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Formate in Serum and Urine after Controlled Methanol Exposure at the Threshold Limit Value

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The proposed use of methanol as an automotive fuel and its introduction as a possible air pollutant has renewed interest in its toxicology (1), as little is known about either the effects of low-dose methanol exposure or biological markers of its toxicity (2). Methanol levels in urine have been shown to correlate with methanol exposure (3–6). However, because methanol toxicity is due to formate, its principal metabolite, (7–9), formate might be a better indicator of toxicity. Some investigators have reported serum and/or urine formate concentrations as biological indicators of methanol exposure (10), although other studies have failed to confirm this (2,4,11). In this report, we describe the effect of 4-hr constant exposure to methanol vapors at the U.S. National Institute of Occupational Safety and Health permissible exposure limit of 200 ppm on serum and urine formate levels in humans at rest. Data presented here are part of a larger study in which neuropsychological and visual performances and methanol in serum and urine are measured before and after methanol exposure. Methanol and neuropsychological data will be presented in a subsequent work.

Of 32 subjects answering an advertisement describing the study, 28 met the inclusion criteria. After the interview and the physical exam, one subject was excluded because of a history of hepatitis B. All subjects gave informed consent, and the study was approved by the Committee on Human Research at the University of California San Francisco.

Inclusion criteria were age between 20 and 55 years, in general good health, and a normal level of folic acid. Exclusion criteria were a positive history of hepatitis or liver disease, central nervous system diseases, and drug or alcohol abuse. A questionnaire was administered for data on medical history, personal habits (smoking, coffee and alcohol consumption), occupational history, and chemical exposure. None of the subjects had known recent occupational exposures to methanol, formic acid, or formaldehyde. Subjects were requested to follow a diet from 24 hr before the experimental session and for the 8-hr duration of the

study. They were requested to avoid sweeteners and soft drinks containing aspartame (Nutra-Sweet), vegetables, fruits, fruit juice, roasted coffee, and alcoholic beverages in order to reduce dietary intake of aspartame, methanol, and formate. Fluid intake was not restricted with the exception of beverages specified in the diet.

The exposure took place in a 2.45 × 2.45 × 2.38 m stainless-steel exposure chamber. The chamber had a total volume of 14.3 m³ and a ventilation rate of 11.8 air changes/hr (2.8 m³/min). Air entering the chamber was filtered through a charcoal filter. Temperature was maintained at 20°C and relative humidity was 40% (12). The vapor-generating system, located inside the chamber, generated vapors at a rate of 43.68 g/hr. An HPLC pump delivered either high-grade purity methanol or water from a small reservoir onto a hot plate (70°C) to generate vapors. An oscillating fan behind the hot plate distributed the vapors throughout the chamber. Air samples collected at various zones inside the chamber (corners, ceiling, floor) and at subjects' breathing zone showed that methanol vapors were uniformly distributed. An infrared spectrometer (Miran 1B, Foxboro Instruments, South Norwalk, Connecticut), placed in the middle of the chamber was calibrated to measure methanol concentrations at a wavelength of 9.53 μm. The pump delivery rate was controlled by a personal computer that received feedback of methanol concentrations from the spectrophotometer every 30 sec. We calibrated the infrared spectrometer several times over the course of the study by a closed-loop calibration method. Calibration was performed between experimental exposures. Samples from the inhalation atmosphere, collected inside the chamber by Tedlar Bag, and calibrators for the spectrophotometer were also determined independently by gas chromatography ($y = 0.18426 + 0.93560x$, $r^2 = 1.000$, range: 25–225 ppm). A concentration of 200 ppm of methanol inside the chamber was achieved before subjects entered the chamber, and it remained stable within the desired range (180–220 ppm) for the full 4-hr exposure time. Analysis of

Methanol will be present as a new air pollutant when methanol-powered vehicles are introduced in the United States. Little is known about the effect of low-dose methanol exposure. It is controversial whether or not formate, the main metabolite responsible for methanol's acute toxicity, is a sensitive biological marker of toxicity or exposure. We studied the effect of a 4-hr exposure at rest to 200 ppm of methanol vapors on endogenous serum formate and on urinary formic acid excretion. A randomized, double-blind study of human exposure to a constant concentration of methanol was performed in a whole-body exposure chamber. Twenty-six healthy volunteers, each serving as his or her own control, participated in sham and methanol exposures. Urine (at 0, 4, 8 hr) and serum specimens (15 time points over 8 hr) collected before, during, and after the exposure were measured for formate. We found no significant differences in serum formate concentration between exposure and control conditions either at any time point or for area under the curve. Mean concentrations at the end of the exposure were: exposed 14.28 ± 8.90 mg/l and control 12.68 ± 6.43 mg/l. A slight, but nonsignificant ($p = 0.08$), increase in urine formate excretion rate was found at 4 hr (exposed 2.17 ± 1.69 mg/4 hr and control 1.67 ± 1.02 mg/4 hr). Age, sex, folic acid level, and smoking were not significant covariates. At 200 ppm, methanol exposure does not contribute substantially to endogenous formate quantities. Serum and urine formate determinations are not sensitive biological markers of methanol exposure at the threshold limit value. **Key words:** biological monitoring, environmental exposure, formate, methanol. *Environ Health Perspect* 102:178–181(1994)

five subjects in pilot exposures, at 200 ppm for 4 hr, showed that serum methanol concentrations increased from a mean of 1.29 ± 0.68 mg/l at 0 hr to a mean of 6.80 ± 1.6 mg/l at the end of exposure (4 hr). This is close to predicted concentrations based on 58% pulmonary retention, a volume of distribution of 0.6 l/kg, and a ventilation rate at rest of about 10 l/min.

Subjects were exposed twice, once to 200 ppm of methanol vapors (experimental exposure) and once to water vapor

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(control exposure). The exposure conditions were randomized and double blinded. Only the industrial hygienist, in charge of the methanol delivery system, was aware of the presence of methanol in the chamber. Volunteers were exposed in groups of three. The methanol concentration inside the chamber was stabilized to 200 ppm before subjects entered and was only slightly affected (within 10% variation) by the door being opened. Subjects were sitting at rest inside the chamber during the full 4-hr exposure. Urine samples were collected before subjects entered the chamber (0 hr), upon exiting the chamber (4 hr) and 4 hr later (8 hr). Blood samples were collected by sampling from a heparin lock placed in an antecubital vein before subjects entered the chamber, every 15 min for the first hour, every 30 min for 3 more hr, and every hour for the final 4 hr. All the experimental sessions were held from 0900 to 1700 hr.

We analyzed serum samples for formate using an enzymatic method with a colorimetric endpoint (13). The sensitivity of the method is 0.5 mg/l, and the coefficient of variation at 12 mg/l is 10%. The same method was used for the urine assay by modifying the size of the sample (80 μ l for serum and 200 μ l for urine).

Data were analyzed using the SAS system and included analysis of variance, paired Student's *t*-test, regression, and analysis of covariance with sex, folic acid level, smoking habit, and age used as covariates.

Twenty-six of the 27 enrolled subjects completed the study, 11 females and 15 males (1 subject declined to continue the study because of blood drawing intolerance). Age was 35.8 years \pm 6.9, (mean \pm SD throughout). Serum folate levels ranged from 3.80 to 25.20 ng/ml (normal value: above 3.1); the mean was 10.25

ng/ml. Seven were smokers (27%). No subject was taking prescribed medications. Two subjects were consuming multivitamin preparations. Data on the urine concentration of one subject taking more than 10 g of ascorbic acid daily were excluded because of an interference by this amount of ascorbic acid on the formate assay.

Serum formate concentrations, at any of the time points, did not show any statistically significant differences between the two exposure conditions. For example (Table 1), the mean serum formate concentration at 1 hr was 10.82 \pm 5.30 mg/l during methanol exposure and 11.95 \pm 6.52 mg/l during control exposure (*p* = 0.15). At the 4 hr time point, the mean serum formate concentrations were higher during methanol exposure than during control exposure (14.28 \pm 8.90 versus 12.68 \pm 6.43 mg/l), although not significantly so (*p* = 0.38). Also, when we compared control and methanol exposure conditions by computing area under the curve (AUC) or by subtracting formate concentration in serum at 0 hr, (i.e., subtracting the endogenous serum formate or baseline) from the serum concentration at significant timepoints, no significant differences were observed (Table 2) between the two conditions.

Small changes in serum formate over time have been observed in the sham condition; both serum formate at 4 hr and serum formate at 8 hr were higher than the preexposure level (*p* < 0.05). However, the paired changes for serum formate (either 0–4 or 0–8 hr) when compared between exposures were not significantly different.

When analyzed by sex, serum formate concentrations during methanol exposure at 0, 4, and 8 hr were 10.44 \pm 8.49 mg/l, 13.36 \pm 8.37 mg/l, and 12.88 \pm 9.07 mg/l for females (*n* = 11) and 11.81 \pm 8.00 mg/l, 14.96 \pm 9.49 mg/l, and 12.00 \pm 4.12

mg/l for males (*n* = 15), respectively. During sham exposure, values were 10.27 \pm 7.55 mg/l, 12.63 \pm 8.67 mg/l, and 12.28 \pm 8.98 mg/l for females and 10.37 \pm 3.68 mg/l, 12.72 \pm 4.48 mg/l, and 13.45 \pm 7.52 mg/l for males, respectively. Analysis of covariance with sex used as covariate was not significant.

One of the study subjects, a white male, had an unusual response to exposure. His serum formate concentrations rose as high as 44.36 mg/l at 3.5-hr and 42.39 at 4-hr during methanol exposure compared to a preexposure baseline concentration of 14.74 mg/l. During the sham exposure, his serum formate concentration was within the group variability. Other subjects exposed at the same time did not show this response. No cause for this unusual response has been identified.

Formate excretion rate (mg/4 hr) for both exposures are presented in Table 3. Formate excretion at the end of the exposure (0–4 hr) was 1.67 \pm 1.02 mg/4 hr in the controls (females 1.85 \pm 0.83; males 1.56 \pm 1.15 mg/4 hr) and for methanol exposure was 2.17 \pm 1.69 mg/4 hr (females 1.93 \pm 0.89; males 2.33 \pm 2.08 mg/4 hr); the difference between the two exposure conditions approached statistical significance (*p* = 0.08) at the end of the exposure (4 hr). Urine concentrations values are presented in Table 4. There were no statistical differences in these comparisons or in the changes over time.

We examined the role of other factors as covariates by regression analysis with various formate measures as the dependent variable, and no significant relation was found when sex, folic acid level, smoking habit, and age were tested.

In this randomized, double-blind study of human exposure to methanol, in which each subject served as his or her own control, a 4-hr exposure to a constant concentration of 200 ppm methanol did not increase serum or urine formate levels.

Methanol is readily absorbed through the respiratory system, and inhalation is the most common route of entry in an occupational setting. Pulmonary retention of methanol has been estimated by Sedivec et al. (3) as being 58% of the inhaled dose. In humans, alcohol dehydrogenase oxidizes methanol to formaldehyde, and formaldehyde dehydrogenase oxidizes formaldehyde to formic acid. Accumulation of formic acid in blood occurs during acute methanol intoxication, and this has been shown in primates to be responsible for the metabolic acidosis and visual toxicity, complicating methanol overdose (7,14–17). Formic acid eventually enters the one-carbon pool, being combined with tetrahydrofolate (THF) to form 10-formyl-THF, which in turn can be directed to other

Table 1. Selected time points for serum formate concentration under exposure and control conditions^a

Time (hr)	Exposed (mg/l)	Control (mg/l)	<i>p</i> ^b
0	11.23 \pm 8.07	10.33 \pm 5.51	0.45
1	10.82 \pm 5.30	11.95 \pm 6.52	0.15
4	14.28 \pm 8.90	12.68 \pm 6.43	0.38
8	12.38 \pm 6.53	12.95 \pm 8.01	0.60
4 minus baseline ^c	3.0 \pm 8.39	2.35 \pm 3.50	0.71

^aValues are expressed as means \pm SD (*n* = 26).

^b*p*-value for a two-tailed hypothesis.

^cBaseline is value of serum formate before the exposure (0 hr).

Table 2. Area under the curve (AUC) for serum formate under exposure and control conditions^a

AUC time (hr)	Exposed (mg/ml/hr)	Control (mg/ml/hr)	<i>p</i> ^b
0–4	64.47 \pm 31.88	61.49 \pm 28.24	0.52
0–6	89.27 \pm 44.30	88.89 \pm 40.71	0.97

^aValues are expressed as means \pm SD (*n* = 26).

^b*p*-value for a two-tailed hypothesis.

Table 3. Urine formate excretion under exposure and control conditions^a

Time (hr)	Exposed (mg/4 hr)	Control (mg/4 hr)	<i>p</i> ^b
0–4	2.17 ± 1.69	1.67 ± 1.02	0.08
4–8	1.04 ± 0.66	1.00 ± 1.08	0.87
0–8	3.21 ± 2.11	2.67 ± 1.76	0.23

^aValues are expressed as means ± SD (*n* = 25).^b*p*-value for a two-tailed hypothesis.**Table 4.** Formate concentration in urine under exposure and control conditions^a

Time (hr)	Exposed (mg/l)	Control (mg/l)	<i>p</i> ^b
0	6.66 ± 4.97	6.29 ± 3.60	0.70
4	7.14 ± 5.17	6.64 ± 4.26	0.59
8	6.08 ± 3.49	5.64 ± 3.70	0.60

^aValues are expressed as means ± SD (*n* = 25).^b*p*-value for a two-tailed hypothesis.

metabolic pathways or can be metabolized to carbon dioxide and water (18,19). Investigations have suggested that a direct relation exists between the rate of formate oxidation and liver content of THF (21).

Several studies have sought a biological marker of methanol exposure. Methanol in urine has been regarded as the most promising because it is easy to measure (19), and it has been shown to correlate well with blood methanol concentration (3). However, because formate is ultimately responsible for methanol toxicity, it may be a better marker from a toxicological standpoint.

Studies of formate concentrations after methanol exposure have produced conflicting results. A recent double-blind study of human exposure to 200 ppm of methanol vapors for only 75 min found no increase in serum formate concentrations (11). As the authors of this study suggested, a change in formate concentration was unlikely after 75 min of exposure. Lee et al. (4) found no changes in serum formate levels when comparing only two time points (before and after a 6-hr exposure) at 200 ppm of methanol vapors, in a limited sample of six healthy males. Baumann and Angerer (20), in a study of 20 workers exposed to methanol vapors in a printing office, found a slight increase in serum formate when samples from before and after an 8-hr work shift were compared. However, this positive finding might also be explained on the basis of dietary changes, variability in exposure concentrations as high as 680 ppm, cutaneous absorption from direct contact, or increased respiratory exposure due to workload. The slight increase that these authors reported was an isolated finding in that neither urine formate concentration nor blood formate correlated with methanol concentration measured in the environmental air or in the alveolar air.

Our results on urinary formate levels support findings of some related studies

(2,4,11), namely, that exposure at the current level of 200 ppm of methanol vapors does not significantly increase the amount of formic acid excreted in urine.

Several field studies have shown a slight correlation between level of exposure to atmospheric methanol and formate in urine. In a field study with a control group, formate was measured in urine collected after an 8-hr shift at the end of the working week on 20 workers exposed to methanol (22). Workers were exposed at air levels below the permissible time-weighted average level of 200 mg/m³ (range 37–231 mg/m³).

The slight increase that these authors found in the exposed group was well within the range of individual variability, thereby precluding its use as a marker of individual exposure. Also the subjects' diets were not standardized. Both an unrestricted diet, by means of dietary methanol or formate intake from foods, and also a restricted diet, by means of protein catabolism, could contribute to variability of endogenous formate levels. Subjects in our study refrained from eating foods known to contain methanol, formate, or aspartame. However, while in the chamber, they had no food, so that at the end of the exposure, they had fasted for 4 hr. Small changes in serum formate were observed during the sham exposure. Possibly the fasting state contributed to these small changes.

One of our subjects showed an unusually high serum formate concentration during methanol exposure but not during the sham exposure. His urine formate excretion rate was well within the group's variability. We have no explanation for this finding, but it nevertheless seems to be an unusual biological response that may occur in a small portion of the population.

The correct time to monitor methanol exposure has been recently debated. To test Liesivuori and Savolainen's (10) finding of delayed elimination of formate in urine,

Franzblau et al. (2) performed an experiment in which four adult subjects were exposed to 200 ppm of methanol in a chamber for 6 hr. Urine formate concentrations were not statistically different at the preexposure, 6-hr, and 16-hr time points. Because this study did not have a control group and the sample size was small, a definitive conclusion cannot be drawn. Yet the findings are consistent with methanol pharmacokinetic parameters such as half-life, volume of distribution, and elimination rate at low concentrations (18,21,24).

Previous studies have lacked at least one of the following: a control group, maintenance of a constant or known exposure, randomization, serial determination of serum and urine formate, an exposure period of 4 hr or more, blinding, and dietary safeguards. Our study included these features in its design and showed no formate increase in serum and urine after methanol exposure at 200 ppm.

The preexposure level for both urine and serum formate can be regarded as a measurement of endogenous level or baseline. The value for urine formate that we report in this study is within the range of values reported by others (18), regardless of the analytical procedure used. Serum formate levels are in good agreement with values reported by Lee et al. [about 10 mg/l (4)], but higher than values reported by Cook and co-workers [3.5 mg/l (11)]. The explanation for the latter lower value can be found, as the authors suggested, in the subjects' strictly controlled diet, but an analytical bias cannot be excluded.

Regression analysis demonstrated no significant effects due to age, sex, folate level, or smoking status. A power analysis revealed an 80% probability that a mean change in serum formate of 5 mg/l could have been detected. This change is meaningful in that it would be far smaller than the amount known to cause toxicity and is small compared to the interindividual variability. Variability in this study design could further be reduced by standardizing other variables including sex, height, weight, and other dietary factors. Analytic variability could also contribute to the overall observed variability. However, analytical variability would represent only a small component of intraindividual variability and intraindividual variability was reduced by analyzing paired samples (exposed and control) in the same batch.

While exposure to several different levels of methanol above the threshold limit value might demonstrate slight increases in formate concentrations, it seems doubtful that this measure would be useful for monitoring individual low-level exposure.

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Health Effects of Gasoline

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