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Exposure to Methyl *Tertiary*-Butyl Ether from Oxygenated Gasoline in Stamford, Connecticut

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ABSTRACT. In 1993, state health officials in Connecticut invited the Centers for Disease Control and Prevention (CDC) to assist in an investigation of exposure to methyl *tertiary*-butyl ether in oxygenated gasoline in Stamford, Connecticut. Venous blood samples were collected from 14 commuters and from 30 other persons who worked in the vicinity of traffic or automobiles, and the samples were analyzed for methyl *tertiary*-butyl ether, *tertiary*-butyl alcohol, benzene, *m-/p*-xylene, *o*-xylene, and toluene. The highest levels of methyl *tertiary*-butyl ether in blood were measured among gasoline service station attendants (median = 15 μg/l, range = 7.6–28.9 μg/l). Blood levels of methyl *tertiary*-butyl ether were highly variable among persons who worked in car-repair shops (median = 1.73 μg/l, range = 0.17–36.7 μg/l) and were generally lowest among commuters (median = 0.11 μg/l, range = < 0.05–2.60 μg/l). Blood levels of methyl *tertiary*-butyl ether were correlated strongly with personal-breathing-zone samples of methyl *tertiary*-butyl ether and blood levels of other volatile organic compounds. This exposure information should prove useful to a future risk analysis of this high-volume chemical.

. IT IS ESTIMATED that more than 83 million Americans live in areas of the country that do not meet the national ambient air quality standard for carbon monoxide (CO).[1] The Clean Air Act Amendments of 1990 require such areas to use oxygenated gasoline, particularly during the winter months when CO levels are highest.[2] The oxygenated gasoline sold in an area must contain an average of 2.7% oxygen, by weight; the expectation is that the use of oxygenated gasoline will reduce highway emissions of CO by 17%.[3] Despite the fact that oxygenates had been used in several cities in recent years, this provision of the Clean Air Act Amendments was first implemented nationwide during the winter season of 1992–1993. Methyl *tertiary*-butyl ether (MTBE) is the oxygenate that is used most extensively.[4] A concentration of 2.7% oxygen, by weight, in gasoline corresponds to a concentration of 15% MTBE, by volume. In 1993, MTBE was among the top 10 chemicals produced in the United States, with an annual production of 24 053 million pounds (increase of 121% from 1992).[5]

In December 1992 investigations in Fairbanks, Alaska, by the Alaska Department of Health and Social Services and by the Centers for Disease Control and Prevention (CDC) suggested that the use of MTBE in oxygenated gasoline might be associated with health complaints, such as headache, eye irritation, and burning of the nose and throat.[6,7] In Connecticut, state health officials regarded MTBE as a possible health concern because of its presence as a ground-water contaminant in certain areas. Health officials did not know, however, whether increased exposure to MTBE, as a result of the oxygenated gasoline program in Connecticut, posed any health risk.

In an effort to address this question, state health officials in Connecticut invited CDC to assist in an investigation of exposure to MTBE in gasoline and to determine possible health effects resulting from that exposure. Given the fact that Stamford is within the New York City Consolidated Metropolitan Statistical Area, oxygenated gasoline (90% contained MTBE) had been in use in Stamford since November 1, 1992. At the time this investigation commenced, state and local health officials were not aware of any health complaints or public concerns related to the use of MTBE in Stamford. Field activities occurred during the first 2 wk of April 1993, at a time that approached the end of the oxygenated gasoline program. Analyses of nine gasoline samples collected from six different stations in Stamford confirmed that MTBE was still in use as a gasoline oxygenate in early April; the MTBE concentration in the gasoline samples ranged from 11.2% to 16.2%, by volume (Marcus E. Haubenstricker, U.S. Environmental Protection Agency [EPA], personal communication, 1993).

Method

Protection of study participants. Prior to initiation of data collection, the protocol for this investigation was reviewed and approved by the CDC Institutional Review Board. After the nature of the procedure was explained fully, informed consent was obtained from each person who provided a venous blood sample. Study participants received no compensation or incentives, but participants did receive a report of the composite results (without personal identifiers) of the blood analyses. Federal law required that the results of the industrial hygiene monitoring report be posted for 30 calendar days in a prominent place at each of the participating work sites.

Recruitment. The participants in this investigation represented a convenient sample of adults who worked in Stamford, Connecticut, and who had opportunities for exposure to gasoline and motor vehicle emissions. Staff from the Stamford City Department of Health approached several large- and small-sized firms in Stamford to solicit their voluntary cooperation in this investigation and to serve as locations for field activities. Staff identified several work places, such as automobile garages and firms with large automotive fleets, at which workers were likely to be exposed to gasoline or motor vehicle emissions. Many employers did not participate in this investigation because they were unable to secure permission quickly from senior management. Once management cooperation was obtained, however, participation among eligible persons was generally good (i.e., almost all agreed to at least complete the questionnaires). Occupationally exposed workers fell into three categories: (1) workers inside car-repair garages (mechanics, supervisors, and service advisors); (2) gasoline service station attendants; and (3) "other" workers, including workers in the city's traffic and sanitation departments who spent time in traffic. In addition, staff from the city health department recruited 14 commuters who worked at the city office building.

Administration of questionnaires. Staff from the Connecticut Department of Health Services and from CDC administered health and exposure questionnaires at the participants' worksites. The questionnaires were similar to those used in an earlier investigation of MTBE exposure in Fairbanks, Alaska, and answers were solicited with respect to 15 health symptoms that the respondent did not attribute to cold or flu. Approximately 10 min were required to complete the health questionnaire, but more time was required if the person experienced many health complaints. Everyone who provided venous blood samples also completed the questionnaire.

Collection and analysis of air measurements. Personal-breathing-zone samples for MTBE, benzene, toluene, and xylene were collected from 37 workers (of approximately 45 workers at 7 different worksites) who were potentially exposed to exhaust emissions and gasoline during the work day.[8] The samples were collected on two sorbent tubes connected in series; the front tube contained 400 mg of coconut-shell charcoal, and the back tube contained 200 mg of coconut-shell charcoal. The charcoal tubes were connected with Tygon® tubing to Gillian Lo Flow Sampler® battery-operated personal-sampling pumps. Air was sampled through the tubes at a nominal flow rate of 0.2 l/min for approximately 8 h. The charcoal tubes were removed after sampling and desorbed in carbon disulfide; an aliquot of this solution was analyzed, using gas chromatography-flame ionization detection (GC-FID) in accordance with the National Institute for Occupational Safety and Health (NIOSH) Method 1615, with modifications.[9,10] The analytical limit of detection for MTBE, toluene, and xylene was 0.01 mg/sample, and was 0.002 mg/sample for benzene. Thus the minimum detection and quantifiable concentrations varied slightly, depending on the size of the sample. Given the potential interferences commonly associated with the analysis, gas chromatography with a mass spectrometer (GC/MS) screening was also performed to confirm the identity of the benzene and MTBE peaks on random samples.

In this report, all air samples are expressed in terms of micrograms per cubic meter ($\mu g/m^3$). Multiplication by 0.277 can be used to convert values for MTBE to parts per billion (ppb).

Collection and analysis of blood samples. All 37 workers who wore personal monitoring devices were asked to provide blood samples, and 27 agreed to do so. Attendants who pumped gasoline that contained MTBE at 12 service stations also were asked to provide blood samples, but only 3 agreed to do so. In summary, 30 persons who worked near automobiles or gasoline agreed to provide blood samples; 29 had blood samples taken at or near the end of a work day, whereas 1 person who pumped gasoline had worked less than 2 h before a specimen of his blood was obtained. In addition, 14 commuters provided blood samples in the morning after arriving at work. Only 1 commuter indicated that he had added gasoline to his car on the day his blood was obtained; the remaining 13 commuters had added gasoline to their car on the previous day or earlier.

At the time the certified laboratory technicians from Stamford's Department of Health collected the venous blood samples, decontaminated collection tubes were used and procedures were followed to protect the measurement of low-level volatile organic compounds. Blood samples were refrigerated and shipped on ice within 1 wk to the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, CDC, for measurement of MTBE, *tertiary*-butyl alcohol (TBA, a metabolite of MTBE),[11] benzene, and other volatile organic compounds, using a modified technique of GC/MS.[12] Quality assurance measures, which were conducted on individual analytes in each sample, checked sensitivity, contamination, and analyte confirmation. The minimum detection limit and maximum linear standard were 0.05 μg/l and 37 μg/l, respectively, for MTBE and 0.25 μg/l and 75 μg/l, respectively, for TBA. Levels that exceed these minimum detection limits are quantifiable, but levels above the maximum linear standard are not. The IL 482 CO-Oximeter (Instrumentation Laboratory, Lexington, MA) was used by the Pulmonary Laboratory at Stamford Hospital to complete analyses of blood for percentage carboxyhemoglobin (COHb) within 4 h of collection.

Statistical analyses. The sample distribution of blood concentrations of MTBE and other volatile organic compounds was tested for normality, and the sample data were not found to be distributed normally. Prior to the calculation of correlation coefficients, we used a log transformation that improved normality. Values below the limit of detection were estimated as the limit of detection divided by the square root of 2.[13] Values for blood concentrations of toluene that were above the maximum linear standard (4 μg/l) were considered to be the maximum linear standard. With respect to TBA, two blood concentrations were only slightly above the maximum linear standard (75 μg/l), and no adjustment was made.

In accordance with the procedures used to analyze blood samples of exposed persons in Fairbanks, Alaska,[7] we separated people in the Connecticut study who contributed blood samples into two groups on the basis of their levels of MTBE in blood; the upper quartile of MTBE was used as the cut-off point.

The small sample sizes necessitated calculation of confidence intervals for odds ratios as mid-*p*-corrected exact-confidence limits, using StatXact statistical software (Cytel Software Corporation, Cambridge, MA). All other statistical analyses were performed with PC-SAS (SAS Institute Inc., Cary, NC).

Results

Measurements of MTBE and other chemicals in blood. We obtained venous blood samples from 44 persons. Levels of MTBE in blood among persons who worked in car-repair shops were highly variable (the highest level of MTBE in blood was 200 times greater than the lowest level of MTBE in blood), and these levels were generally much higher than levels of MTBE found in the blood of commuters. The 3 persons who pumped gasoline had blood MTBE levels that were one or two orders of magnitude higher than the levels measured among commuters (Fig. 1). Persons in the "other" category of workers had levels of MTBE in blood that were comparable with blood MTBE levels of commuters.

Blood levels of TBA, a metabolite of MTBE, were higher than blood levels of MTBE (Fig. 2). The differences in median level of TBA in blood, by job group, were consistent with those observed for median levels of MTBE in blood.

Levels of MTBE in blood were correlated strongly with levels of TBA in blood, as well as with blood levels of other volatile organic compounds, including benzene, toluene, *m-/p*-xylene and *o*-xylene, all of which are found in gasoline (Table 1).

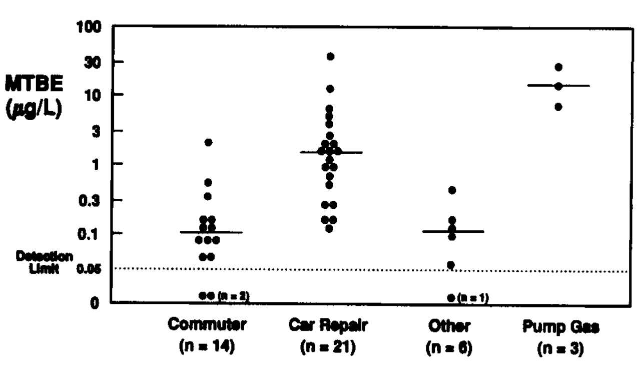

Fig. 1. Comparison of blood MTBE levels, by job group (Stamford, Connecticut; April 1993).

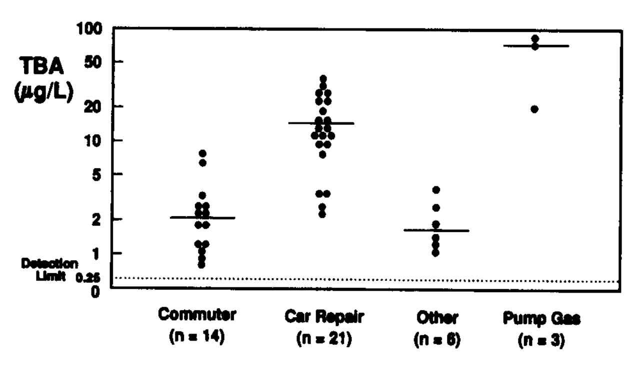

Fig. 2. Comparison of blood TBA levels, by job group (Stamford, Connecticut; April 1993).

Measurements of COHb were higher among current smokers than among nonsmokers, and this difference exceeded the differences among job categories (Table 2). Smoking was also an important determinant of blood benzene levels; the commuters who smoked had blood benzene concentrations that were comparable with blood benzene concentrations among people who pumped gasoline, but who did not smoke. The highest level of benzene in blood (0.98 μg/l), however, was measured in a male car-repair worker who did not smoke.

Association between blood MTBE levels and the presence of health symptoms. The 11 people with the highest levels of MTBE in blood (≥ 2.4 μg/l) were significantly more likely to report one or more key symptoms (headache, irritated eyes, burning of the nose and throat, cough, dizziness, spaciness or disorientation, and nausea) than were persons with lower levels of MTBE in blood (odds ratio [OR] = 8.9, 95% confidence interval [95% CI] = 1.2-75.6). This analysis combined both commuters and other workers. It should be noted that the 14 commuters were interviewed about their current symptoms in the morning, whereas the 30 people who worked in the vicinity of motor vehicles and traffic were interviewed at the end of the day; therefore their responses may not have been comparable.

The time of day that symptoms were reported was controlled for by conducting another analysis in which commuters were excluded. The 8 workers with the highest levels of MTBE in blood (> 3.8 μg/l) were sig-

Table 1.—Correlation Coeficients Between Measurements of MTBE,* TBA,† and Other Volatile Organic Compounds in Blood (Stamford, Connecticut, April 1993)

Compund	MTBE	TBA	Benzene‡	Toluene‡	*m*-/*p*-Xylene	*o*-Xylene
MTBE	1.0	0.94 (44)§	0.76 (31)	0.72 (30)	0.77 (41)	0.76 (38)
TBA		1.0	0.72 (31)	0.71 (30)	0.76 (41)	0.76 (38)
Benzene			1.0	0.73 (30)	0.63 (28)	0.68 (26)
Toluene				1.0	0.78 (28)	0.83 (26)
m-/*p*-Xylene					1.0	0.94 (37)
o-Xylene						1.0

Note: Correlations were calculated on log-transformed values. Samples for which quality control parameters were not acceptable were not included in the calculations; therefore, sample sizes varied by analyte.
*Methyl *tertiary*-butyl ether.
†*Tertiary*-butyl alchohol.
‡Analyses of benzene and toluene were restricted to nonsmokers.
§Number of observations appear within parentheses.

Table 2.—Median Levels of Carboxyhemoglobin (COHb) and Benzene in Blood, by Job Category, Gender, and Smoking Status (Stamford, Connecticut; April 1993)

	Nonsmokers				Smokers			
		%COHb	Benzene*			%COHb	Benzene*	
Job	No.	Median	Median	(Range)	No.	Median	Median	(Range)
Commuter								
Men	7	0.60	0.12	(0.10, 0.20)	1	2.60	0.29	
Women	4	0.70	0.12	(0.11, 0.14)	2	4.80	0.36	(0.14, 0.58)
Car Repair								
Men	12	1.05	0.19	(0.11, 0.98)	8	3.80	0.42	(0.17, 0.67)
Women	1	0.90	0.27					
Gasoline Attendant								
Men	3	0.70	0.36	(0.32, 0.47)				
Other								
Men	4	0.70	0.16	(0.10, 0.22)	2	4.85	0.29	(0.19, 0.39)

*Measured as μg/l.

nificantly more likely to report one or more key symptoms than were the remaining 22 workers (OR = 21.0, 95% CI = 1.8–539.0). Muscle aches and fatigue were also more common among workers who experienced the highest levels of MTBE in blood than among those with lower levels of MTBE in blood, although this difference was not significant statistically (OR = 6.0, 95% CI = 0.7–57.7). None of the workers who had the highest levels of MTBE in blood reported diarrhea, difficulty breathing, skin irritation, fever, sweats or chills, or fainting. Only 1 of 8 workers who had the high level of MTBE in blood was a smoker. The ORs for the presence of one or more key symptom and the upper quartile of benzene concentration in blood (OR = 2.1, 95% CI = 0.1–22.9) and upper quartile of TBA (OR = 2.1, 95% CI = 0.2–17.1) also were not significant statistically. None of the workers with the highest COHb levels (> 2.0%) reported any of the key symptoms.

Measurements of MTBE and other chemicals in air. Personal-breathing-zone samples for MTBE among workers who worked near traffic ("other" workers) did not exceed the minimum detectable concentration. Some of these workers, however, had actually traveled less than 5 miles (8 km) on the day personal-breathing-zone samples were collected. Time-weighted average concentrations among mechanics who repaired motor vehicles ranged from less than the minimum detectable concentration (108 $\mu g/m^3$) to 43 464 $\mu g/m^3$ (12.04 ppm). Inhalation exposures varied by and within location. Some of the mechanics worked on diesel-powered vehicles on the day of sample collection and, therefore, had minimum opportunity for exposure to MTBE.

In this limited study, we observed that personal-breathing-zone concentrations of MTBE were correlated very strongly with personal-breathing-zone concentrations of benzene ($r = .95$, $p < .0001$). An exposure of 1.0 ppm MTBE corresponded to a benzene exposure concentration of approximately 0.08 ppm.

Correlations between air and blood measurements. Paired blood samples and personal-breathing-zone samples were collected from 27 individuals. Personal-breathing-zone air samples of MTBE were correlated strongly with both levels of MTBE (Fig. 3) and TBA (Fig. 4) in blood. The estimated correlation coefficient was .80 between air MTBE and blood MTBE ($p = .0001$) and was 0.70 between air MTBE and blood TBA ($p = .0001$).

Personal-breathing-zone samples of benzene were correlated with blood levels of benzene (Fig. 5); the correlation coefficient was .63 ($p = .007$) for nonsmokers, .81 ($p = .004$) for smokers, and .61 ($p = .0007$) overall. The correlation coefficients between paired blood and personal-breathing-zone samples for the other volatile organic compounds measured were .70 ($p = .0001$) for toluene and .56 ($p = .003$) for xylene.

Discussion

At the beginning of this investigation, little was known about human exposure to MTBE from oxygenated gasoline. Advances in analytic techniques that enable measurement of low levels of volatile organic

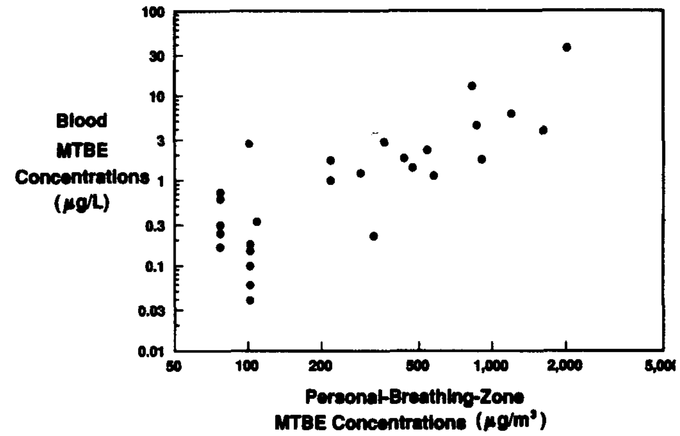

Fig. 3. Blood levels of MTBE and personal-breathing-zone concentrations of MTBE (Stamford, Connecticut; April 1993).

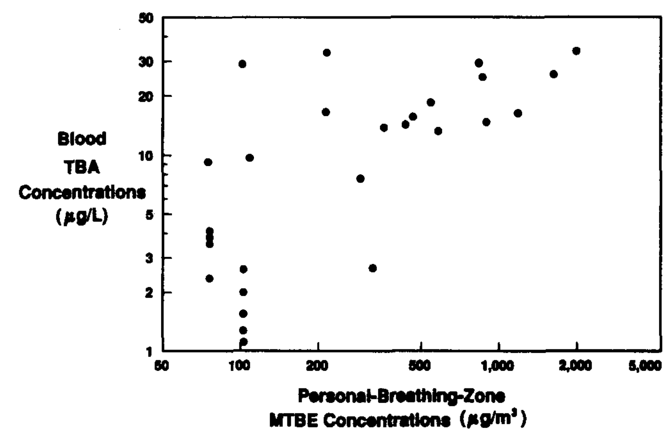

Fig. 4. Blood levels of TBA and personal-breathing-zone concentrations of MTBE (Stamford, Connecticut; April 1993).

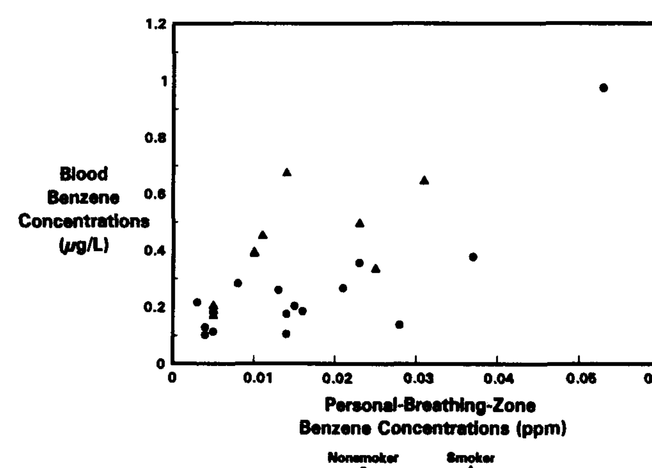

Fig. 5. Blood levels of benzene and personal-breathing-zone concentrations of benzene (Stamford, Connecticut; April 1993).

compounds in blood permitted us to confirm that even people who had no occupational exposure to gasoline or motor vehicle emissions had detectable levels of MTBE in their bodies. The highest levels, measured among car mechanics and gasoline service station attendants, were more than 100 times higher than the lowest levels, measured among commuters. Blood concentrations of MTBE were correlated strongly with personal-breathing-zone air concentrations.

The reference frame for MTBE levels in blood is quite limited. In the earlier investigation of MTBE exposure in Fairbanks, Alaska,[7] the range of MTBE levels in blood among workers exposed to gasoline and motor vehicle emissions during the oxygenated fuel program was similar to that observed among car repair and gasoline station attendants in this investigation. In an investigation of MTBE exposure in Albany, New York, where no oxygenated fuel program was implemented and MTBE was used only as an octane enhancer in premium gasoline, blood levels of MTBE among car-repair mechanics and gasoline service attendants were substantially lower than among similarly exposed workers in this investigation (David Mannino, CDC, personal communication, 1993). In Albany, all MTBE levels among commuters were below the limit of detection, and thus much lower than the levels of MTBE in the blood of all but 2 commuters in this investigation.

With regard to some of the other volatile organic compounds measured in blood in this investigation, comparison values are available from 600 or more randomly selected, nonoccupationally exposed participants of the Third National Health and Nutrition Examination Survey (NHANES III).[14] Among 14 commuters in this investigation, 1 had a blood benzene level above the upper 95th percentile of the NHANES III subset, and another commuter had blood levels of *m-/p*-xylene and *o*-xylene above the upper 95th percentiles. Four of 30 car-repair workers had blood benzene levels above the upper 95th percentile of the NHANES III subset. Almost all of the car-repair and gasoline station workers had blood levels of *m-/p*-xylene that exceeded the upper 95th percentile, and approximately half had blood levels of *o*-xylene and toluene that were above the upper 95th percentiles.

Blood levels of MTBE that we measured may not have represented some participants' maximum blood level of MTBE on that day. Results of recent pharmacokinetic studies indicate that blood levels of MTBE decrease quite rapidly after exposure has ceased; after 30 min, blood levels of MTBE decline by 50% (D. Ashley, CDC, personal communication, 1993).

We sampled a relatively small number of workers who were employed in a few job categories. Blood levels of MTBE varied greatly among persons who were exposed occupationally to automobile emissions and gasoline, indicating that an exposure classification based primarily on job title could be very inaccurate. Even within the same work place, personal-breathing-zone concentrations and blood measurements were variable. Despite the fact that personal-breathing-zone concentrations of MTBE were correlated strongly with blood levels of MTBE and TBA, dermal exposure may also have influenced blood levels of MTBE.

Air monitoring is useful, but ambient-air monitoring and personal-breathing-zone monitoring can differ for many reasons, particularly if the monitoring occurs at different times. In Stamford, the EPA obtained area air samples inside four of the garages in which study participants had worked, but the samples had been obtained approximately 1 wk subsequent to the wk during which the blood and personal-breathing-zone samples were obtained. In three of the four garages, the upper range of MTBE values from area air samples was several times lower than the upper range of MTBE values obtained from the personal-breathing-zone measurements (Kenneth T. Knapp, EPA, personal communication, 1993). In any study of acute health effects and MTBE exposure, the exposures should be measured at the same time that symptoms are measured—not at some other point in time. Personal-breathing-zone measurements are preferable to area sampling for occupationally exposed workers.

Persons with high blood concentrations of MTBE reported a high prevalence of one or more of the key symptoms (headache, irritated eyes, burning of the nose and throat, cough, dizziness, spaciness or disorientation, and nausea) than had been associated previously with MTBE exposure in Fairbanks, Alaska.[6,7] This association appeared to be specific to these symptoms; none of the workers with higher levels of MTBE in blood reported difficulty in breathing, diarrhea, fainting, sweats or chills, skin irritation, or fever. Previous anecdotal reports have linked headache and other health complaints with exposure to MTBE among refinery workers and among members of a family exposed to contaminated groundwater.[15,16] Recent controlled exposure studies of young, healthy volunteers have not demonstrated an increase in health complaints following short-term exposure to pure MTBE.[17] Although this investigation focused on acute health effects, it should be noted that MTBE has been associated with developmental toxicity and carcinogenicity in laboratory animals[17]; the American Conference of Governmental Industrial Hygienists has proposed that MTBE be designated as an animal carcinogen.[18]

This investigation was conducted in early April 1993—at the end of the oxygenated gasoline program in Stamford and at the beginning of spring. Daily maximum temperatures often approached or exceeded 60 °F during this period. The mild weather permitted the opening of the windows and service doors in the garages. Dilution ventilation may have resulted in substantially reduced concentrations of many air contaminants, including MTBE, compared with what conditions may have been like during colder months. In addition, recent evidence indicates that automobile emissions of MTBE are higher at colder temperatures (C. Prakesh, Environment Canada, personal communication, 1993). It is possible that blood and air monitoring results and responses to the symptom questionnaire would have been different had we conducted this investigation several months earlier.

Another limitation of this investigation was the restriction of study participants to healthy working adults. Time and resource constraints limited our ability to include a larger and more representative population. Large numbers of potentially vulnerable groups, such as the elderly, children, and people whose health did not permit them to work, were not represented among the study participants. General, nonoccupational exposures were not well represented in this preliminary investigation. Participation at any particular work site depended on the willing cooperation of employers and workers. It is possible that the people who chose to participate differed in some way from those who did not participate. In this community, publicity about the health effects of oxygenated gasoline was minimal, and it most likely did not influence participation.

Exposure to gasoline may have confounded these results. In both blood and air concentrations, MTBE was correlated strongly with other volatile organic compounds. In fact, the workers with the highest personal-breathing-zone samples of MTBE were exposed to potentially hazardous levels of benzene.[8] In some car-repair garages, "raw gasoline" was used as a cleaning agent. In addition, cars in repair garages are, in most cases, there because they are not running properly, and therefore may produce products of incomplete combustion. It is not clear whether symptoms that have been associated with MTBE might actually be attributed to a synergistic effect between MTBE and other gasoline constituents or to these other constituents alone, or perhaps to a MTBE contaminant or combustion product of MTBE or another gasoline constituent. It is also possible that people who were exposed to gasoline might have overreported symptoms. Epidemiologic studies of larger, more methodically sampled populations that include exposures to gasoline, absent MTBE, and that permit adequate statistical power may be useful to resolve this and other health-related issues.

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