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ASSESSMENT OF POTENTIAL HEALTH RISKS OF GASOLINE OXYGENATED WITH METHYL TERTIARY BUTYL ETHER (MTBE)

Office of Research and Development
U.S. Environmental Protection Agency

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1. INTRODUCTION

The Clean Air Act Amendments of 1990 require the use of oxygenated gasoline in the 39 areas of the country that exceed national health standards for carbon monoxide (CO). Carbon monoxide pollution is caused by incomplete burning of fuels used in internal combustion engines and is generally more severe during cold winter temperatures. That is why the oxygenated gasoline program covers just the typically coldest winter months in areas exceeding the CO standards. Essentially, gasoline is diluted by adding oxygenates, such as ethanol or methyl tertiary butyl ether (known as MTBE), which also reduces certain other organic compounds. The result is decreased emissions of CO and some other toxic air pollutants (e.g., benzene). However, some trade-offs are also expected to be necessary between (1) the expected reductions in CO, benzene, etc., and (2) increased emissions of MTBE and certain other substances (e.g., formaldehyde).

Typically, MTBE-oxygenated gasoline contains approximately 15% MTBE by volume within conventional gasoline. This volume of MTBE translates into approximately 2.7% oxygen by weight, which is the federally mandated standard. Oxyfuels with MTBE are widely used. There were seven metropolitan areas that had requirements for oxyfuels (at lower oxygenate levels than currently used) before 1992. The Denver, CO, program began in 1988, and five of the other programs have been operating since 1989. Methyl tertiary butyl ether constitutes about 80% of the oxygenates sold in the Phoenix and Tucson, AZ, and Denver programs. Independent of the oxyfuels program, MTBE is used as an octane enhancer. It is rarely used in regular gasoline at roughly 0.2% (ranging up to about 2.5%) of MTBE; and a significant portion of premium gasoline contains 2 to 9% MTBE.

An analysis of the ambient air quality in the oxygenated gasoline areas by the U.S. Environmental Protection Agency's (EPA's) Office of Mobile Sources (OMS) indicates that there were many fewer violations of the CO standard from November 1992 through the end of February 1993 than in similar periods in previous years (U.S. Environmental Protection Agency, 1993b). Based on this analysis, OMS determined that nationwide, the number of CO exceedances in all nonattainment areas decreased by 80% on average. Exceedances were reduced by 95% in the 21 new oxygenated gasoline programs and by 50% in the programs that began prior to 1992 (these programs generally required about 2% oxygen by weight prior to 1992). The eight California programs experienced an 80% reduction while

implementing a program requiring a lesser standard of only 2% oxygen by weight (about 9% MTBE by volume). Although normal variations in meteorological conditions or patterns of vehicle use might have contributed to the decline in CO exceedances in some nonattainment areas, OMS concluded that the aggregate national data suggest strongly that oxygenated gasoline had the kind of positive effect overall that was intended.

This assessment updates EPA's Office of Research and Development (ORD) February 1993 report, entitled "MTBE-Oxygenated Gasolines and Public Health Issues" (U.S. Environmental Protection Agency, 1993a). The February report was developed to assist the EPA's Office of Mobile Sources and Regions VIII and X in evaluating health symptom complaints by some residents in Fairbanks and Anchorage, AK and Missoula, MT. In Fairbanks, Missoula, and Denver, publicized hotlines were available that solicited comments on oxyfuels, thereby facilitating communication about complaints. People in Fairbanks and, to a lesser degree, in Missoula made their health complaints public through these hotlines in the 1992-93 oxyfuel season. On the other hand, in Denver, where oxyfuels with 8% MTBE were introduced in 1988, there were a few complaints about odor and health symptoms initially (28 health complaints out of a total of about 2,670 complaints) (Livo, 1993); however, in the 1990-91 winter season, in which oxyfuels contained about 14% MTBE, almost no odor or health complaints were made to a publicly advertised hotline. The presence of hotlines and media reports of complaints introduce confounding factors that make it difficult to interpret the meaning of reported symptoms. Individuals in other areas having MTBE oxyfuels have not made mass health complaints, but all areas in the MTBE oxyfuels program do not have such hotlines and even if they did, the types of complaints being made elsewhere could very easily go unreported. In any case, such self-selected complaints are an insensitive indicator of the acute effects of interest and are not useful to predict health risks, although they are valuable in identifying the need for epidemiological or controlled studies.

The primary finding of ORD's February report (U.S. Environmental Protection Agency, 1993a) was that the paucity of key information made quantitative risk assessment impossible. However, because there were suggestions of the potential for health effects, research was needed to fill in important knowledge gaps. Therefore, a research and assessment program was initiated (primarily funded by the U.S. Environmental Protection Agency [EPA] and industry [especially the American Petroleum Institute, the Oxygenated

Fuels Association, and the Synthetic Organic Chemical Manufacturer's Association]) in January 1993 to provide information as inputs to policy decision making for the next oxyfuel season in the Fall of 1993. The results of the research from the participating institutions were presented and discussed at the "Conference on MTBE and Other Oxygenates: A Research Update" (1993) in Falls Church, VA, on July 26-29, 1993.

This assessment of potential health risks draws upon the earlier information on MTBE and integrates the results of the very recent research effort. Although the optimal approach for an assessment involves evaluating data in published papers that have undergone peer review, such a publication process typically takes at least 1 year. Thus, it was necessary to evaluate the data provided within non-peer-reviewed reports or in presentations made at the Conference on MTBE and Other Oxygenates (1993). Most, if not all, of these reports and presentations underwent reviews within the organization conducting the research. In a few cases, the work has been subjected to external peer-review (see reference list). The ORD critically evaluated the cited reports insofar as possible and attempted to describe the various apparent strengths and weaknesses of particular studies. Nevertheless, when summaries (e.g., abstracts) or preliminary findings of unpublished reports are being evaluated, the potential exists that further analyses by the researcher or independent examination of the entire data set could result in additional or different conclusions.

The following discussion centers on the current scientific information about potential health risks of MTBE. A few other key air pollutants associated with use of MTBE oxygenated fuels are discussed briefly. Ideally, a full report would provide quantitative risk-benefit comparisons of CO and MTBE, and analyze the relative risks presented by other gasoline components (including the entire gasoline mixture) and their combustion products. However, as will be discussed, the available information is too sparse to make such comparative risk estimates. The health risk evaluation focuses on the general public, not people in occupations (e.g., gas station attendants, taxi drivers) having higher exposures to oxyfuels. Several studies of occupationally exposed people were conducted to obtain data on people likely to have higher exposures than the general public. However, this risk evaluation treats these people as representative of a highly-exposed, generally healthy group of people to provide a perspective on what might happen to healthy members of the general populace receiving lower and less frequent exposures to MTBE. The discussion is organized in three

sections: (1) health effects; (2) air quality and exposures; and (3) a summary discussion of potential risks that integrates current health effects and exposure information. Because research on the effects of low temperatures (down to −20 °F) on emissions from vehicles using MTBE oxyfuels is not yet complete, this work will be reported later.

2. HEALTH EFFECTS

Although MTBE is the focus of this report, benzene, formaldehyde, and 1,3-butadiene are also briefly addressed because the addition of MTBE can affect the emissions of these major fuel-related air toxics. Methyl tertiary butyl ether is primarily an evaporative emission, but some is present in tailpipe emissions, especially if the catalyst is not fully performing (e.g., before it is warmed-up or when it is malfunctioning). Benzene is primarily a tailpipe emission and can also be present in evaporative emissions. Formaldehyde and 1,3-butadiene are strictly tailpipe emissions.

Throughout, it is important to understand that conventional gasoline without oxygenates or with very low levels of oxygenates can cause health effects, and that health effects are related to the level and duration of exposure. These fuels and their combustion products are complex mixtures that contain toxicants such as benzene, 1,3-butadiene, CO, formaldehyde, hexane, toluene, xylenes, and ethylbenzene. Although it is beyond the scope that is possible in this document, the potential of the mixtures and the individual components to cause cancer and noncancer health effects should be considered and weighed against potential added risk from MTBE in order to provide a complete analysis. Although chemicals may pose different types and degrees of health hazards, public health concerns only occur above certain exposure concentrations, which are different for each chemical. Variations in exposure durations and patterns are also very important in determining the nature and severity of potential health effects. For example, short-term exposures to a chemical can cause different effects from long-term exposures. The level of physical activity (e.g., exercise) being performed during the time of exposure and the health status of the person being exposed can also influence the degree of health effects caused by each chemical. Furthermore, when people are exposed to evaporative and combustion emissions from vehicles, they are exposed to a complex mixture of hundreds of chemicals, not just to MTBE alone. This exposure to

the mixture will affect the health outcome. In the epidemiological studies to be discussed here, people exposed to mixtures were evaluated. In the human clinical and animal studies discussed below, exposures were to "pure" MTBE (i.e., MTBE in filtered air), not to a complex mixture of MTBE oxyfuel. Thus, joint interpretation of studies of MTBE alone and in mixtures is needed to predict effects.

This section focuses on the nature of potential health effects, not exposures or consequent risks, which are covered later (see Sections 3 and 4).

2.1 Carbon Monoxide

The Clean Air Act directs the Administrator of the EPA to establish National Ambient Air Quality Standards (NAAQS) for several widespread air pollutants, based on scientific criteria and allowing for an adequate margin of safety to protect public health. The CO NAAQS is 9 ppm for an 8-h average and 35 ppm for a 1-h average; neither is to be exceeded more than once per year. So many U.S. citizens are potentially exposed to CO that Congress made its reduction a national priority by requiring [Section 211(m) of the Act] oxygenated gasoline programs in cities that do not attain the CO NAAQS, beginning on November 1, 1992.

The EPA has documented the detrimental health effects that CO can have on populations (U.S. Environmental Protection Agency, 1991a). Carbon monoxide is a colorless, odorless, and nonirritating gas that is readily absorbed from the lungs into the bloodstream, there forming a slowly reversible complex with hemoglobin (Hb) known as carboxyhemoglobin (COHb). The presence of COHb in the blood reduces the amount of oxygen available to vital tissues, affecting primarily the cardiovascular and nervous systems. Although the formation of COHb is reversible, the elimination half-time is quite long because of the tight binding between CO and Hb. This can lead to accumulation of COHb, and extended exposures to even relatively low concentrations of CO may produce substantially increased blood levels of COHb.

The effects of exposure to low concentrations—such as the levels found in ambient air—are far more subtle and considerably less threatening than those occurring in frank poisoning from high CO levels. Maximal exercise performance in healthy individuals has been shown to be affected at COHb levels of 2.3% and greater. The reductions in

performance at these levels are small and are likely to affect only competing athletes rather than people engaged in the activities of daily life. Central nervous system effects, observed at peak COHb levels of 5% and greater, include reduction in visual perception, manual dexterity, learning, driving performance, and attention level. Of most concern, however, are adverse effects observed in individuals with chronic heart disease at COHb levels of 3 to 6%. At these levels, such individuals are likely to have reduced capacity for physical activity because they experience chest pain (angina) sooner. Exercise-related cardiac arrhythmias have also been observed in some people with chronic heart disease at COHb levels of 6% and may result in an increased risk of sudden death from a heart attack. Carboxyhemoglobin levels (3 to 6%) of concern for induction of cardiovascular effects among people with chronic heart disease would be expected, on average, with exposures during light exercise to CO ambient air concentrations of 60 to 100 ppm (1 h) or 20 to 45 ppm (8 h).

The NAAQS set by EPA are intended to keep COHb levels below 2.1% in order to protect the most sensitive members of the general population (i.e., individuals with chronic heart disease) with an adequate margin of safety. Elderly people, pregnant women (due to possible fetal effects), small children, and people with anemia or with diagnosed or undiagnosed pulmonary or cardiovascular disease are also likely to be at increased risk for CO effects. However, the present NAAQS for CO is considered to be adequately protective of these effects.

2.2 Methyl Tertiary Butyl Ether[1]

2.2.1 Odor Thresholds and Dermal Effects

Although the strong odor of MTBE may lead one to think that very high concentrations of it are in the air, this is not necessarily true. Recent experimental studies of MTBE odor thresholds indicate that this compound can be detected (as a distinct but unidentified odor) at concentrations around 0.18 mg/m^3 and recognized (identified) at levels around 0.32 to 0.47 mg/m^3, depending on its purity (Clark, 1993). By contrast, the detection and recognition thresholds for various blends of gasoline were as much as 10-fold higher than those for MTBE alone: 0.32 to 2.09 mg/m^3 for detection; 2.77 to 4.03 mg/m^3 for

[1]Throughout this report, concentration units are presented as mg/m^3. When necessary, a conversion was made on the basis that 1 ppm MTBE = 3.6 mg/m^3 MTBE.

recognition. When MTBE and gasoline were mixed together (15% MTBE, 85% gasoline), the threshold concentrations of the mixtures generally lay between those for MTBE and the gasoline blends alone: 0.32 to 0.94 mg/m^3 for detection; 0.68 to 2.48 mg/m^3 for recognition. These values represent ranges for six subjects of varying sensitivity to odors, such as would be found in the general population. However, other individuals may be either considerably more or less sensitive. Also, the particular blend of gasoline may make some difference in its detectability either with or without MTBE.

Direct exposure of the skin, eyes, and other tissues to MTBE causes irritation similar to that of conventional gasoline (SNAMPROGETTI S.p. A., 1980). Prolonged or frequent contact with either conventional gasoline or MTBE oxyfuel may result in drying, chapping, or cracking of the skin. If either type of fuels come into contact with the eyes, eye irritation may result. Because each of these effects potentially linked with skin exposure to MTBE-blended gasoline is also linked to exposure to conventional gasoline, normal precautions should apply when handling any type of gasoline, regardless of type or oxygen content.

2.2.2 Short-Term Exposure Effects

Epidemiological Studies

Alaska Studies. Shortly after MTBE oxyfuel was introduced in Alaska on November 1, 1992, the Alaska Division of Public Health's Section of Epidemiology began to receive numerous calls from individuals in Anchorage and Fairbanks reporting recent onset of illness that they associated with the introduction of MTBE oxyfuel in their communities. By the fourth week of November, over 150 health complaints had been received on a publicized citizens hotline. The pre-existence of these hotlines may have added an additional confounder to subsequent epidemiological investigations in Alaska. Most individuals reported minor symptoms. Studies conducted by the Centers for Disease Control and Prevention (CDC) and the State of Alaska were initiated in response to these complaints. In November and December of 1992, while MTBE oxyfuel was still in use, the CDC and the State of Alaska undertook a field epidemiology study in Fairbanks (Beller and Middaugh, 1992); the State of Alaska conducted a similar study in Anchorage (Chandler and Middaugh, 1992). There were limitations to the extent of the health questionnaire and the number of people interviewed. All the gasoline in these cities contained elevated MTBE. No group

could be identified that had no exposure to MTBE oxyfuel, preventing controlling for exposure.

Initially, the CDC contacted 34 people who had earlier complained of health symptoms to the Fairbanks hotline, which had been set up for MTBE oxyfuels comments. They used information from these people to establish a "case" definition. A case was defined as a person who reported, for either the first time, or with increased frequency since October 14, 1992, symptoms of headaches or two of the following symptoms: cough, nose or throat burning, eye irritation, nausea or vomiting, dizziness, or sensation of spaciness or disorientation. The case definition excluded individuals who reported symptoms, such as fever, diarrhea, or muscle aches, likely due to infectious causes. The CDC then administered a symptom questionnaire by telephone to a systematic sample of 41 residents and found that 41% of the participants were cases (i.e., reported the presence of the case symptoms).

Using questionnaires similar to those described above, the Alaska Department of Health and Social Services and the CDC conducted interviews during late November through early December of three groups of people in Fairbanks presumed to have tiered levels of exposure: (1) taxi drivers, (2) health care workers who typically commute, and (3) university students who spent less time around vehicles (Beller and Middaugh, 1992). A similar study in Anchorage included three groups (taxi drivers, health center employees, and hospital employees) (Chandler and Middaugh, 1992). Analysis of the Fairbanks data in Table 1 showed that there was a statistically significant difference between the number of cases among the taxi drivers and health care workers compared to students. The statistical analysis of the Anchorage data was not reported, but it was stated that the taxi drivers had a higher proportion of complaints. In both cities, headaches were the most common symptom reported. The headaches were generally mild and of short duration (less than 1 h or between 1 and 24 h). Other common symptoms were eye and throat irritation and cough. Many people associated their symptoms with exposure in a vehicle or while refueling. Most of the people interviewed did not judge their symptoms to be severe enough to consult a physician. In Fairbanks, there was not a significant increase in hospital emergency room visits for headache, implying that the complaints were not severe and were not resulting in widespread serious morbidity.

TABLE 1. PERCENTAGE OF CASES IN FAIRBANKS AND ANCHORAGE

Interviewees	Fairbanks	Anchorage
Taxi drivers	33% (4 of 12)	46% (12 of 25)
Health care workers	29% (26 of 90)	
Students	15% (15 of 101)	
Health center workers		25% (7 of 29)
Hospital workers		27% (29 of 108)

Source: Beller and Middaugh (1992); Chandler and Middaugh (1992).

Gordian et al. (1993) found no significant difference in health insurance claims (outpatient treatment for diagnoses of upper or lower respiratory tract disease, headache, or asthma) in Anchorage over the last three winters or in Anchorage compared to other Alaska cities for the 1992-93 MTBE season, suggesting that serious health effects were not occurring. A study such as this has many limitations, such as the potential for misclassification of responses. By its nature, it does not address the issue of whether MTBE is associated with symptoms and, therefore, cannot be used to draw a negative conclusion about such an association.

Investigators with the National Center for Environmental Health of the CDC, in collaboration with the State of Alaska, the National Institute for Occupational Safety and Health (NIOSH), and EPA conducted a two-phase study in Fairbanks investigating the potential relationship between MTBE oxyfuel exposure and symptomatic responses (Centers for Disease Control and Prevention, 1993a). They also investigated the relationship between MTBE oxyfuel exposure and blood levels of MTBE and a major metabolite of it, tertiary butyl alcohol (TBA). Phase I was conducted in the first 2 weeks in December 1992, while MTBE was in the gasoline supply; Phase II was conducted in mid-February 1992, 6 weeks after MTBE oxyfuels had been removed. During Phase II, MTBE was present in some regular unleaded (at 1%) and premium (at 5 to 6%) gasoline as an octane enhancer. Each phase of the study involved a systematic telephone survey, and investigations of symptom responses and blood levels of MTBE and TBA in occupationally and nonoccupationally (i.e., commuters) exposed individuals.

In the telephone surveys, participant telephone numbers were selected in a systematic fashion from the Fairbanks telephone directory. The time of day of the telephone survey was not reported (i.e., the temporal relationship between exposures and questioning was not reported). For the occupational survey, workers selected by convenience included those who spent most of their work day in vehicles (e.g., meter and telephone technicians) or at service stations and automobile dealerships. Participants were asked about a list of 15 health complaints, including the seven key complaints of headache, eye irritation, burning of nose/throat, cough, nausea, dizziness, and spaciness. Specifically, they were asked if they had experienced these symptoms for the first time, or with increased frequency, during the period from October 1, 1992 (Phase I survey conducted December 3 to 5) or during the period from January 1, 1993 (Phase II survey conducted February 10 to 20). Participants were requested to report only complaints that they could not attribute to a cold or flu. Table 2 shows a clear difference in symptom reporting rates between each of the two study phases. The presence of any preexisting medical condition was not reported.

TABLE 2. PERCENTAGE OF PEOPLE IN FAIRBANKS REPORTING SYMPTOMS

	Telephone Survey		Occupational Groups	
Symptom	Phase I[a] (n = 41)	Phase II[b] (n = 100)	Phase I (n = 18)	Phase II (n = 28)
Headache	34% (14)	10% (10)	72% (13)	4% (1)
Eye irritation	37% (15)	18% (18)	67% (12)	7% (2)
Burning of nose/throat	29% (12)	12% (12)	50% (9)	0% (0)
Cough	22% (9)	8% (8)	28% (5)	0% (0)
Nausea	15% (6)	2% (2)	33% (6)	4% (1)
Dizziness	15% (6)	4% (4)	44% (8)	0% (0)
Spaciness	12% (5)	6% (6)	33% (6)	0% (0)

[a]Phase I = While MTBE oxyfuel in use.
[b]Phase II = After MTBE oxyfuel removed.

Source: Centers for Disease Control and Prevention (1993a).

In the occupational exposure investigations, 18 people in Phase I (early December) and 28 people in Phase II (early-mid February), 12 of whom participated in Phase I, were recruited, including drivers, mechanics, and service station attendants. Each subject

answered a questionnaire inquiring about the presence (in the previous 6 weeks) of 15 symptoms, including the seven key symptoms. Each subject had a blood sample drawn at the beginning and at the end of their work shift for determinations of MTBE and TBA concentrations. Each subject was also asked about the presence of any symptoms on the day of their blood draw. Air concentrations of MTBE were also determined at the workplace.

Results for the occupational exposures showed that during Phase I, the median preshift blood concentration of MTBE was 1.15 μg/L (range 0.1 to 27.8 μg/L), rising to a postshift median of 1.80 μg/L (range 0.2 to 37.0 μg/L); whereas during Phase II, the median preshift blood concentration was 0.21 μg/L compared with 0.25 μg/L postshift. It is not clear why the preshift levels of MTBE in Phase I are as high as they are. A larger gradient in pre- to postshift levels would have been expected. The differences in blood MTBE concentrations between Phase I and II were statistically significant. Postshift blood TBA concentrations in the 28 workers from Phase II (median = 4.2 μg/L, range 0.9 to 20.3 μg/L) was statistically significantly lower than the postshift blood TBA concentration in the 18 workers from Phase I (median = 5.55 μg/L, range 1.6 to 76.5 μg/L) (Etzel, 1993). Postshift blood TBA concentrations in the 12 subjects who participated in both Phase I and Phase II dropped from a median of 5.6 μg/L (range 1.6 to 72.2 μg/L) in Phase I to 3.9 μg/L (range 0.9 to 13.4 μg/L) in Phase II. The latter decline was not statistically significant (Etzel, 1993). The relatively small decline in TBA between Phase I and Phase II cannot be easily explained.

There was a statistically significant correlation between the air concentration measurements of MTBE during Phase I and subjects' blood concentrations. There was also a complex inverse relationship between blood TBA and exposure duration that was difficult to explain. There was a greater prevalence of complaints among the occupationally exposed individuals during Phase I compared with Phase II (Table 2). Although the four individuals in the highest quartile of postshift blood MTBE concentration appear more likely to report one of the key symptoms on the day blood was drawn than the 14 people in the lower quartiles, this difference was not statistically significant.

Nonoccupational exposures to MTBE oxyfuels were investigated in both Phase I and Phase II using commuters in Fairbanks. Seven people participated in Phase I. Six of these seven participated in Phase II along with one additional participant. Each person had a blood sample taken for MTBE analysis before leaving for work and upon arrival at work. The

median blood MTBE concentrations during Phase I were 0.18 μg/L (range 0.05 to 0.3 μg/L) prior to leaving for work and 0.83 μg/L (range 0.09 to 3.0 μg/L) after arriving at work; this increase was statistically significant. During Phase II, these values were statistically significantly lower, 0.09 and 0.10 μg/L, respectively.

The results of the Fairbanks studies need to be interpreted with caution. There may have been bias in the reporting of symptoms due to extensive negative publicity about MTBE. Furthermore, the small sample size may have not given the study adequate power to detect relationships even if they existed. People questioned in Phase I had a higher symptom rate than those in Phase II. However, given the limitations described above, causal relationships between MTBE and symptoms cannot be determined. The study did demonstrate that MTBE and TBA are detectable in the blood of exposed individuals, even at relatively low exposure concentrations.

Because Anchorage was studied only while MTBE oxyfuel was in use, it is not possible to determine whether there was a relationship between MTBE and symptoms there.

Stamford, Connecticut, and Albany, New York Studies. Because of the high degree of publicity associated with MTBE oxyfuels in Alaska, it was desirable to conduct a similar study in (1) an area using MTBE oxyfuels, but in which there was no evidence of widespread consumer complaints (Stamford) (Centers for Disease Control and Prevention, 1993b), and (2) in an area without MTBE oxyfuels for comparison purposes (Albany) (Centers for Disease Control and Prevention, 1993c).

From April 5 to 16, 1993, the CDC in cooperation with the State of Connecticut Health Department, conducted an investigation in Stamford. The study in Stamford differed from the study in Fairbanks in that there was no telephone survey. Although attempted, it was difficult to obtain cooperation from subjects contacted by telephone. Consequently 221 adult subjects were recruited by convenience for the study. The selection process was not random. The subjects were categorized by job as "car repair or gasoline sales", "professional driver", "other", or "commuter". The "other" category constituted workers who spent most of their time around traffic or motor vehicles, such as meter readers. "Commuters" did not have occupations associated with exposures to either gasoline vapors or combustion emissions. Each participant was administered a questionnaire, similar to the Fairbanks questionnaire

consisting of 15 health questions including the seven key symptoms. The period of time covered by the questionnaire was approximately 1 mo prior to administration. Of the 221 subjects, 44 had samples of blood taken for MTBE determinations. Thirty of these 44 worked around automobiles and had blood drawn at or near the end of a work day. The remaining 14 subjects were commuters and had their blood drawn upon arriving at work in the morning. Subjects were also asked if they experienced an unusual odor while pumping gasoline.

Because most of the participants who were not commuters were male, results reported here are for male participants (Table 3). Among males, the prevalence of any one of the seven key symptoms and the prevalence of two or more of any of the key symptoms was highest in the "other" category (67 and 50%, respectively). However, because of the few subjects in the "other" category, this relative ranking may not be meaningful. Headache and cough in the "other" category were the most commonly reported symptoms. The highest blood concentrations of MTBE were associated with people who had the greatest exposure to vehicular fumes and exhaust. Gasoline service station attendants had median blood MTBE levels of 15.19 μg/L and median TBA levels of >75 μg/L. Median blood MTBE levels in both the "car repair" and "commuter" job categories were 1.73 μg/L and 0.12 μg/L, respectively; TBA medians were 15.17 μg/L and 2.06 μg/L, respectively. Good associations were found between blood MTBE levels and personal breathing zone measurements of MTBE, and between blood TBA and breathing zone measurements of MTBE. The CDC reported that the 11 individuals with the highest (upper quartile, $\geq$2.4 μg/L) blood MTBE levels were statistically significantly more likely to report one or more key symptoms than the other 33 people studied. Although people with higher blood TBA levels (>17 μg/L) appeared more likely to report one or more key symptoms, this association was not statistically significant (White, 1993). Further comparisons were made of the subjects having occupational exposure (i.e., commuters were excluded from the analysis); the eight workers with the highest blood MTBE levels were significantly more likely to report symptoms than the remaining 22 workers. There was no apparent relationship between symptom prevalence by occupational category and the median blood MTBE or TBA concentrations associated with each category. However, the small numbers of subjects studied, the wide range of blood MTBE and TBA levels within each category, and the wide variability of response prevents a

TABLE 3. PERCENTAGE OF MALES IN STAMFORD REPORTING SYMPTOMS

Symptom	Commuter (n = 59)	Professional Driver (n = 57)	Car Repair or Gas Station Attendant (n = 48)	Other[a] (n = 12)
Headache	25% (15)	26% (15)	27% (13)	42% (5)
Eye irritation	19% (11)	7% (4)	21% (10)	17% (2)
Burning of nose/throat	7% (4)	0% (0)	15% (7)	33% (4)
Cough	15% (9)	5% (3)	15% (7)	42% (5)
Nausea	0% (0)	0% (0)	2% (1)	8% (1)
Dizziness	2% (1)	5% (3)	6% (3)	17% (2)
Spaciness	3% (2)	2% (1)	10% (5)	8% (1)
One or more	42% (25)	35% (20)	52% (25)	67% (8)
Two or more	14% (8)	7% (4)	23% (11)	50% (6)

[a]Workers who spent a high percentage of time around vehicular traffic (e.g., meter readers).

Source: Centers for Disease Control and Prevention (1993b).

definitive conclusion. Lastly, subjects who reported an unusual odor associated with pumping gasoline or using a motor vehicle were more likely to report one or more key symptoms.

Investigation in Albany occurred over the week of May 3, 1993, and involved 264 adult subjects recruited by convenience in a nonrandom fashion. Subjects were divided into three groups: Group 1 consisted of auto mechanics and gas station attendants, similar to the "car repair or gasoline sales" category in Stamford. Group 2 consisted of policemen, parking garage workers, toll booth workers, etc., and could be considered to be similar to a combination of the "professional driver" and "other" category in Stamford. Group 3 consisted of students and office workers, similar to the "commuter" category in Stamford. As in Stamford, mostly men participated; thus, only results for males will be reported. The 15-question symptom questionnaire was administered to each subject. A subset of 38 volunteers had blood samples drawn, as in Stamford; 20 worked around automobiles, and the remaining 18 were commuters. Auto mechanics and gas station attendants had median blood MTBE levels of 0.42 μg/L (range 0.09 to 1.50 μg/L); workers in Group 2 with some occupational exposure had a median level of 0.08 μg/L (range nondetectable to 0.15 μg/L); Group 3 people (e.g., students, office workers) with less gasoline exposure did not have

detectable levels of MTBE in their blood. These levels are substantially below those measured in Stamford.

When men only were considered (Table 4), there was no difference among the three groups with respect to reporting on any key symptom, or on two or more key symptoms. The prevalence of any one key symptom was between 42 to 49%. The prevalence of two or more key symptoms was between 9 to 18%. If the "other" category from Stamford is not considered, these data are very similar to the Stamford results. The similarity of responses across job categories suggests that the symptom reports may not be due to gasoline exposure. An important finding in Albany was that subjects who reported cold, flu, or allergies in the prior month were more likely to report the presence of any key symptom, even though they were instructed not to do so. It is uncertain whether a similar pattern was present in the other studies. It should also be noted that by the time the study was instituted in Albany, allergy season had begun and could have played a role in the reporting of symptoms and might account for the relatively high symptom reports. Finally, any comparisons of data among different cities must be approached with great caution. Methodological differences and other confounders, particularly the marked differences in ambient temperatures between springtime in Stamford and Albany, and winter in Fairbanks, could account for different observations.

TABLE 4. PERCENTAGE OF MALES IN ALBANY REPORTING SYMPTOMS

Symptom	Mechanics, Gas Station Attendants (n = 33)	Other[a] (n = 39)	Students, Office Workers (n = 83)
Headache	21% (7)	36% (14)	20% (17)
Eye irritation	18% (6)	21% (8)	16% (13)
Burning of nose/throat	6% (2)	3% (1)	11% (9)
Cough	15% (5)	15% (6)	26% (22)
Nausea	6% (2)	0% (0)	4% (3)
Dizziness	3% (1)	10% (4)	5% (4)
Spaciness	0% (0)	3% (1)	6% (5)
One or more	42% (14)	49% (19)	48% (40)
Two or more	9% (3)	18% (7)	18% (15)

[a]Policemen, parking garage workers, and toll booth workers.

Source: Centers for Disease Control and Prevention (1993c).

New Jersey Studies. Investigators at the Environmental and Occupational Health Sciences Institute (EOHSI) conducted two epidemiological studies in the State of New Jersey. In the first study, they (Mohr et al., 1993; Mohr, 1993; and Weisel, 1993a,b) investigated the symptomatic responses of 237 garage workers from the New Jersey Departments of Transportation and Treasury. Workers were given two questionnaires: one questionnaire elicited responses to questions about the presence of "MTBE" and "non-MTBE" symptoms over the previous 30 days. Questionnaire symptoms for MTBE included headache, nausea, daytime sleepiness while driving, daytime sleepiness at other times, cough, light headedness, and eye irritation. Non-MTBE symptoms investigated included diarrhea, fever, sweats or chills, and muscle aches. The second questionnaire was administered pre- and postshift and also asked about the presence of MTBE and non-MTBE symptoms at those times. Both questionnaires covered the same symptoms considered by CDC. Respondents were classified according to whether they worked in northern New Jersey, which at the time of the study was still using MTBE oxyfuels, or southern New Jersey, which was not using MTBE oxyfuels. Air samples taken in the garages showed that MTBE was present in the northern garages; a few of the garages in the south had MTBE, but the levels were overall lower than those in the north. Personal air exposures were measured in a subset of workers.

The EOHSI is in the process of analyzing and evaluating the personal sampler data so only preliminary information is available and a quantitative evaluation is not possible (Weisel, 1993a,b). For example, while relative MTBE levels can be quantitatively determined, absolute concentrations cannot until the study is completed. Thus, concentrations listed below are approximations, rather than precise values. Categorically, approximate concentrations are as follows: very high (>22 mg/m^3), high (6 to 22 mg/m^3), medium (3 to 6 mg/m^3), low (1 to 3 mg/m^3), not detectable (<1 mg/m^3). Sampler measurements were taken over a 3-day period (8-h time-weighted-average for each day), for nine sites in the north and four sites in the south. One individual was measured per site at six sites, two people per site were measured at two sites, and three people per site were measured at one site.

In the north, all locations examined had at least high levels of MTBE detected for one individual. Seven sites were categorized as high or very high on all days tested. There were two individuals who had low or medium levels. There were another two people who had

undetectable concentrations of MTBE on one day, but high levels on the other two test days. In the south, there are measurements for four people (one at each of four sites). People at two of these sites had high levels on two of the test days. One site had low levels on one day and undetectable levels on the other two days; the fourth site had undetectable levels on all three days. In summary, there appeared to be some degree of "mixing" between north and south, based on the occasional presence of high levels of MTBE at a few of the southern sites. Nevertheless, from a general and qualitative perspective, measured exposures in the north were higher than in the south. Northern levels were typically high (approximately 6 to 22 mg/m^3), whereas the south typically had low (approximately 1 to 3 mg/m^3) or undetectable levels (approximately <1/ mg/m^3). Such limited data for over a 3-day period cannot be quantitatively extrapolated to the whole of the questionnaire period (30 days) or to all participants. However, again on a qualitative basis, it is reasonable to assume that generally the group in the north had a substantially higher exposure to MTBE oxyfuels than the group in the south.

When all workers were compared, there was no significant difference in symptoms between northern New Jersey (n = 115) and southern New Jersey (n = 122) groups in either the 30-day questionnaire or in the pre-/ postshift questionnaire. Power calculations performed by EOHSI with their cross-sectional data show that, assuming a background headache prevalence of 10%, their study had 70% power (at the 0.05 level of significance) to detect a headache prevalence of 20%, 92% power to detect a 25% prevalence, and 99% power to detect a 30% prevalence. The investigators then narrowed the studied groups further according to: (1) attendants who pumped gas for more than 5 h/day (n = 13 north; 15 south), (2) attendants who worked on cars for more than 4 h/day (n = 62 north; 67 south), (3) attendants who spent more than 25 h per week driving vehicles (n = 29 north; 25 south), and (4) attendants with the highest personal exposure monitor levels of MTBE (approximately 6 to 22 mg/m^3 based on three consecutive days of 24-h personal sampling) against a matched low-exposure (approximately 1 to 3 mg/m^3) group (n = 8 high; 8 low). In none of the cases did the 30-day questionnaire show a difference between northern and southern New Jersey. Among the attendants who pumped gasoline for more than 5 h/day, there was a difference in pre-/postshift symptom reporting between northern New Jersey and southern New Jersey, but this effect was independent of time (i.e., pre- or postshift).

Between these two latter groups, there was a significant difference in age. But, when these groups were age-, sex-, and education-matched, this north/south difference disappeared. When symptoms were compared as a function of pre-/postshift and north versus south in all of the other groups, there was no north/south effect. These results suggest that MTBE oxyfuel exposure in a variety of cohorts of garage workers did not cause any difference in health complaints.

In an attempt to identify a sensitive subpopulation for the effects of MTBE oxyfuel exposure, Fiedler et al. (1993) administered a symptom questionnaire to 13 subjects reporting multiple chemical sensitivity (MCS). Persons with MCS usually report symptoms and illnesses in response to low-level exposure to a variety of chemicals and substances commonly encountered in the environment. To compare the responses of the MCS subjects, the questionnaire was also administered to five subjects with chronic fatigue syndrome (CFS) and six healthy control subjects. Subjects were asked to assess symptoms associated with situations in which they could be exposed to MTBE such as refueling and driving (subjects were not asked whether the fuel they had used contained MTBE). They were asked to rate on a scale from "no discomfort" to "severe discomfort" the symptoms of headache, burning in nose and throat, dizziness, gastrointestinal upset, sleepiness, cough, and spaciness. There was a nonsignificant tendency for MCS and CFS subjects to report more symptoms while refueling (but not while driving) when compared with the healthy subjects. On a total symptoms score range of 0 (no discomfort) to 28 (severe discomfort), the MCS subjects scored 5.3, compared to 4.8 for the CFS subjects and 1.2 for the healthy subjects. The data suggest that MCS subjects experience greater discomfort in conjunction with refueling. However, it is not possible to draw any firm conclusions from this study of MCS subjects because of the small sample sizes and because it was impossible to distinguish between subjects using MTBE oxyfuel and those not using MTBE oxyfuel.

Human Clinical Studies

To help address the issue of a direct causal relation between MTBE exposure and symptoms, two studies of the sensory, symptomatic, cellular, and eye responses of healthy human subjects exposed to MTBE in air in a controlled exposure chamber were conducted.

In the EPA investigation, 37 healthy, nonsmoking subjects (18 male, 19 female) between 18 and 35 years of age were studied (Gerrity et al., 1993; Gerrity, 1993; House, 1993a). Each subject was exposed for 1 h to both clean air and 5 mg/m^3 "pure" MTBE in air on different days. The temperature and relative humidity in the chamber were maintained at 75 °F and 40%, respectively. The endpoints selected for the EPA study were based on the observation that the symptomatic reports from Alaska resembled the types of symptoms associated with low-level organic solvent exposure. The endpoints for the EPA MTBE study can be divided into four categories.

1. Indicators of symptomatic response including headache, nasal irritation, throat irritation, cough, eye irritation, odor quality, and dizziness (measured before and during exposure):

    - Two symptom questionnaires (one computerized and one that replicated the EOHSI questionnaire)

    - Computerized analog air quality rating test

2. Indicators of behavioral response (measured before and at the end of exposure):

    - Neurobehavioral evaluation system test battery
        - Symbol-digit substitution (coding performance)
        - Switching attention (selective attention)
        - Mood scales

3. Indicators of upper airways inflammation (measured before, immediately after, and 18 h after exposure):

    - Nasal lavage
        - Types and numbers of epithelial and inflammatory cells
        - Albumin
        - Biochemical mediators of inflammation

4. Indicators of eye inflammation:

    - Densitometric indicator of eye redness (measured before and immediately after exposure)

    - Noninvasive tear film breakup (measured before and immediately after exposure)

- Impression cytology (before and 18 h after exposure)
  - Types and numbers of epithelial and inflammatory cells
  - Biochemical mediators of inflammation

Prior to exposure testing, each subject had a determination of his/her individual odor threshold for MTBE in water. In addition, blood concentrations of MTBE and its metabolite, TBA, were measured in two subjects. Blood samples were taken at regular intervals during exposure and for 7 h after exposure. These data provide a benchmark to compare exposures between the present study and field studies where blood samples were drawn.

Seventy-six percent of all subjects correctly detected the presence of the odor of MTBE in water at a concentration of 0.24 μL/L. These data compare reasonably well with the data of TRC Environmental Corporation reporting a detection threshold of 0.13 μL/L. Thus, it can be assumed that the subjects studied had normal odor thresholds for MTBE.

Blood concentrations of MTBE rose rapidly during exposure but did not plateau during exposure. Peak MTBE concentrations in the two subjects studied for pharmacokinetics were 8.2 and 14.1 μg/L, respectively. After exposure, blood concentrations fell rapidly, with half-lives of 36 and 37 min, respectively, derived using a model with a single compartment for elimination. By 7 h postexposure, blood concentrations had fallen to 0.2 and 0.6 μg/L, respectively. Blood TBA concentrations rose steadily during exposure and maintained a steady concentration of 7 to 10 μg/L up to 7 h postexposure. Even though the number of blood samples is too low for precise estimates of concentrations of MTBE in a population, the blood MTBE concentrations are consistent with measurements in the CDC studies.

There was no effect of MTBE on the reporting of headache and nasal irritation symptoms using either the computerized questionnaire or the analog approach. The results from using the EOHSI questionnaire in the clinical study also showed no significant MTBE effects and therefore were consistent with the results of the EOHSI epidemiology study. The neurobehavioral test battery showed no effect of MTBE exposure. None of the markers of nasal and eye inflammation showed a statistically significant response from MTBE exposure compared with clean air. Methyl tertiary butyl ether exposure also had no statistically significant effect on eye redness or on tear film breakup times. The primary hypothesis tested in this protocol was that MTBE would cause changes in the reporting of symptoms of headache, nasal irritation, air quality, perception, and odor strength perception. Power

calculations performed on the symptom data showed that (at $p<0.05$) there was adequate power to detect a 0.5 point change (on a five-point scale) with ≥90% power for odor level, headache, and nasal irritation. A 0.25 point change in nasal irritation could have been detected with 80% power. Thus, the study had adequate statistical power to detect MTBE-related changes in symptoms, if they had been present. For the other objective endpoints, statistical power calculations are not appropriate. Considering the relatively large number of subjects for such endpoints in a controlled study and inspection of the great similarity of means between the MTBE and control groups and their relatively small standard deviations (see Gerrity et al., 1993), the conclusion of the lack of statistically significant effects is valid.

Investigators at Yale University (Cain et al., 1993) replicated the EPA study (Gerrity et al., 1993). A total of 43 subjects (22 males, 21 females) between the ages of 18 and 34 years participated. All of the endpoints studied by the EPA investigators were also studied by the Yale investigators, although slightly different methods for measuring eye redness, tear film breakup times, and eye inflammation were used. The MTBE exposure concentration was slightly higher in the Yale study (6 mg/m^3). In addition to a clean air and an MTBE exposure for 1 h at 75 °F, each subject in the Yale study also underwent a 1-h exposure to a complex mixture of 16 volatile organic compounds (VOCs) commonly found in gasoline (C4, C5, and C6 saturates; and C4 and C5 olefins). This exposure to a surrogate gasoline served as a positive control for the MTBE exposure. In the pilot phase of investigation, the VOC mix was found to have no detectable odor. Consequently, isopropyl mercaptan (the odorant used in natural gas) was added to provide an unpleasant odor. The total VOC concentration of the atmosphere was approximately 7 ppm (about 20 mg/m^3). Besides the addition of the VOC exposure and the slightly higher MTBE exposure concentration, the only other major difference between the EPA and Yale studies was that at Yale, exposures of a given individual were separated by only 3 days, as opposed to 1 week in the EPA study (each person received both an air and an MTBE exposure).

When MTBE exposure was compared to clean air exposure, Cain et al. (1993) found essentially the same results as the EPA study (i.e., MTBE exposure had no statistically significant effects on symptoms, the neurobehavioral test battery, nasal inflammation, eye inflammation, eye redness, and tear film breakup times). Results of statistical power

calculations on the Yale symptom data by ORD (House, 1993b) were similar to those of the EPA study. Likewise, for the objective measures, means of the MTBE and control groups were very similar and standard deviations were small. Thus, the design of the study was sufficiently robust to have confidence in the negative outcome. When the VOC exposure was compared with clean air exposure, it was found that the VOC exposure caused an increase in inflammatory cells in the nasal lavage on the day following exposure (Cain et al., 1993). The timing of this increase and the amount of increase was consistent with previous work done at the EPA laboratories in which subjects were exposed to a different mix of VOCs (25 mg/m^3) simulating an indoor air environment (Koren et al., 1992).

Pharmacokinetic data were also collected on four subjects from the Yale study and evaluated by ORD (Gerrity, 1993). After exposure, the subjects had peak blood MTBE concentrations of 16.6, 14.8, 17.4, and 19.7 μg/L. When adjusted for exposure concentration, the concentrations are comparable to those of the EPA study. When a single exponential elimination curve was fit to the Yale data by ORD, the mean clearance half-time was 80 min (range 57.8 to 128.3 min). The TBA concentrations at 90 min postexposure had a mean of 10.3 μg/L (range 7.9 to 13.3 μg/L).

Taken together, the EPA and Yale investigations provide a consistent picture. They show that controlled human exposure to MTBE in air under the conditions studied does not cause increased symptoms or measurable responses (irritation, behavioral changes) in healthy adult subjects.

Blood Concentrations of Methyl Tertiary Butyl Ether and Tertiary Butyl Alcohol

In the CDC epidemiological studies and the EPA and Yale human clinical studies, MTBE and TBA were measurable in the blood of exposed people. In the epidemiological studies, other gasoline-related compounds (e.g., benzene, toluene, xylene) were also present in blood. In Stamford, people with higher blood levels of MTBE had more health symptoms; however, there was no statistically significant association between higher blood levels of TBA and symptoms. There was no statistically significant MTBE blood level-symptom association in Fairbanks. Although MTBE and TBA were detectable in the blood of subjects in the clinical studies, no increase in symptoms was observed. Such data offer further confirmation that exposure occurred, but they are not predictive of effects for two

main reasons. First, a relatively small number of people were examined compared with the numbers needed to obtain quantitative estimates of the relationship between blood markers and effects if such a relationship existed. Second, the half-life of MTBE is quite short (not known definitively, but likely to be around 60 min), presenting special problems. For example, shortly after an exposure, if a person has two blood samples drawn 60 min apart, the second blood sample will have half of the MTBE present in the first sample. Under such circumstances, a single-point measure of blood MTBE cannot accurately portray total work-shift exposure, and, even if it did portray a later portion of exposure, there are no data to allow a connection between the temporal relationship of exposures and effects, assuming there were effects. The metabolite of MTBE, TBA, has a substantially longer half-life in the blood (several hours or a few days), but using TBA as a quantitative biomarker would also be limited by the number of people tested. Developing models to relate blood levels of a compound to effects is an exceptionally arduous task, as evidenced by the extremely large body of research needed for such accepted models for lead and CO. Thus, the blood level data of MTBE and TBA collected are useful in confirming that exposure occurred and for developing hypotheses for future research, but the blood data, per se, cannot be used to draw conclusions about effects.

In assessing health effects, the optimal paradigm is to evaluate exposure-dose-response relationships, with exposure being defined as the breathing zone concentration and dose being defined as the mass/unit delivered internally. Preferably, the target site dose is known, but in the case of MTBE, the target site itself is unknown; the blood concentration can be assumed to be a surrogate. Because it is dose to a target site that causes an effect, interpretations at this level avoid the variability imparted by exposure-dose relationships and allow comparisons that would be difficult otherwise. In the specific case of MTBE and TBA, as yet there is no evidence showing that either is a valid indicator of dose, as discussed above. Even if future research shows one of the compounds to be a quantitative biomarker, the number of people having blood concentration measurements in these studies is likely to be too small for quantitative evaluation. Nevertheless, a qualitative comparison between the blood levels of MTBE and TBA in the epidemiological and human clinical studies is of interest.

In making comparisons of the blood data, Gerrity (1993) first normalized the Yale human clinical data to account for the differences in exposure concentrations between the EPA and Yale studies (5 and 6 mg/m^3, respectively). Adjusting for preexposure baselines, the Yale MTBE and TBA levels were reduced by 17.6%. A total of six subjects had blood measurements. The 60-min measurements show a median concentration of 14.0 μg/L MTBE (range 8.2 to 16.47) and 7.19 μg/L TBA (range 6.10 to 9.98). The exposures involved caused no increase in symptoms.

When actual human clinical MTBE levels are compared to MTBE levels in people working in garages in Fairbanks and Stamford and gas station attendants in Stamford, the human clinical levels were above the median levels for the garage workers and near the median for attendants. In Stamford, but not in Fairbanks, there was a statistically significant association between higher MTBE levels and higher symptom prevalence. Similar comparisons of blood TBA levels presents a slightly different picture. The human clinical TBA levels were within the range of the epidemiological subjects, but they were below the median for Stamford workers and slightly above the median for Fairbanks garage workers. In Stamford, there was no signficant association between high blood levels of TBA and symptoms. Such comparisons between the clinical and epidemiological studies should be interpreted cautiously. Considering the number of subjects measured, there likely is no major difference among all the groups. Furthermore, the bloods were drawn from the clinical and epidemiological subjects following very different exposure regimens. For example, the highest exposed Stamford garage workers had 8-h exposures to about the same concentrations of MTBE (within a complex mixture) used in the 1-h clinical exposures (with MTBE only).

Animal Studies

In rats, when inhaled MTBE is absorbed into the body, 99% of it is eliminated in 4 h (Ferdinandi et al., 1990). The half-life of MTBE in the blood of rats was about 30 min; the half-life of TBA was 1.5 to 3.5 h, depending on exposures and sex of the rats (Ferdinandi et al., 1990). Laboratory rats exposed for 6 h to high concentrations of MTBE (2,900, 14,400, or 28,800 mg/m^3) experienced several types of effects (IRIS, Integrated Risk Information System, 1993a). Activity levels in male rats were increased at 2,900 and

14,400 mg/m^3 and decreased at 28,800 mg/m^3 during the first hour following exposure; female rats showed similar but statistically nonsignificant effects. At the two highest levels tested, increased lacrimation (tearing) occurred and effects on the nervous system (decreased muscle tone, and staggered walking) were observed. Recovery occurred soon after exposure stopped. These studies indicate that short-term exposure to environmentally unrealistic levels of MTBE can cause reversible effects on the nervous system. However, the endpoints used in the rodent study would not detect the kind of symptoms reported by some Fairbanks, Anchorage, and Missoula residents.

Respiratory irritancy was examined in mice exposed to five concentrations of MTBE (300 to 30,000 mg/m^3) for 1 h (Tepper et al., 1993). A standard test used to evaluate lung irritancy from reflex changes in breathing rate and pattern was used. The severity of the sensory irritation ranged from "slight" (at 300 mg/m^3) to severe (at 30,000 mg/m^3). Pulmonary irritation was suggested at 30,000 mg/m^3 only, but data from other endpoints did not support this contention. The concentration resulting in 50% decrease in frequency of breathing as interpolated by linear regression from the five MTBE concentrations was 16,584 mg/m^3. According to the Standard Test Method for Estimating Sensory Irritancy of Airborne Chemicals (American Society for Testing and Materials, 1984) as applied to this interpolated value, 500 mg/m^3 would be considered to be a safe 8-h exposure (i.e., not causing significant sensory irritation) for healthy humans with an average degree of susceptibility.

Methyl tertiary butyl ether has produced developmental effects in reproductive and developmental toxicity studies with rats (Neeper-Bradley, 1991) and mice (Tyl and Neeper-Bradley, 1989), but not with rabbits (Tyl, 1989). A two-generation reproduction study in rats found no adverse effects at 1,440 mg/m^3; at 10,800 mg/m^3, rat pups had reduced body weights (at birth) and reduced weight gains during postnatal development (Neeper-Bradley, 1991). Exposures of mice to 14,400 and 28,800 mg/m^3 in a developmental toxicity study resulted in reduced pup viability, and at 28,800 mg/m^3, cleft palate (Tyl and Neeper-Bradley, 1989). The no-observed-adverse-effect level (NOAEL) from the mouse developmental toxicity study was 3,600 mg/m^3. Although the mouse developmental toxicity study had exposures only during the period that organs were forming (Days 6 to 15 of pregnancy), the two-generation rat reproduction study involved exposures of both parental

animals prior to mating as well as during pregnancy and lactation. Still, both types of studies included exposures during the critical period of organ development and showed adverse effects. Some chemicals can cause adverse developmental effects after very short exposures during critical periods of the development process. Such an effect may be expressed as a malformation or death, or expressed as an effect on growth (prenatal or postnatal) or functional performance. A more extended duration of daily exposure or repeated exposure incidents might exacerbate that particular expression of toxicity or might cause additional or different developmental effects. Postnatal exposures can also produce effects on viability, growth, or performance, but if exposures occurred both pre- and postnatally (except with malformations), it is usually not possible to differentiate whether the effect was caused by pre- or postnatal exposures. Such is the situation currently with MTBE, and the possibility cannot be ruled out that a single exposure of sufficient magnitude could produce an adverse developmental effect in laboratory animals.

In concordance with approaches established by the EPA Guidelines for Developmental Toxicity Risk Assessment (Federal Register, 1991), Clegg (1993) developed a preliminary assessment of the developmental toxicity of MTBE. A lowest-observed-adverse-effect level (LOAEL) of 10,800 mg/m^3 and a NOAEL of 1,440 mg/m^3 for developmental toxicity were identified from the two-generation reproductive toxicity test (Neeper-Bradley, 1991). For this inhalation study, uncertainty factors of 3 were applied for extrapolation from rats to humans and of 10 to account for sensitive human subpopulations in accord with current EPA practice for inhalation exposure. This calculation results in a preliminary estimate (with uncertainty spanning at least an order of magnitude) of 48 mg/m^3, at which no adverse developmental toxicity is likely to occur in humans (including sensitive subpopulations). The exposure level that might produce effects in humans is highly uncertain. Estimation of such a level would depend on the magnitude and duration of exposure; the disposition, metabolism, and pharmacokinetics of the compound in humans; and the sensitivity of humans to the effect as compared to animals that were tested. It is generally important in assessments of developmental toxicity to consider that short-term exposures may result in adverse effects, if they occur during the appropriate window of sensitivity. However, no information exists for MTBE in animals or humans to determine more accurately the minimum level and duration of exposure that might adversely affect the developing organism.

Thus, it is assumed that even a short exposure has the potential to result in developmental toxicity if the exposure concentration is sufficiently high.

2.2.3 Long-Term Exposure Effects

Pursuant to a 1988 consent order under the Toxic Substances Control Act, EPA required that industry conduct extensive studies of the health effects of MTBE in laboratory animals to estimate potential effects in humans. The studies evaluated all major organ systems using routine types of methods and included tests for reproductive and developmental effects (described earlier). Chronic carcinogenicity assays were also performed.

Noncancer Effects

In 1991, EPA evaluated the noncancer chronic effects of MTBE based on subchronic studies and developed a health metric called an inhalation reference concentration (RfC). When chronic exposure studies were reported, the RfC was revised to incorporate these new data. The current RfC for MTBE is 3 mg/m^3 (IRIS, Integrated Risk Information System, 1993a). An RfC (for any chemical) is defined as an inhaled concentration, with an uncertainty spanning about an order of magnitude, that can be inhaled continuously over a lifetime by people (including sensitive populations) and is thought not to pose any appreciable deleterious noncancer hazard. The RfC for MTBE is based on studies of rats exposed to 1,450, 10,800, or 28,800 mg/m^3 MTBE for 6 h/day, 5 days/week for 24 mo (Chun et al., 1992). At the two higher concentrations, there was excess mortality in males. The noncancer effects observed at 10,800 mg/m^3, the LOAEL, were increased liver and kidney weights, increased severity of spontaneous kidney lesions, increased incidence of prostration (extreme exhaustion) in female rats, and swollen periocular tissue in male and female rats. Kidney effects were also observed in male rats, but are considered less relevant to a quantitative human noncancer risk assessment because the enhanced progression of the male kidney lesions caused by MTBE may be due, in part, to the buildup of a protein ($alpha_{2u}$globulin) that has not been found in female rats or other animal species, including humans. A NOAEL of 1,450 mg/m^3 was established based upon the studies. According to the RfC methodology, this NOAEL was dosimetrically adjusted to approximate an equivalent continuous exposure level in humans and divided by a 100-fold uncertainty factor to obtain

the RfC. The uncertainty factor reflects a factor of 10 to protect unusually sensitive individuals and a factor of 10 to account for both interspecies extrapolation and the lack of certain information from the chronic exposure bioassay.

In a chronic inhalation study (Burleigh-Flayer et al., 1992), male and female mice were exposed to 1,450, 10,800, or 28,800 mg/m^3 for 6 h/day, 5 days/week for 18 mo. Male mice from the high-exposure group exhibited an increased mortality rate, maybe due to an increased frequency of kidney disease (obstructive uropathy). Ataxia (staggered walking) was observed in all animals exposed to the high MTBE concentration. Other effects reported in both sexes of the high-concentration group included decreased body weight gain and absolute body weight (males only), increased liver and kidney weights (females only), decreased brain weight, and a slight decrease in urinary acidity. Histopathologic evaluation revealed no lesions in any organ except the liver. Cellular changes in the liver occurred at the highest exposure level in both sexes, but were only statistically significant in the male mice. No concentration-related effects were reported at the mid-exposure level. Thus, the 10,800 mg/m^3 exposure level is considered a NOAEL for this study.

In the associated subchronic study, rats were exposed to 2,900, 14,400, or 28,800 mg/m^3 MTBE for 6 h/day, 5 days/week for 13 weeks (Dodd and Kintigh, 1989). As in the chronic study, there were no noticeable effects on some of the parameters or organs studied, such as the lungs. However, the overall weight of evidence indicates that the 14,400-mg/m^3 level was moderately adverse to several organ systems in the rats, as indicated by decreased brain length and increased relative kidney, adrenal, and liver weights. The NOAEL in the rats was 2,900 mg/m^3. Neither brain nor adrenal effects were noted in the chronic rat study (Chun et al., 1992), and brain effects (decreased brain weight) were not observed at 10,800 mg/m^3 in the mouse study (Burleigh-Flayer et al., 1992).

Potential for Carcinogenicity

Pertinent data in humans that is useful for determining whether or not MTBE causes cancer is not available. Therefore, the focus is on the animal data. The EPA's Office of Health and Environmental Assessment (summarized by Parker et al., 1993) has performed an evaluation of the cancer tests in the Chun et al. (1992) and Burleigh-Flayer et al. (1992) chronic studies mentioned above. This current evaluation must be considered to be

preliminary until additional data are considered, including a recently reported oral exposure animal bioassay from the Bologna Insititute of Toxicology (ARCO Chemical Company, 1993) and additional mechanism studies of kidney toxicity. The complete assessment will then be subjected to review by an EPA-wide work group.

The two available chronic animal cancer bioassays of MTBE (Chun et al., 1992, and Burleigh-Flayer et al., 1992) were assessed. In these bioassays, groups of 50 mice and groups of 50 rats of each sex were exposed to MTBE. Mice were exposed 6 h/day, 5 days/week for 18 mo to either filtered air or MTBE in filtered air at concentrations of 1,400, 10,800, or 28,800 mg/m^3. Rats were exposed to the same conditions for 24 mo, except for the mid- and high-dose males, which were autopsied early due to excessive mortality. Chemical-induced toxicity, reduced survival, lack of clinical chemistry information from blood and urine samples, and considerably less-than-lifetime exposures make these studies difficult to use for a carcinogenicity hazard characterization without considerable uncertainty.

An increase in rare kidney tumors was observed only in the mid- and high-dose groups of male rats. The increased incidence of kidney tumors in mid-dose male rats is statistically significant compared to concurrent controls. In spite of high mortality leading to the early termination of the high-dose study group, kidney tumor incidence is elevated, but with the probability of observing a significant response compromised. A question always arises as to whether kidney tumors present in exposed male rats are due to the accumulation of a species- and sex-specific protein ($alpha_{2u}$globulin) and its associated pattern of damage (nephropathy) in the kidney tubule cells. If so, the resulting increase in tumors would not contribute to the weight-of-evidence for human carcinogenicity. The data were evaluated according to criteria set forth by the EPA (U.S. Environmental Protection Agency, 1991b). Very little evidence exists suggesting that MTBE causes $alpha_{2u}$globulin accumulation, although additional information from ongoing studies will help to refute or to substantiate this claim. The findings of nephropathy and a rare kidney tumor in one female rat makes it difficult to conclude that the renal tumors can be attributed solely to this hypothesized $alpha_{2u}$globulin mechanism. Therefore, because the mechanisms of kidney tumorigenesis are not yet understood, the kidney tumors are viewed as contributing to the overall weight-of-evidence for MTBE carcinogenicity. Excessive mortality in the mid- and high-dose groups indicates

that the maximal tolerated dose may have been exceeded, thereby increasing the uncertainty of interpreting the data in terms of human cancer hazard.

Testicular tumors were statistically significantly increased in both the mid- and high-dose groups of male rats compared to concurrent controls. A dose-response trend is clearly evident. The meaning of the MTBE interstitial cell testicular tumor response in the test rats for prediction of human carcinogenic risk can be questioned, however, because of high spontaneous background incidences of interstitial cell tumors in this strain of rat. The statistical significance of the finding disappears if the incidences in test animals are compared to the average levels in historical controls. Concurrent controls are generally recognized to be the most appropriate group to use for the purpose of determining the statistical significance of observed differences between experimental groups, unless there is a fault with the controls. The significant increase in testicular tumors when compared to concurrent controls, coupled with the dose response, is justification for viewing this tumor type as contributing to the overall weight of evidence for MTBE carcinogenicity.

Methyl tertiary butyl ether caused an increase in liver tumors in mice at the high dose. Evidence of toxicity observed at the high dose causes the human hazard significance of high-dose chemically induced mouse liver tumors to be the subject of debate. The MTBE mouse study is a less-than-lifetime study of 18 mo, rather than a 2-year lifetime study. The shortened time of the exposure decreases the sensitivity of the bioassay. A tumor response was noted at the high dose, in spite of the shortened length of the bioassay. A statistically significant increase in carcinomas was observed in male mice and latency was decreased. In female mice, there was a statistically significant increase in adenomas (and adenomas and carcinomas, driven by the adenomas). There is no way to know whether a longer exposure period would have provided an expanded pattern of response in the mid-dose groups.

Methyl tertiary butyl ether has not been observed to be mutagenic in most systems tested. It was found to be positive in mouse lymphoma tests (McGregor et al., 1988). Two MTBE metabolites are considered potential human carcinogens—formaldehyde and TBA. Formaldehyde is mutagenic and is classified by EPA as a "probable human carcinogen" (IRIS, Integrated Risk Information System, 1993b). Oral exposure to TBA induced a statistically significant increase in thyroid adenomas in female mice and appeared to increase

renal tumors in male rats, but this increase was not statistically significant (National Toxicology Program, 1991a,b, 1992).

Although certain MTBE tumor responses are statistically significant, none of the responses is considered truly robust, and the lack of a strong, clear-cut response diminishes confidence in the data. Available mutagenicity data on MTBE are primarily negative, although a metabolite (formaldehyde) is mutagenic. Furthermore, controversy exists regarding each of the tumor endpoints, and the studies have shortcomings that impede developing clear-cut inferences about potential human hazard. Although more robust responses in both the rat and mouse would add strength to the concern for the carcinogenicity, taken together, the responses seen provide "limited" evidence of animal carcinogenicity. Each of these responses is suggestive of potential carcinogenicity and adds to the hazard concern. Carcinogenicity of an MTBE metabolite is yet another concern. As stated above, further evaluation of the data base, including the recent Italian study (ARCO Chemical Company, 1993), will be undertaken before a final carcinogenicity classification is determined. At the present time, the data suggest that a tentative "C" classification (possible human carcinogen, based on limited animal evidence) is supportable.

Although major uncertainties exist in the data base, quantitative cancer risk indices were developed to facilitate comparison to other chemicals having carcinogenic activity. This type of analysis has a "what if" objective—that is, if MTBE were a carcinogen, what might the impact be? The comparative cancer potency estimates for MTBE span a 70-fold range, although they are relatively low when compared to other chemicals. Because of the uncertainties, the absolute potency values are not of importance.

Additionally, it must be remembered that MTBE is being added to gasoline, a mixture that can cause cancer in laboratory animals. Gasoline mixtures also include other carcinogens such as small amounts of benzene (Class A, a known human carcinogen) and 1,3-butadiene (Class B2, a probable human carcinogen). There is a trend for reduced tailpipe emissions of benzene when MTBE is added to the gasoline (see Section 3.1.1). From an additivity perspective, putting MTBE in gasoline is unlikely to affect the current cancer classification of the mixture.

2.3 Formaldehyde, Benzene, and Butadiene

All gasoline-fueled automobiles will emit formaldehyde, benzene, and 1,3-butadiene. These pollutants are of interest primarily because of their cancer potential. Benzene is classified as a proven human carcinogen, and 1,3-butadiene and formaldehyde are classified as probable human carcinogens (Grindstaff et al., 1991; U.S. Environmental Protection Agency, 1985, 1989).[2] If exposure concentrations of all these chemicals were equal, the estimated cancer risk from exposure to formaldehyde would be similar to the risk from exposure to benzene. The risk from exposure to 1,3-butadiene would be several times greater. However, exposure concentrations to these chemicals, although not well quantified, are different.

Acute exposure to formaldehyde can cause noncancer effects (U.S. Environmental Protection Agency, 1987; Grindstaff et al., 1991). Irritation of the eyes, nose, and throat is the most common effect observed in humans from short-term exposure to formaldehyde and can be observed at exposure levels as low as 0.1 mg/m^3. Short-term exposures to 3 or 4 mg/m^3 do not produce noticeable lung effects. Formaldehyde exposure has been linked with a number of behavioral and physiological effects such as thirst, dizziness, headache, and apathy. Residents of homes in which formaldehyde concentrations ranged from 0.06 to 0.6 mg/m^3 have reported these symptoms along with an inability to concentrate and sleep. Tolerance to low levels of formaldehyde can occur in individuals after 1 to 2 h of exposure, but symptoms can return if exposure is interrupted and then resumed. It should be noted that some of the symptoms of acute formaldehyde exposure described in the scientific literature are among those investigated in the MTBE epidemiological and human clinical studies.

[2]Benzene has a cancer classification of A, a human carcinogen based on sufficient evidence from epidemiological studies; formaldehyde is classed as B1, a probable human carcinogen based on sufficient evidence from animal studies and limited evidence from human studies; 1,3-butadiene is classed as B2, a probable human carcinogen based on sufficient evidence from animal studies and inadequate data from epidemiological studies.

3. AIR QUALITY AND EXPOSURES

3.1 Air Quality

3.1.1 Air Samples

To obtain some degree of information of air concentrations of pollutants of interest, Zweidinger (1993) has analyzed air samples collected over 8-h periods in Fairbanks, Stamford, and Albany for aldehydes, MTBE, and other VOCs. However, due to study limitations to be discussed later, the data cannot be used to quantitatively define air quality in a city. The Fairbanks samples were collected by the State of Alaska during three phases: Phase 1 was immediately prior to the phase out of 15% MTBE in gasoline (December 1 to 12, 1992; 25 VOC and 35 aldehyde samples); Phase 2 was during the phaseout (December 18 to 22, 1992; 31 VOC and 26 aldehyde samples); and Phase 3 was after the phaseout (February 2 to March 5, 1993; 73 each VOC and aldehyde samples) of MTBE oxyfuels. Based on the analysis of gasoline samples collected in Fairbanks during Phase 2 and Phase 3, the percent of MTBE in gasoline decreased from 8.5 to 1% (unleaded regular) and 14.7 to 5.6% (premium). The Stamford samples were collected by EPA Region 1 (April 13 to 14, 1993; 30 each VOC and aldehyde samples) and represented another part of the country where MTBE-oxygenated gasoline was also sold. The Albany samples were collected by the New York State Department of Health (May 5 to 27, 1993; 20 each VOC and aldehyde samples) and represented an area of the country where MTBE was present only as an octane enhancer in gasoline. The Fairbanks Phase 1 samples were analyzed by the Oregon Graduate Center (VOC) and Desert Research Institute (aldehydes). All other ambient samples were analyzed by EPA's Atmospheric Research and Exposure Assessment Laboratory. The samples from each city consisted of roadside intersections, gas stations (pump island), garage service bays, residential neighborhoods, and indoor air and background sites. Indoor, service bay, and background sites were not collected in Albany, and no service bay samples were collected in Fairbanks during Phase 2. Also, occupationally oriented samples were collected from the interiors of commercial cars and trucks in Fairbanks during early Phase 1 and Phase 3. Significant differences in ambient temperature and other meteorological conditions existed among the cities where samples were collected. Also, only a relatively few samples were collected in a given area, and the samples were collected over only a few days. Therefore, the data cannot be used to quantitatively define the air quality in a city.

Rather, the data can be used to estimate approximate ranges of air quality in the locations sampled.

The highest average concentrations of MTBE (0.011 mg/m^3), benzene (0.629 mg/m^3), total nonmethane organic carbon (80.5 ppm C), and formaldehyde (0.038 mg/m^3) were found in garage service bays. One of the highest average concentrations for a single compound was found to be 1,1,1-trichloroethane (methyl chloroform), which exceeded 38.0 mg/m^3 in service bays (Fairbanks, Phase 3). Aside from the service bays, MTBE concentrations were next highest at gas stations (Fairbanks: 0.194 mg/m^3 Phase 1; 0.134 mg/m^3 Phase 2; and 0.020 mg/m^3 Phase 3). The Stamford gas station MTBE concentrations were the lowest (0.013 mg/m^3) but were likely the result of sampler location (Albany average was 0.086 mg/m^3). Whereas samplers in Fairbanks and Albany were located on the pump island, the samplers in Stamford were located at least 15 ft away from the pump island. Indoor and outdoor MTBE concentrations were similar and averaged about 0.025 mg/m^3 in the Phase 2 Fairbanks samples, falling to 0.0037 mg/m^3 in Phase 3, with the exception of one home where the average indoor value was 0.072 mg/m^3. This home had an attached garage and also had elevated levels of benzene (0.138 mg/m^3) and other compounds associated with gasoline. Indoor MTBE concentrations in Stamford averaged 0.002 mg/m^3. Methyl tertiary butyl ether concentrations measured inside vehicles in Fairbanks averaged 0.024 mg/m^3 in Phase 1 (not including one sample of 0.241 mg/m^3) and averaged 0.019 mg/m^3 in Phase 3 (not including one sample of 0.127 mg/m^3).

Formaldehyde concentrations were higher indoors (0.012 to 0.034 mg/m^3) than outdoors (0.0025 to 0.025 mg/m^3), which is generally the case, and levels appeared typical of those seen in indoor air studies.

Benzene levels were higher in Fairbanks (average roadside levels were 0.026 mg/m^3, December; 0.042 mg/m^3, Phase 3) than the other cities (Stamford, 0.003 mg/m^3; Albany, 0.0014 mg/m^3).

The Auto/Oil Air Quality Improvement Research Program examined the impact of MTBE on motor vehicle toxic emissions (Reuter et al., 1992). This work with 20 vehicles (1989 models with 3-way catalysts) showed that, at 75 °F, there is a trend for MTBE to cause a net reduction in the total mass of air toxics. Individually, there is a trend for emissions of benzene to decrease and emissions of formaldehyde to increase; 1,3-butadiene

was not substantially altered when MTBE was added. When ORD's cold-temperature emission studies are completed, more will be known about these changes in air toxics emissions. Although some models are available, these changes in emissions cannot be quantitatively extrapolated to estimate impacts on air quality (and exposures) within a city with sufficient precision for the purposes of this report.

3.1.2 Air Concentrations in Vehicle-Related Microenvironments

The Environmental and Occupational Health Sciences Institute and the Research Triangle Institute (RTI) completed a study of field measurements of MTBE concentrations inside automobiles during an approximate 30-min commute and during a fill-up of the gas tank (Lioy et al., 1993). Field measurements were collected in New Brunswick, NJ (two stations with full service and Stage II vapor recovery); Westchester County, NY (three stations with self service and Stage II vapor recovery); and Fairfield County, CT (five stations with self service and no Phase II vapor recovery). One new model automobile (1992 Corsica) and one older model automobile (1985 Caprice or 1986 Monte Carlo) were assigned to each commuter route. The samples were collected in the front passenger side of the automobile. The number of samples per automobile ranged from 14 to 20 for the commute and from 3 to 5 for the fill-up. The driver's window was turned down during the fill-up. The time to complete the fill-up was about 2 min, and the total time at the gas station was 5 to 10 min. In addition to the measurements inside the automobile, a few measurements were collected near the breathing zone of the person refueling the gas tank.

Average concentrations of MTBE during the commute were found to range from 0.018 to 0.275 mg/m^3 (Lioy et al., 1993). Average concentrations during the fill-up ranged from 0.036 to 1.8 mg/m^3. In addition to the measurements inside the automobile, several measurements were collected near the person refueling the gas tank. These concentrations were found to range from 0.7 to 14 mg/m^3. Inside the older model automobiles, concentrations were higher, probably reflecting differences between the automobile design and "wear". An effect of Stage II vapor recovery could not be evaluated due to many confounding factors.

International Technologies Inc. (IT) completed a set of field measurements of MTBE concentrations in the personal breathing zone during fill-up, at the pump island, and around

the property line of gas stations (Johnson, 1993). This study was done in coordination with the above EOHSI/RTI study at the same ten gas stations. All concentrations for this study, even those in the intermittent breathing zone, were from a 4-h continuous sample. Average fence-line (typically taken at the apparent property line) concentrations were found to range from 0.018 to 0.234 mg/m^3 MTBE (Johnson, 1993). The highest fence-line concentrations ranged from 0.36 to 0.5 mg/m^3 MTBE. The highest breathing zone and pump island concentrations ranged from 0.7 to 9 mg/m^3 MTBE. These breathing zone concentrations are comparable to the 4-h continuous sample occupational concentrations in a recent NIOSH study (National Institute for Occupational Safety and Health, 1993). For the NIOSH study, the mean breathing zone concentration for station attendants was 2 mg/m^3, with some of the highest concentrations exceeding 14.4 mg/m^3.

As should be expected, these 4-h breathing zone concentrations described above are lower than reported by the Clayton Environmental Consultant study (Clayton Environmental Consultants, 1991), which collected samples only during the fill-up period (approximately 2 min). In the Clayton study, mean MTBE concentrations in the breathing zone for oxyfuels having 12 to 13% MTBE were 13 mg/m^3, with vapor recovery, and 30 mg/m^3, without vapor recovery. The absolute range among these MTBE concentrations was 0.32 to 137 mg/m^3. Although several stations were monitored, the highest and lowest measurements were made at one station, illustrating the variability of breathing zone exposures. A wide range of ambient air concentrations within the breathing zone can be expected. Ambient air concentrations measured at a gas station will be highly dependent upon the wind speed and direction. In addition, breathing zone concentrations can be dramatically influenced by how one stands relative to the wind. Also, any spill of fuel while filling the tank can very dramatically increase the inhaled concentration.

3.2 Human Exposure Estimates of Methyl Tertiary Butyl Ether

The data on air quality and microenvironments (e.g., during refueling, inside cars, in personal garages) are too limited for a quantitative estimate of population exposures. At best, they can be used to estimate approximate broad ranges of potential exposures. Because of the interest in MTBE, the present evaluation focuses on this compound, even though any potential health effects might result from complex pollutant mixtures of which

MTBE is only one component. Furthermore, potential exposures of only the general public, not occupationally exposed groups, were evaluated.

There is a need to estimate both acute and chronic exposures to elucidate health risks. Table 5 outlines the personal activities that have been considered in developing an annual human exposure estimate (Huber, 1993). Gasoline fill-up is divided into two parts to account for both the fill-up (1.5 fill-ups/week) and the remaining time spent in the station environment. The distribution of hours spent in each microenvironment is based to some extent on a reasonable interpretation of available population activity studies. The greatest difficulty arose in trying to distribute the balance of time spent in one's residence, office, or outdoors. In this example, which represents one exposure scenario, the typical time one spends either at home or in a workplace is relatively large. Therefore, if there are elevated concentrations in these environments, they will become the largest contributor to annual average human exposures.

Table 5 also summarizes concentration estimates within the microenvironments based on available data reported in the previous section (Section 3.1.2) and some model estimates (Huber, 1993). The upper bound of these concentrations and the assumptions used are believed to be a reasonable worst case, not the worst case possible on infrequent occasions. Thus, it would be expected that most people would experience lower exposures. The high values for residential garage and house assume an attached garage with evaporative emissions from the automobile or a small gasoline spill with the garage door closed. The high value for outdoors assumes that one would live near a gas station or a heavily used highway.

The components of the annual average human exposure calculations using the assumptions described above are shown in Table 5. This table clearly identifies the commute and gasoline fill-up as the most important microenvironments, unless there are significant evaporative emissions in a residential garage. Several annual estimates were developed using the Table 5 values. These estimates are for 4- and 6-mo MTBE oxyfuel seasons and assume that MTBE concentrations are 10% of these values for the remainder of the year. This 10% assumption is based on the belief that the amount of MTBE in the ambient air is proportional to the amount of MTBE in the fuel (1.5% in all nonoxyfuel versus 15% in oxyfuel). It is very difficult to estimate MTBE levels during the nonoxyfuel season because MTBE is used at varying percentages in some premium gasolines and more rarely in regular gasolines, and,

TABLE 5. METHYL TERTIARY BUTYL ETHER EXPOSURE ESTIMATES

Activity	Occurrence	Time/Year (h)	Concentration (mg/m^3)	Exposure ($mg/m^3 \cdot h$)
1. Gas fill-up	1.5/week @ 2 min	2.6	36.0	93.6
	Other @ 10 min	13.0	3.6	46.8
2. Commute/in vehicle	10 h/week	520	0.36	187.2
3. Auto shop	4/year @ 15 min	1.0	1.8	1.8
4. Public garage	10 min/day	60.83	1.8	109.5
5. Residential garage	2 min/day	12.16	3.6 (H)[a]	43.8
			0.018 (L)	0.22
6. Residence	10 h/day + weekend	4,160	0.036 (H)	149.8
			0.018 (L)	74.9
7. Office	40 h/week	2,080	0.036	74.9
8. School/public buildings	17 h/week	884	0.036	31.8
9. Outdoors	20 h/week	1,040	0.36 (H)	374.4
			0.036 (L)	37.4

[a]H = High; L = Low.

although premium fuels have a higher percentage of MTBE, less is used. The 1.5% MTBE chosen is an assumption that is likely to be a high or excessively high estimate. Table 6 shows the annual exposure estimates based upon these variables. These exposure scenarios were cast to represent reasonable worst-case exposure estimates for the working adult population not receiving occupational exposure to gasoline, with some conservative judgements after considering all available measurements. Exposure for children is expected to be lower because they do not pump gas and spend less time commuting in heavy traffic.

It can be assumed that a gasoline fill-up scenario, although brief, would result in the highest acute exposure concentrations. The highest human exposure is expected when one is near evaporative emissions. Thus, exposure would be greatest when handling gasoline. The highest reported MTBE concentration was 137 mg/m^3, although levels as low as 0.32 mg/m^3 were also measured at the same station, illustrating the variability in fill-up exposures (Clayton Environmental Consultants, 1991). A more typical worst-case MTBE concentration

TABLE 6. ANNUAL AVERAGE METHYL TERTIARY BUTYL ETHER EXPOSURE ESTIMATES[a]

4-mo Oxyfuel Season		6-mo Oxyfuel Season	
High[b] (mg/m^3)	Low (mg/m^3)	High[a] (mg/m^3)	Low (mg/m^3)
0.05	0.03	0.07	0.04

[a]Assumes 1.5% average MTBE in gasoline in nonoxyfuel season.
[b]High or low exposure estimates from Table 5 used.

in the breathing zone during fill-up would be 36 mg/m^3 MTBE for a few minutes (Johnson, 1993; Lioy et al., 1993; Clayton Environmental Consultants, 1991). However, higher concentrations are possible, especially in the case of an accidental spill.

For purposes of comparison to the 1-h human clinical exposure studies (at 5 and 6 mg/m^3), 1-h time-weighted average MTBE concentrations were calculated for two exposure scenarios, using high concentration data. The first scenario assumed highest measured values and involved a 2-min fill-up (137 mg/m^3), a 30-min commute associated with a fill-up (1.8 mg/m^3), and a 28-min remaining commute (0.275 mg/m^3); the average is 5.6 mg/m^3 MTBE. The second scenario used the MTBE levels on Table 5. Scenario 2 assumed a 2-min fill-up (36 mg/m^3), 2 min in a personal garage (3.6 mg/m^3), a 30-min commute (0.36 mg m^3), 10 min in a public garage (1.8 mg/m^3), and 16 min in a public building (0.036 mg/m^3); the average is 1.8 mg/m^3 MTBE.

4. HEALTH RISK ESTIMATES

Health risk is evaluated by integrating knowledge of health effects and exposure. Most chemicals, including MTBE, can cause health effects at some exposure concentration and duration. The issue then, is the likelihood of people encountering exposures that are capable of causing health effects, which is the topic of this section. Uncertainties always exist in risk assessment. As will be discussed below, some of the uncertainties regarding MTBE do not overwhelm the ability to reach conclusions; in other cases, the uncertainties preclude anything more than qualitative estimates. This section presents risk estimates for the general

public (including highly exposed people such as commuters), not for those who receive higher occupational exposures. People with occupational exposures to MTBE oxyfuels were subjects in the epidemiological studies in an attempt to detect effects at higher exposures, providing a potential boundary to interpret the possibility of effects at lower levels that might be encountered by some of the general public.

4.1 Carbon Monoxide

No quantitative assessment of changes in CO health risks that may result with MTBE use is made here. Such an assessment is needed to consider the relative benefits and risks of CO and MTBE. Therefore, developing a CO risk assessment would be of value. It should include a total exposure assessment; that is, an evaluation of all exposure sources (e.g., personal and public garages, street canyons, indoors), not just outdoor ambient concentrations represented by stationary monitors to test for attainment of the CO NAAQS. Efforts should include estimates of the potential for sensitive subpopulations (by number and geographical location) to experience adverse levels of COHb.

4.2 Methyl Tertiary Butyl Ether

From the human clinical studies, it appears that healthy members of the public are unlikely to experience the symptoms of interest (e.g., headache) after a 1-h exposure to MTBE under temperate conditions and concentrations (5 or 6 mg/m^3) that are higher than those commonly encountered. The exception is that when people refuel their cars on some, but not all, occasions, they may receive brief (1- to 3-min) exposures to substantially higher concentrations of MTBE than those used in the chamber studies. The influence of dose-rate on symptoms, assuming there are symptoms, is not known. Therefore, even though the clinical studies used high 1-h average concentrations relative to common high public exposure scenarios, there is a possibility that a higher brief peak exposure could influence the outcome. Because there were two independent clinical studies that used both subjective (i.e., symptom reporting) and objective (i.e., eye/nose inflammation, behavior) measures, the findings are robust for the study conditions. However, these studies are limited in that they used MTBE in air and did not include representatives of subpopulations who might be more sensitive. For example, it is conceivable that MTBE-gasoline mixtures might cause effects

different from "pure" MTBE. It should be recognized that the clinical studies used relatively young healthy subjects.

Most epidemiological studies (including the ones described here) cannot, by their very nature, demonstrate cause-effect relationships because observed effects might have causes in addition to the pollutant under investigation that are difficult or impossible to sort out. Rather, epidemiological studies have the potential to show associations between exposures and effects. The study comparing workers from the New Jersey Departments of Transportation and Treasury found no significant difference in health symptoms between workers in northern New Jersey (when MTBE oxyfuels were in use) and southern New Jersey (when MTBE oxyfuels were not in use). The number of workers questioned was adequate to detect a relatively small increase in reports of health symptoms. The north-south MTBE exposure difference was confirmed by a limited number of air and personal sampler measurements. The workers spent most of their day with cars (e.g., pumping gas, driving vehicles) and thus would be expected to have a higher fuel exposure than members of the general public. With the understanding that quantitative comparisons between Stamford and Albany cannot be made because of methodological differences, it is still useful to discuss the differences in the acquired data. There was no clear difference between symptom prevalance from commuters in Stamford (with MTBE oxyfuels) and students/office workers in Albany (without MTBE oxyfuels). Generally, there was not a large difference between workers receiving occupational exposures to fuels in Stamford and Albany. Also, there was not a large difference between commuters and people who had higher occupational exposures in Stamford. However, in the Albany study, it appears possible that there may have been confounding between flu/allergy symptoms and MTBE test questions of symptoms. Therefore, comparisons between Stamford and Albany have very substantial uncertainty.

From the human clinical and epidemiological studies described above, it does not appear that healthy members of the general population receiving MTBE exposures under relatively temperate conditions experience health symptoms of concern. For most environmental chemicals, there are susceptible subpopulations who either receive higher-than-usual exposures because of their activities or have inherently greater sensitivity. It may therefore be reasonably assumed that although there are probably at least some people at greater risk to MTBE, they have not been identified. One epidemiological study attempted to

do so by questioning people reporting multiple chemical sensitivity. Although they did not have significantly more symptoms than other healthy people, the number of subjects, and hence the detectability of effects, was low. Another possible risk factor is temperature. Ambient temperature may influence exposure and delivered dose of MTBE in several ways. Temperature affects evaporation of the fuel and exposure durations. For example, at lower temperatures, there is less evaporation, but people will drive with their car windows up (reducing air dilutions of MTBE inside the car). Also, at subarctic temperatures, people will breathe differently, thereby affecting the amount of MTBE actually inhaled in outdoor scenarios (e.g., vehicle refueling). The above is not meant to be an exhaustive list of possible risk factors, but does illustrate that only a few of the multiple possibilities have been examined.

The epidemiological studies in Alaska are far more difficult to interpret. In Fairbanks, there was clearly a decrease in health symptoms after MTBE oxyfuel use ceased. However, the price of gasoline (which had increased about 14¢/gal) and the extremely high public concern about potential health effects of MTBE also decreased when these fuels were removed. This confounding precludes clear interpretation of the results. If the other epidemiological or human clinical studies had shown moderate or strong associations between MTBE exposure and symptoms, then it would have been probable that at least part of the decrease in symptoms in Fairbanks was due to the cessation of MTBE oxyfuel use. Even so, an influence of MTBE on Fairbanks symptoms cannot be ruled out. Most significantly, Fairbanks is unique because of subarctic temperatures and thermal inversions that can result from its topography and meteorology. Thus, exposures could be quite different from other areas of the country. The other studies discussed here were conducted under temperate conditions and had differences in study design, preventing precise comparisons between them and the Fairbanks studies. In addition, in the early Fairbanks and Anchorage studies (see Table 1), those people with higher exposure due to their occupation reported more symptoms, suggesting an association not found in the other studies. However, it is also conceivable that differences among these groups (other than exposure) might have influenced symptom prevalence. The symptom prevalence data from Anchorage cannot be associated with MTBE oxyfuel exposure because there is no comparable (even roughly comparable) group without MTBE oxyfuel exposure.

In the Stamford study, people with higher concentrations of MTBE in their blood had a greater symptom prevalence. Such a relationship was not present in Fairbanks. In addition, TBA blood concentrations were not associated with symptom prevalence. As discussed earlier, there is no evidence that blood levels of MTBE or TBA are quantitative indicators of effects. They do show that exposure occurred.

The available information shows that developmental toxicity is produced at high laboratory exposures of mice and rats to MTBE. As discussed earlier, toxicity in rats is not observed at 1,440 mg/m^3, and 48 mg/m^3 MTBE is a reasonable preliminary estimate (with uncertainty spanning at least an order of magnitude) of a level at which no adverse developmental toxicity is likely to occur in humans (including sensitive subpopulations). Available information shows that 1- to 3-min exposures to consumers during fuel fill-ups as a typical worst case would be 36 mg/m^3; other data show a range from 0.32 to 137 mg/m^3. In some, but not all fill-ups, short-duration exposures greater than 48 mg/m^3 might occur. The chance of a human hazard increases as exposure exceeds 48 mg/m^3. No information exists for MTBE in animals or humans to determine more accurately the minimum level and duration of exposure that could adversely affect the developing organism. Thus, it is assumed that even a short exposure has the potential to result in developmental toxicity if the exposure concentration is sufficiently high. When one compares the estimates of acute exposure in a gasoline fill-up scenario to the animal NOAEL, the human exposures to MTBE range from 10 to 4,500 times lower than the animal NOAEL. In making similar comparisons for a 30-min commuting scenario, the human exposures to MTBE would range from an average of 5,000 to 80,000 times lower than the animal NOAEL.

There is a stronger basis for drawing conclusions about chronic noncancer effects. As discussed earlier, the RfC is 3 mg/m^3 MTBE. According to the definition of the RfC, sensitive subpopulations are not expected to suffer adverse effects if exposed continuously for 70 years to this concentration. If the RfC of 3 mg/m^3 is compared to even the highest annual exposure estimate of 0.07 mg/m^3, chronic noncancer effects from MTBE would not be expected.

Chronic inhalation exposures of rats and mice have produced two types of tumors in rats and one tumor type in mice at very high concentrations of MTBE. Deficiencies in the presently available chronic bioassays have contributed to uncertainties about how important

the three animal tumor types are for defining a human hazard. The occurrence of rare kidney tumors in the rat may be of particular hazard concern, although there is a question as to whether the kidney tumors are even relevant for assessment of human hazard. The rat bioassay itself is compromised by toxicity and excessive mortality in two of the three dose groups. The occurrence of testicular tumors in rats at high doses contributes to the overall weight of evidence, even though the magnitude of the hazard significance can be questioned. The liver tumors in male and female mice occur at the highest dose only, but in a less-than-lifetime study. Some knowledge about MTBE metabolites adds to the basis of hazard evidence because one metabolite has positive animal and some human data, whereas the other has positive animal data. The carcinogenicity assessment is not yet completed because the existing unresolved issues are important scientifically, and additional information from new studies is expected in the next few months. A tentative view of the carcinogenicity data suggests that there is "limited animal evidence" for carcinogenicity (i.e., a tentative C classification). A sensitivity analysis of cancer risk indices also suggests that, if MTBE is carcinogenic, its potency is not likely to be greater than that already assigned to gasoline itself, which currently has a hazard classification of "probable" human carcinogen.

4.3 Benzene, Formaldehyde, and Butadiene

Even when more information is available on the impact of MTBE on air toxics emissions, it will not be possible to quantitatively relate emissions changes to exposure levels with sufficient precision to quantitate cancer risk changes, if any. However, the trend would likely be for a small (if any) decrease in potential cancer risk due to the reduction in the mass of these air toxic emissions.

If the symptom complaints are related to the use of MTBE oxyfuels, the increased formaldehyde emissions may be one of several factors contributing to the complex of acute health complaints. However, without better knowledge of formaldehyde exposure changes, there are major uncertainties in such a speculative association.

4.4 Summary of Risk Estimates

- There is unlikely to be a substantial risk of acute health symptoms among healthy members of the public receiving "typical" environmental exposures under temperate conditions (i.e., not subarctic temperatures). This leaves the question open about more subtle health risks, especially among susceptible subpopulations. If acute symptoms are being caused by MTBE, they appear to be mild and transient.

  - Acute (1-h) exposure to typically encountered high ambient levels of "pure" MTBE does not appear to cause health symptoms, eye or nose irritation, or behavior changes in young, healthy adults under room temperature conditions (e.g., 75 °F). However, it is possible that there are more sensitive members of the population who would respond and that higher concentrations than those used in the human clinical studies could cause effects.

  - Preliminary reports of epidemiological studies in New Jersey did not detect differences in symptoms reported by workers (drivers, mechanics, refuelers) in northern New Jersey (with MTBE oxyfuels) and southern New Jersey (without MTBE oxyfuels).

  - There were not large differences in symptom reports between a variety of worker and commuter subgroups in Stamford (with MTBE oxyfuels) and between the Stamford and Albany (without MTBE oxyfuels) populations studied. However, it is possible that cold symptoms or other factors confounded the Albany results, inhibiting the ability to make inter-city comparisons.

- Symptom reports in Fairbanks clearly decreased when MTBE oxyfuels were removed. However, the situation is confounded since the heightened public concern about the potential health effects, higher costs (14¢/gal), and distinctive odor with MTBE oxyfuel use decreased when MTBE oxyfuels were removed. Even so, the unique meteorology and topography of Fairbanks prevents ruling out an association between MTBE oxyfuels and symptoms. The symptom prevalence data from Anchorage cannot be interpreted relative to MTBE oxyfuel risk because no similar group not having MTBE oxyfuel exposure was studied.

- Animal studies have shown developmental effects from repeated exposures to high concentrations of MTBE. Human developmental risk cannot yet be defined quantitatively. However, based on the concept that a short-term exposure during a critical period of sensitivity can potentially cause a developmental effect, there is potential risk for developmental toxicity as human exposure exceeds 48 mg/m^3, which would include some gasoline fill-up scenarios. Most public exposures to MTBE are well below this concentration and are not of concern. Methyl tertiary butyl ether is not unique among gasoline constituents in having developmental effects in

laboratory animals. Although it is beyond the scope that is possible in this document, the potential of the mixtures and the other individual components of gasoline to cause developmental toxicity should be considered and weighed against potential added risk from MTBE in order to provide a complete analysis.

- Based on several studies of laboratory animals exposed chronically to MTBE and annual human exposure estimates, it does not appear that there is a significant risk for MTBE to cause chronic noncancer effects. The potential risk of noncancer health effects from chronic exposure to MTBE as part of a complex mixture with gasoline is not known.

- At the present time and on a tentative basis, there is no reason, to say there is a serious carcinogenicity public health hazard from the inhalation of MTBE, although some hazard is possible and necessarily should be further evaluated. Although unfinished, the current carcinogenicity assessment supports a hazard classification of "possible" human carcinogen, based upon "limited" animal evidence. Data from a newly reported, but not yet available, oral exposure animal bioassay and additional information on kidney toxicity may modify (i.e., an increase is possible, a decrease is not likely) the tentative carcinogenicity classification. Crudely estimated dose-response analyses suggest that the potency of MTBE would be relatively low. Methyl tertiary butyl ether is being added to a gasoline, which itself has a whole-mixture hazard classification of "probable" human carcinogen and a relatively low estimated potency. Although it is not known what effect the addition of MTBE has on the carcinogenic activity of the oxyfuel mixture, the MTBE component itself seems to be no worse than the nonoxygenated gasoline mixture.

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