after collection of the final urine specimen. All urine specimens were analyzed for methanol, formic acid, and specific gravity.

Analyses for Methanol, Formate, and Specific Gravity

For analyses of methanol and formic acid in urine, a Hewlett-Packard gas chromatograph (model 5890A, Palo Alto, California) equipped with split injector and flame ionization detector was used. Chromatography was conducted on a DB-wax capillary column (30 m, 0.53 mm internal diameter, 1.0 μm film thickness from J&W Scientific, Folsom, California) at an oven temperature of 30°C with a mixture of 80 percent helium and 20 percent hydrogen as carrier gases. The injector and detector temperatures were set at 250°C. The column head pressure for methanol was 4.0 lb per square inch (psi), which gave a linear velocity of 97 cm/second, and it was 1.5 psi with a linear velocity of 39 cm/second for formate. The split ratio was 1:7 for methanol determination, and 1:20 for formate determination.

For methanol determination, 0.5 ml of urine was placed into glass vials (10 ml) containing 1.5 g of anhydrous sodium sulfate. The sealed vials were heated at 80°C for 30 minutes in an automated headspace sampler (the Hewlett-Packard Headspace Sampler, model 19395 A with constant heating time accessory). One milliliter of headspace of the heated samples was injected into the split injector automatically by the sampler. The detection limit for methanol was 0.25 mg/L. Added methanol showed 91 percent recovery at a concentration of 8 mg/L (N = 10) with coefficient of variation of 1.4 percent.

Formate concentrations in urine samples were determined by a modified procedure of Schweda,[13] requiring esterification of formate with ethanol to ethyl formate, a volatile compound. In brief, 0.5 ml of urine was placed in a glass vial (10 ml), and 0.5 ml of the esterification mixture (7:2:1 V/V mixture of ethanol:concentrated sulfuric acid:acetonitrile) was added at 0°C. The vials were quickly sealed and reacted for 45 minutes at 55°C in the automated headspace sampler described above. One milliliter of headspace of the sample was then injected into the split injector. The detection limit for formate was 1.0 mg/L. Added formate showed 96 percent recovery at a concentration of 23 mg/L (N = 10) with coefficient of variation of 2.3 percent. The urine specific gravity was determined by refractometry.

Human Subjects

Four men and one woman participated in this experiment. The number of subjects studied in this experiment (five) is the maximum which could be studied simultaneously in the exposure chamber. Four subjects were nonsmokers; the one individual who smoked was not permitted to do so while in the exposure chamber. 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 the entire week of the experiment. Two of the subjects were accustomed to consuming modest quantities of dietetic beverages sweetened with aspartame. This practice was not proscribed during the experimental period, but these two subjects provided a log of their consumption of such beverages. None of the five subjects had known occupational or avocational exposure to methanol, formic acid, or formaldehyde. All subjects provided written informed consent. The consent form and research protocol had been approved by the Human Subjects Review Committees of the University of Michigan School of Public Health and the General Motors Research Laboratories.

Statistical Analyses

All statistical analyses were performed using SYSTAT (version 5.03, SYSTAT, Inc., Evanston, Illinois). Because of repeated measurements applied to the same subjects, paired *t*-tests were performed. Comparisons were considered to be statistically significant if the p value was less than or equal to 0.05.

Results

The daily duration of methanol exposure of each subject was timed individually, and lasted 7 hours per day in all cases. Methanol exposures were not interrupted for lunch or any other breaks. Subjects remained sedentary during exposure periods.

The methanol concentrations to which subjects were exposed remained remarkably stable during the entire week of the experiment. The lowest and highest methanol concentrations were 189.6 and 208.5 ppm, respectively. Overall, the mean methanol concentration for the entire week was 200.9 ppm, and the 8-hour time-weighted average (TWA) methanol exposure for the week was 176 ppm.

Morning urine specimens were collected at approximately the same time each morning (7:45 A.M. ± 15 minutes). Subjects entered the exposure chamber soon thereafter on Monday through Friday. The time delay between last methanol exposure (Monday through Friday) and collection of a urine specimen the following morning (Tuesday through Saturday) averaged 16.7 hours, with a range of 16.2 to 17.2 hours.

The results of measurements of methanol and formic acid in urine specimens are summarized in Tables I and II. Unfortunately, not all subjects produced enough volume of urine at each collection to permit laboratory analyses for methanol, formic acid, and specific gravity. However, no subject missed contributing more than 2 of the 12 possible specimens during the entire experiment. The number of specimens successfully analyzed is noted for each day and time. All analyses involved at least four of the five participating subjects, except for Saturday morning when only three subjects provided adequate urine specimens.

TABLE I. Mean Concentrations of Methanol in Urine*

Day and Time of Specimen Collection	Number of Specimens	Methanol Concentration Uncorrected for SpGr Mean (SD)	Methanol Concentration Corrected to SpGr = 1.015 Mean (SD)
Monday AM	4	1.2 (0.6)	1.2 (0.6)
PM	5	6.2 (1.4)	6.2 (1.5)
Tuesday AM	4	1.9 (1.1)	1.9 (1.1)
PM	4	6.3 (1.8)	6.3 (1.8)
Wednesday AM	5	1.1 (0.5)	1.1 (0.5)
PM	5	6.7 (1.8)	6.6 (1.8)
Thursday AM	5	1.4 (0.6)	1.4 (0.6)
PM	5	7.0 (1.7)	7.0 (1.7)
Friday AM	4	0.9 (0.1)	0.8 (0.1)
PM	5	6.1 (1.3)	6.0 (1.2)
Saturday AM	3	1.1 (0.5)	1.0 (0.5)
Sunday AM	4	1.3 (0.7)	1.3 (0.7)

*All units are milligrams of methanol per liter of urine.
SpGr specific gravity
SD standard deviation

TABLE II. Mean Concentrations of Formic Acid in Urine*

Day and Time of Specimen Collection	Number of Specimens	Formic Acid Concentration Uncorrected for SpGr Mean (SD)	Formic Acid Concentration Corrected to SpGr = 1.015 Mean (SD)
Monday AM	4	26.1 (11.5)	25.8 (11.3)
PM	5	19.5 (10.4)	19.5 (10.3)
Tuesday AM	4	25.1 (11.7)	24.9 (11.6)
PM	4	17.3 (10.2)	17.2 (10.0)
Wednesday AM	5	27.9 (13.0)	27.6 (12.8)
PM	5	27.8 (11.7)	27.6 (11.5)
Thursday AM	5	20.8 (7.7)	20.6 (7.5)
PM	5	22.8 (7.5)	22.8 (7.4)
Friday AM	4	31.8 (3.6)	31.4 (3.5)
PM	5	38.7 (14.3)	38.5 (14.0)
Saturday AM	3	12.7 (6.0)	12.6 (5.9)
Sunday AM	4	25.0 (8.2)	24.7 (8.2)

*All units are milligrams of formic acid per liter of urine.
See Table I for abbreviations.

In all cases comparisons of morning to afternoon methanol concentrations in urine using paired *t*-tests were statistically significant, regardless of correction of methanol concentrations for specific gravity (e.g., Monday A.M. versus Monday P.M., Tuesday A.M. versus Tuesday P.M., etc.; see Table I). All such p values were less than 0.034.

Multiple paired *t*-tests of all combinations of "A.M." methanol measurements were performed (7 sets of morning measurements; 21 paired analyses). There were no significant interday changes in the morning concentrations of methanol over the seven days of observation. Similar pairwise comparisons of the "P.M." methanol measurements (i.e., Monday, Tuesday, Wednesday, Thursday, and Friday P.M.; 10 paired analyses) also demonstrated no significant differences in postexposure methanol concentrations in urine (see Table I). Correction of urine concentrations of methanol for specific gravity had no effect on these results.

Cross-shift pairwise comparisons of formic acid concentrations (i.e., Monday A.M. versus Monday P.M., Tuesday A.M. versus Tuesday P.M., etc) were not statistically significant, regardless of correction for specific gravity (see Table II). Pairwise comparison of all "A.M." formic acid measurements (7 different morning measurements, a total of 21 paired analyses) also revealed an absence of differences that were statistically significant. There was no apparent trend in the morning formic acid concentrations over the week of the experiment.

Table III lists the minimum, maximum, and mean morning formic acid concentrations of each subject during the week of the experiment. There was considerable intrasubject and intersubject variability in these results.

TABLE III. Individual Means and Ranges of Concentration of Formic Acid in Morning Urine Specimens*

Subjects	No. of Specimens	Low Value	High Value	Mean Value
Subject 1	7	17.4	35.4	25.5
Subject 2	6	29.1	43.8	36.3
Subject 3	6	20.9	36.9	25.2
Subject 4	5	5.9	12.3	9.2
Subject 5	5	14.9	31.4	24.0

*All units are milligrams of formic acid per liter of urine.

Discussion

We have performed a human exposure chamber experiment in which five subjects were exposed for 7 hours per day on 5 consecutive days to a test atmosphere that contained the maximal permissible concentration of methanol (200 ppm). The experimental protocol involved a full workweek of (sedentary) methanol exposure, with the important caveat that the subjects had no opportunity for cutaneous methanol exposure.

Subjects were instructed to avoid all ethanol-containing beverages during the week of the experimental protocol. All subjects appeared highly motivated in this regard, and all reaffirmed their avoidance of ethanol-containing beverages on multiple occasions during the experiment. Our gas chromatograph method of measuring methanol in urine also permitted determination of ethanol in urine, and there was no evidence from these results to suggest that any subject had ingested ethanol. However, it should also be noted that, given the urine half-life of ethanol, measurement of ethanol in morning urine specimens may be an insensitive method for detecting modest amounts of ethanol ingested 10 to 14 hours earlier.

Subjects' exposure to methanol was confirmed by continuous measurement of methanol in the test atmosphere, and the "cross-shift" change in the methanol concentrations measured in spot urine specimens (preshift versus postshift). The cross-shift changes in the urine methanol concentrations observed in this experiment are similar in magnitude to previously reported results.[4,14]

Two subjects reported consuming up to six 12-oz drinks sweetened with aspartame on each day of the protocol. It is well known that the metabolic breakdown products of aspartame include methanol. However, a previous study has shown that adults administered "abuse-level" doses of aspartame (up to 200 mg/kg in a single bolus) do not have elevated excretion of urinary formate beyond 8 hours following ingestion.[15] In another study, subjects ingested eight successive hourly servings of beverage "spiked" with 600 mg of aspartame, the equivalent of three 12-oz servings of diet beverage.[16] The concentration of formate in urine did not increase significantly from baseline (i.e., time zero, prior to ingestion of first serving) through measurements made up to 17 hours following the last oral dose of aspartame. In light of these results, the reported daily consumption by two subjects of up to six cans of diet soda would appear to be trivial, and would not be expected to have any measurable impact on formic acid excretion in urine during the course of this study.

The primary objectives of this experiment were to assess whether "chronic" occupational methanol exposure results in a buildup of formate in urine over the course of a workweek, and, whether measurement of formate in urine collected 16 hours following cessation of exposure to methanol reflects inhalational methanol exposure on the preceding day. These are essential assumptions that form the foundation of the current ACGIH recommended BEI for methanol based on measurement of formic acid in urine.[9,10] Our results fail to provide support for either of these assumptions.

The study published by Liesivuori and Savolainen[9] is the sole basis of the current BEI for methanol using formic acid, and the design of the present study differs in a number of significant ways. Probably the most important distinction is that their study was a field study of active workers with occupational methanol exposure, as opposed to a controlled experiment. The authors acknowledge that some of their subjects may have experienced "spills of liquid methanol on the skin," and this would have explained some of the "very high [urinary] formic acid concentrations" which they observed. We believe that cutaneous methanol exposure is a likely cause of the discrepancies between the two studies.

Another potential difference is that our subjects were sedentary while in the exposure chamber (exercise was not possible with five subjects in the exposure chamber simultaneously). The activity level of subjects is not described in the previous study, but it would be reasonable to assume that the workers in that study were not sedentary. Pulmonary absorption of methanol is linearly related to minute ventilation,[4] and so higher physical activity would result in increased minute ventilation, and increased pulmonary absorption of methanol. It is possible that differences in physical activity may have contributed to differences in results between the two studies.

Our study of sedentary subjects exposed to 176 ppm TWA would be equivalent to a study of subjects with exertion involving a doubling of minute ventilation and exposed to 88 ppm TWA of methanol. The regression equation in the paper of Liesivuori and Savolainen relating TWA methanol exposure and urinary formate excretion suggests that with exposure to 88 ppm TWA the mean urinary concentration of formate in specimens collected 16 hours following cessation of methanol exposure would be approximately 25 to 30 mg/g creatinine (all measurements of formate in urine are corrected for creatinine in their paper.[9] No baseline (i.e., preexposure) measurements of formic acid in urine of exposed subjects were reported, but comparison subjects without methanol exposure ($N = 18$) had 15.1 ± 6.1 mg/g creatinine of formic acid in morning urine samples.

Although 25 to 30 mg/g creatinine of formic acid is higher than 15.1 mg/g creatinine, it would be difficult to interpret the significance of this magnitude of change in urinary for-

mate concentration in an individual. Formic acid concentrations in urine vary considerably among nonexposed individuals. Among our four subjects for which data were available, the Monday morning formic acid concentrations in urine ranged from 12.3 to 40.2 mg/L (mean 26.1 mg/L). There was also considerable intraindividual variability in formic acid concentrations in morning urine specimens during the week of the experiment (see Table III). The overall range of formic acid concentrations in morning specimens, both interindividual and intraindividual variability, that we observed is consistent with what has been reported by other investigators. Reported ranges of formic acid concentrations in urine among nonexposed subjects (i.e., interindividual variability) have been quite broad: 6.5 to 47.4 mg/L,[7] 0 to 25 mg/L,[3] and 0 to 89 mg/L.[17] Intraindividual variability among nonexposed subjects has also been reported as relatively broad (e.g., 9.3 to 28.7 mg/g creatine and 26.0 to 64.0 mg/g creatinine are two examples.[6] Mean values (and standard deviations) of formic acid concentrations in urine of nonexposed subjects have also varied considerably: 12.7 ± 11.7 mg/L;[7] 11.9 ± 6.4 mg/L;[3] 18 ± 28 mg/L;[17] 7.4 ± 1.9 mg/L;[18] 7.8 ± 1.9 mg/g creatine (geometric mean);[14] and 28.8 ± 9.6 creatinine.[6] A change of 15 to 30 mg/L (or mg/g creatinine) or formic acid in urine is well within the range of values reported among subjects without methanol exposure. For a BEI for methanol based on formate in urine to be used for monitoring of individual exposure (as opposed to group averaging), the magnitude of change in urine formate would need to be quite large to reliably distinguish true methanol exposure from normal intraindividual variability.

Another difference in study design is that subjects in the experimental protocol were specifically instructed to avoid ethanol-containing beverages during the week of the experiment. Possible ethanol consumption among workers studied by Liesivuori and Savolainen is not mentioned.[9] Consumption of alcoholic beverages could have increased or decreased the excretion of formic acid, depending on the timing of ingestion in relation to collection of urine specimens.

The statistical analyses employed in the present study include 134 paired *t*-tests. No adjustments for multiple comparisons have been employed for two reasons: 1) the theoretical justifications for making such adjustments are not well grounded or universally accepted[19]; and 2) the primary conclusions of the present study are a failure to reject the null hypotheses. Adjustment for multiple comparisons (i.e., reducing the threshold for significance from, for example $p = 0.05$ to $p = 0.01$) would only serve to make it more difficult to reject the null hypotheses, and would reinforce our conclusions. Our approach, to not adjust, is conservative.

In summary, we have shown that with near-maximal permissible pulmonary exposure alone, there is no accumulation of formate in urine following 5 consecutive days of methanol exposure. In addition, measurement of formic acid in urine collected 16 hours after exposure does not appear to be related to inhalational methanol exposure on the preceding day. Our results suggest that the formic acid BEI for methanol needs revision and additional study.

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