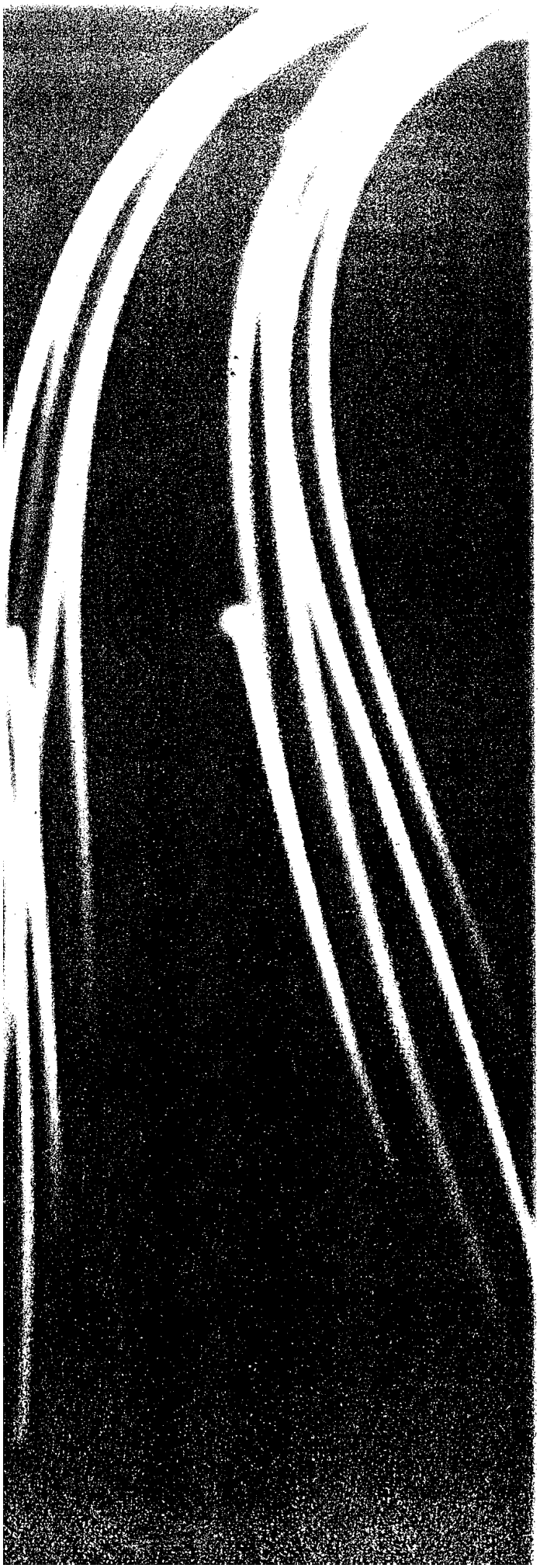

4 Potential Health Effects of Oxygenated Gasoline

PREPARED BY

Ronald L. Melnick,
National Institute of Environmental Health Sciences

Mary C. White,
Centers for Disease Control and Prevention

J. Michael Davis,
U.S. Environmental Protection Agency

Richard W. Hartle,
Centers for Disease Control and Prevention

Burhan Ghanayem,
National Institute of Environmental Health Sciences

David L. Ashley,
Centers for Disease Control and Prevention

G. Jean Harry,
National Institute of Environmental Health Science

Errol Zeiger,
National Institute of Environmental Health Sciences

Michael Shelby,
National Institute of Environmental Health Science

Charles H. Ris,
U.S. Environmental Protection Agency

CONTENTS

SCOPE OF THE CHAPTER

Soon after the oxygenated gasoline program was introduced nationally in the winter of 1992-1993, anecdotal reports of acute health symptoms were received by health authorities in various areas of the country. Such health symptoms had not been anticipated but have subsequently focused attention on possible health risks associated with using oxygenated gasoline. Potential health effects of oxygenated gasoline were evaluated in two separate reports, one prepared by an interagency group of health scientists under the auspices of the Interagency Oxygenated Fuels Assessment and Steering Committee of the National Science and Technology Council (NSTC, 1996) and the second by the Health Effects Institute (HEI) and a panel of experts (HEI, 1996). Both of these reports underwent extensive external peer review and were then reviewed by the National Research Council (NRC, 1996). This chapter summarizes the information on the health effects of oxygenated gasoline that was presented in the NSTC and HEI reports, with particular attention given to comments from the NRC review. The HEI report provides an extensive review on health effects caused by ingestion of moderate to large quantities of ethanol and concludes that these effects would not likely occur at the low ambient air levels associated with the use of ethanol in oxygenated fuels.

HUMAN EXPOSURE (NONOCCUPATIONAL)

The exposure of human populations to emissions related to the use of oxygenated gasoline is a critical component of any attempt to assess the potential human health risks or benefits associated with oxygenated fuels. At issue is not just how much oxygenate exposure occurs in connection with using oxygenated fuels but the change in exposure, if any, to the array of chemicals constituting the evaporative and combustive vehicle emissions and photochemically transformed products resulting from the use of oxygenated gasoline versus the use of conventional gasoline.

The objective of the winter oxygenated fuels program is to reduce human exposure to CO, but empirical data to illuminate whether, or how much, CO exposure is actually reduced with use of oxygenates are quite limited. Vehicle emissions and ambient air quality data provide at best only a rough indication of the direction in which human population exposure levels would be expected to change, but they are not currently adequate to gauge accurately either acute or long-duration exposures of human populations. Uncertainties increase progressively as one moves from emissions characterization to environmental (i.e., air, soil, or water) quality characterization to exposure characterization, in large part because the number of variables that come into play increases progressively at each stage. For example, emissions are a function not only of the type of fuel, but also of operating conditions and other factors (type and condition of vehicle, temperature, altitude, etc.). Air quality in turn is a function not only of emissions, but also of meteorological and topographical variations in different locales, as well as the characteristics of the vehicle fleet (e.g., the age and condition of vehicles in an area). Exposure is a function not only of air (as well as other media) concentrations at different times of the day and year, but also of human activity patterns that may bring individuals into contact with a pollutant at various times and for various durations. In short, assuming that CO emissions are reduced

from vehicles using oxygenated fuels, indefinite is the extent to which human exposures to CO are reduced. At present, one cannot simply extrapolate directly from emissions data or even air quality data to estimate quantitative changes in population exposure levels associated with using oxygenated fuels.

To support a meaningful quantitative comparative assessment of oxygenated and conventional gasolines, it would be necessary to have sufficient data collected on random samples of human populations to estimate accurately the distribution of exposure levels to key oxygenated fuel and conventional fuel emissions and by-products. Such information would not only provide a basis for estimating an average or typical exposure, but it would also enhance scientific confidence that upper-tail exposures had been reasonably well determined. In lieu of adequate distributional data, a rough estimate of instantaneous exposures in the upper tail of the distribution may possibly be obtained from measurements taken in selected microenvironments where certain activities or scenarios typically occur (e.g., around gasoline stations during refueling, in vehicles during transit). However, it is not possible at present to estimate "average" or "typical" exposures because of the lack of adequate distributional data. Even if adequate concentration data existed for certain microenvironmental acute exposure scenarios, exposure assessment, particularly assessment of chronic exposures, requires adequate data on the range, duration, and frequency of activities that bring people into contact with the pollutants of interest.

As described in the Interagency Health Assessment (NSTC, 1996) and the HEI Report (HEI, 1996), a limited number of studies have been conducted to measure MTBE exposure in various occupational and nonoccupational settings. These studies have focused primarily on exposures around gasoline stations, particularly during refueling and are especially relevant to those in the general population who refuel their own vehicles ("self-service" customers) as well as to workers whose job involves refueling of multiple vehicles. No single study has attempted to evaluate meteorological variations; indeed, relatively few measurements have been obtained under conditions of direct relevance to the oxygenated fuels program, that is, during winter months with 2.7% oxygenated gasoline. Nevertheless, as far as available data on acute exposures to the general population are concerned, refueling appears to pose the highest potential for acute inhalation exposures to oxygenates. Various studies that have collected personal breathing zone samples of MTBE during gasoline refueling suggest that such exposures, which typically amount to 2-5 minutes in duration, may range as high as 2 to 32 ppm MTBE; however, most of the data for exposure during refueling are below 10 ppm for 1 to 20 minute sampling periods.

To estimate longer term average exposures (e.g., daily or annual), one must have empirical data and/or make assumptions about the concentrations and durations of exposures during the course of daily activities. Based on limited empirical data and various explicitly conservative provisions (e.g., rounding up of average concentrations to the next higher half order of magnitude, assuming a person lives in a house with an attached garage where a fuel spill occurred with the door closed, assuming outdoor activities are in the vicinity of a gasoline station or a heavily traveled highway), the Interagency Health Assessment offered estimates of time-weighted average exposure levels of 0.018 and 0.035 ppm MTBE for two different presumed "worst-case" exposure scenarios during an oxygenated fuels season (NSTC, 1996); estimated annual exposures based on either a 6-month or 4-month oxygenated fuels season for these two scenarios were on the order of about 0.01 to 0.02 ppm MTBE. The HEI Report made no attempt to derive such an estimate but did present

data from various studies in tabular and graphical forms (see Fig. 2 in HEI, 1996). The NRC Review concluded that "HEI could have performed a quantitative risk assessment using the exposure data represented by ... maximum (approximately 0.01 ppm) daily MTBE exposures as estimates of exposure" (NRC, 1996, p. 71). The difference between the NRC and Interagency high-end estimates is almost certainly not as great as the uncertainty bounds or confidence limits that would surround these numbers. Indeed, it is not even possible to quantify these confidence limits in a meaningful manner, given that they are based on qualitative assumptions about the various exposure scenarios. Thus, any attempt to characterize chronic health risks based on such estimates should explicitly note the inherent uncertainty of the resulting risk estimates.

It should also be noted that, owing to the lack of data, no oxygenated fuel exposure analysis conducted thus far has attempted or been able to include dermal or oral exposures to MTBE in estimating presumed worst-case or upper bound exposures. Skin contact and ingestion exposure are different from the routine types of inhalation exposures that occur during operation or refueling of a vehicle. For the general population, dermal contact with fuel would probably constitute an infrequent acute exposure. Ingestion of oxygenates might occur either acutely or chronically but would probably be of greatest relevance to general population exposures in terms of possible long-term, low-level ingestion of contaminated drinking water (see Chapter 2 on Water Quality). Nevertheless, true worst-case or upper-bound exposures might well reflect contacts through these other two routes. Thus, additional caution, apart from the uncertainties resulting from a lack of empirical distributional data, may be in order when referring to or otherwise attempting to use presumed worst-case or upper-bound exposure estimates that are based solely on inhalation exposure.

In summary, it is possible to generate estimates of high-end exposure levels to MTBE, and such estimates may be usable in preliminary risk characterizations, particularly if the estimates are coupled with toxicity potency or reference values. In the case of oxygenated fuels, however, such estimates involve significant assumptions and consequently are highly uncertain. Moreover, even this type of exercise would not address the critical question of the comparative risks and benefits of using oxygenated fuels in relation to conventional fuels. A meaningful answer to this key question will require more than just data on human exposures to oxygenates; it will also need quantitative evaluations on how exposures to CO, benzene, 1,3-butadiene, aldehydes, and numerous other toxic compounds in fuels and their combustion and transformation products are altered with use of oxygenated gasoline versus conventional gasoline.

HUMAN EXPOSURE (OCCUPATIONAL)

As discussed in the reports by the Health Effects Institute (HEI, 1996) and the Interagency Health Assessment (NSTC, 1996), the predominant occupation with potential exposure to MTBE as an oxygenate is that of service station attendant. Extent-of-exposure studies by government and industry indicate time-weighted average exposures to MTBE while dispensing fuel are typically at or below 1 ppm, with maximum averages of less than 6 ppm. Although HEI gives no overall range or average for this occupational category, its presentation of median values from specific studies is within this range. Both reports note

that several microenvironmental conditions, including climate, amount of fuel dispensed, and amount of oxygenate in the fuel, affect the extent of exposure.

Automotive mechanics comprise another important occupational category with potential exposure to MTBE. Evaluations of these exposures, again conducted by government and industry, are summarized in the NSTC and HEI reports. Time-weighted average exposures range up to approximately 12 ppm, averaging approximately 0.1 ppm.

Other occupations with available MTBE exposure information are those associated with automobile traffic (i.e., service station managers, parking attendants, taxicab drivers, etc.) and those involved in manufacturing and distributing MTBE. Of 14 samples collected among the former group in support of an epidemiologic evaluation, only one had detectable levels, reported at 0.10 ppm (NSTC, 1996). Among the latter group, time-weighted average exposures reported by American Petroleum Institute (API) member companies range up to approximately 700 ppm (6-9 h exposure samples collected during transport of pure MTBE). The geometric mean of more than 300 long-term samples from all operations was 0.3 ppm; the highest mean for any category was 1.7 ppm (API, 1995).

In summary, the available environmental data suggest that among employees exposed to MTBE from its use as an oxygenate in gasoline (primarily service station attendants and mechanics), time-weighted average exposures may range up to approximately 12 ppm and average below 1 ppm. Employees involved with manufacturing or transporting MTBE may be exposed up to 700 ppm, with average exposures less than 1 ppm.

METABOLISM, DISPOSITION, AND TOXICOKINETICS OF MTBE IN ANIMALS

Although very limited information is available on the toxicokinetics of ETBE, TAME, and other gasoline oxygenates, more data were reported on the metabolism, disposition, and elimination of MTBE.

MTBE is rapidly absorbed into the circulation of rats after oral, intraperitoneal, intravenous, or inhalation exposure (Bio-Research Laboratories, 1990a; 1990b; 1990c; 1990d). However, dermal absorption of MTBE is somewhat limited and slower than absorption by other routes. The relative bioavailability of dermally applied MTBE is low (20-40%), and it is likely that dermal absorption of MTBE may be limited by its high volatility (Bio-Research Laboratories, 1990b). Peak blood concentrations of MTBE are rapidly attained; however, the time to achieve these levels varied as a function of the route of exposure and the dose administered. The time to achieve peak blood levels varied from 5-10 min after intravenous or oral exposure to 2-4 h after dermal or inhalation exposure. Once in the blood, MTBE is distributed to all major rat tissues. Distribution studies suggested that neither MTBE nor any of its metabolites has the potential for bioaccumulation in animals. The reported half life of MTBE ranged from less than 1h after oral, i.v., and inhalation exposures to 1-2 h after dermal application. On the other hand, the half life of TBA was longer than MTBE and ranged from 1-3 h after all routes of administration (Bio-Research Laboratories, 1990a; 1990b; 1990c; 1990d).

Metabolism and elimination of MTBE and its metabolites also proceed rapidly regardless of the route of administration. From the available experimental evidence, it is established

that MTBE undergoes hepatic oxidative demethylation via the cytochrome P450 enzymes to yield TBA and formaldehyde (Bio-Research Laboratories, 1990b; Brady *et al.*, 1990). TBA may be eliminated unchanged in the expired air or may undergo secondary metabolism, resulting in the formation of 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid; both metabolites are eliminated in the urine. In vitro evidence also suggested that TBA may undergo oxidative demethylation to produce formaldehyde and acetone (Cederbaum and Cohen, 1980). Identification of $^{14}CO_2$ in the expired air of ^{14}C-MTBE-treated rats indicates that a portion of the administered MTBE dose undergoes complete oxidation. It is likely that complete oxidation of MTBE to CO_2 may proceed via the formaldehyde intermediate. Differences in the disposition and toxicokinetic parameters of MTBE in rats after various doses suggest that there is a potential for saturation of MTBE metabolizing enzymes at high exposure levels and after bolus administration of MTBE.

Although human studies showed that exposure to MTBE, similar to exposure in animal studies, leads to the appearance of TBA in blood, no reports of MTBE metabolism to formaldehyde in humans are available. However, there is no evidence showing that humans would metabolize MTBE differently than animals. Further, because MTBE metabolism is catalyzed by the cytochrome P450 enzymes, coexposure to environmental chemicals may alter MTBE metabolism and its potential toxicity.

Elimination of MTBE and its metabolites occurs primarily via the lungs and the kidneys. Exhaled organic compounds are mostly MTBE and TBA and the ratio of the two components is dose- and route-dependent. Clearance of unchanged MTBE via the lungs is thought to be a function of the blood/air partition coefficient (11.5) (Borghoff *et al.*, 1996) and appears to be directly proportional to the peak blood levels of MTBE. A small percentage of the administered MTBE dose to rats is eliminated as CO_2 (0.1-1.1% of dose after oral, i.v., and inhalation exposure), and a negligible portion is eliminated in the feces (0.1-1.3% of dose) after similar exposures (Bio-Research Laboratories, 1990a; 1990b; 1990c; 1990d).

Urinary elimination of MTBE-derived radioactivity is also dose- and route-dependent and two urinary metabolites, 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid, were identified in the urine of rats that received ^{14}C-MTBE. These two metabolites are most likely formed via the secondary metabolism of TBA. The metabolism of MTBE to formaldehyde has been demonstrated in vitro. However, metabolism of MTBE to formaldehyde in vivo requires additional investigation.

In order to assess the contribution of MTBE metabolites to MTBE's overall toxicity, the qualitative and quantitative behavior of MTBE in both humans and animals must be fully investigated. Determining the rates of metabolism as well as the internal dose of MTBE and its main metabolites (TBA and formaldehyde) will be critical for understanding the mechanisms of MTBE-induced toxicity. Further, these data will be essential for extrapolating effects observed in animals to humans and for more accurately assessing the potential human health risks resulting from exposure to MTBE.

METABOLISM AND TOXICOKINETICS IN HUMANS

To date, only a limited number of studies on the metabolism and toxicokinetics of MTBE in humans has been performed. These studies (Buckley *et al.*, 1995; Cain *et al.*, 1996; Johanson *et al.*, 1995; Prah *et al.*, 1994) evaluated levels of MTBE or TBA in blood or breath following short-term exposure to MTBE in chambers. One study involved significantly higher exposure concentrations, but all were consistent in their primary findings.

When human subjects are exposed to air containing MTBE, levels of the oxygenate in their blood and breath show a rapid increase but do not reach a steady-state level even after 1 h. Upon removal of the subjects from the chamber, the blood MTBE levels drop rapidly but show a multiexponential decrease leading to blood levels that are higher than pre-exposure levels, even after 8 h postexposure ($t_{1/2}$ values were 2-5 min, 15-60 min, and >190 min). The multiexponential character of the MTBE excretion indicates that this compound is distributed into tissue or is bound to some blood component. The slower decrease in blood MTBE levels after 60-90 min postexposure to MTBE was not seen in rats (Borghoff *et al.*, 1996). Except for total body weight, the fraction of body weight that is fat is the most dissimilar physiological parameter between rats and humans that may account for this difference. The lack of a large fat fraction in young rats may account for the failure to detect a secondary, longer half-life phase of MTBE in this species. TBA levels in human blood also rise quickly after the exposure begins, but the plateau period is much longer than for MTBE.

To date, toxicokinetic experiments in humans have involved short-term, single exposures of healthy individuals to undiluted MTBE; however, most environmental and occupational exposures are repeated events and usually involve a mixture of MTBE with other gasoline components. The frequency and time of exposure depends on many factors, including job activities and frequency of gasoline refueling. Internal dose levels of MTBE also may be compounded by lower level exposures during commuting or other activities. It is unclear whether repeated exposures of individuals, as occurs during commuting, will result in elevated background internal dose levels of MTBE or if excretion rates are fast enough to prevent accumulation in these types of exposures. Studies are needed to evaluate the toxicokinetics of MTBE when it is included as a component of gasoline and when repeated exposures occur.

ACUTE HUMAN HEALTH EFFECTS

Nature of the Available Data

A relatively small number of epidemiologic investigations and surveys have been conducted to examine the occurrence of acute health symptoms among people who were exposed to fuels containing oxygenates, primarily during the 1992-93 oxygenated-fuel season. These studies were prompted by anecdotal reports of acute complaints of symptoms after the introduction of oxygenated gasoline in some areas and focused primarily on the set of symptoms (headache, eye irritation, burning of the nose or throat,

cough, nausea or vomiting, dizziness, and a sensation of spaciness or disorientation) that had been reported most frequently by community residents in Fairbanks, AK, at the start of the 1992-93 oxygenated fuel season. These symptoms are not specific to exposure to oxygenated gasoline and can be caused or triggered by a variety of other environmental and occupational exposures, including exposure to conventional gasoline.

Most of the studies conducted to date were designed to be screening or exploratory in nature and were not formal studies designed to test specific hypotheses. All of these studies were highly responsive to public concerns and displayed creativity in coping with serious limitations in time and resources. The same limitations apply to many of these studies: inadequate sample size, potential bias in sample selection, inadequate exposure information, and reliance on highly subjective measures of effect. Ideally, larger and more carefully planned epidemiologic studies would have followed to test some of the hypotheses generated by anecdotal reports and these initial investigations. Although such studies have been recommended (USEPA, 1995), they have not been conducted to date, and no new epidemiologic studies are expected to be completed in the near future.

In their review, the NRC Committee concluded that "the available data consistently indicate that exposures to gasoline containing MTBE in occupational settings are associated with an increased rate of acute symptoms" (NRC, 1996, p. 10) and noted that both the report of the HEI Oxygenates Evaluation Committee (HEI, 1996) and that of the Interagency Working Group (NSTC, 1996) had "failed to acknowledge" this consistency (NRC, 1996, p.90). In light of these comments, we re-examined the results from the available field studies, controlled exposure studies, and anecdotal reports of acute symptoms for any consistencies in findings or evidence of dose-related effects.

Acute Health Effects at Higher Exposure Levels

The highest potential exposures to MTBE occur in the workplace, and although exposures within any one job category can vary by orders of magnitude, the highest occupational exposures to MTBE have been measured during the transport of MTBE and MTBE-containing fuel. Three controlled human exposure studies of the sensory, symptomatic, cellular, and eye responses of healthy human subjects exposed to MTBE in air have been conducted, in which short-term (1 or 2 h) exposures to MTBE at concentrations similar to those that have been measured in some MTBE manufacturing and transportation operations (from 1.4 ppm up to 50 ppm) (Prah *et al.*, 1994; Cain *et al.*, 1996; Johanson *et al.*, 1995). In two studies (Prah *et al.*, 1994; Cain *et al.*, 1996), subjects were exposed only once for 1-h to MTBE, and in the third study (Johanson *et al.*, 1995), subjects were exposed for three successive 2-h periods to progressively higher concentrations of MTBE. These controlled human exposure studies tested pure MTBE compound, not a mixture of MTBE and gasoline, and included only healthy volunteers. Taken together, these three studies consistently showed that controlled exposure to pure MTBE in air under laboratory conditions (around 24 ^{o}C) did not cause increased symptoms or any notable adverse effects (e.g., irritation, behavioral changes) among healthy adult subjects.

Little information is available about the occurrence of acute health symptoms among workers involved in either the manufacture or distribution of MTBE or MTBE-containing fuels. The American Petroleum Institute canvassed 18 member companies to collect information about health complaints that had been passively received from workers and consumers from 1984 to 1994 (McCoy *et al.*, 1995). Given the unstated but presumed

large total workforce of these 18 companies, this passive reporting system picked up few complaints (complaints had been received from 71 workers over this period). The most common health complaints were headache, dizziness, nausea, and respiratory tract irritation, and the complaints were most frequent during the 1992-93 oxygenated fuel season. A greater number of complaints came from workers involved in MTBE distribution than in MTBE refueling or MTBE production. It is not possible to make any conclusions about the relative likelihood of complaints in one job category compared with another because this reporting process had obviously low and perhaps variable sensitivity, and no information was available on the total number of workers in each job category. Mehlman (1995) collected information about the acute health symptoms that were being reported among refinery workers who were members of the Oil, Chemical, and Atomic Workers Union and exposed to MTBE. The most common complaints were headaches, sinus problems, fatigue, and shortness of breath. However, given the limited nature of this survey, it is not possible to estimate the prevalence of specific symptoms among refinery workers or to examine dose-response relationships in complaints among refinery workers with different exposures.

Gasoline station attendants and automotive mechanics also can experience higher exposures to MTBE-containing gasoline, although at levels substantially lower than those of some workers involved in manufacturing or transporting of oxygenated gasoline. In Fairbanks, AK, complaints of health symptoms (such as headache, eye irritation, burning of the nose and throat, and dizziness), were fairly common among a nonrandom, convenient sample of 18 workers (10 of whom were mechanics, service station attendants, or workers at car dealerships) while oxygenated gasoline containing MTBE was in use (Moolenaar *et al.*, 1994). The four workers with the highest blood levels of MTBE all reported one or more key symptoms, whereas 9 of the remaining 14 workers reported one or more of these symptoms (this difference was not statistically significant). These complaints essentially disappeared after the oxygenated gasoline program was suspended. In two small-scale field studies primarily of mechanics that were conducted in the spring of 1993 in Stamford, CT, (CDC, 1993a; White *et al.*, 1995), and in New Jersey (Mohr *et al.*, 1994), most workers reported no adverse health effects related to oxygenated gasoline. In Stamford, all of the gasoline sold at the time of the investigation was oxygenated, and thus it was not possible to identify a comparison group of workers who were exposed to only conventional gasoline. Qualitatively, the prevalence of the most common symptoms occurring over the last month, such as headache and cough, were not appreciably higher among men who worked around cars and gasoline stations in Stamford than that reported in a similar investigation about one month later in Albany, NY, where exposure to MTBE was generally much lower because no oxygenated gasoline program was in place (CDC, 1993b). Personal breathing-zone air monitoring and biological monitoring of MTBE levels in blood, however, clearly demonstrated that exposures to MTBE can be highly variable among mechanics, even among workers in the same garage. The availability of blood MTBE measurements among a subsample of 30 workers permitted a more precise classification of these workers by exposure level. Workers with the highest blood MTBE levels (>3.8 µg/L) were significantly more likely to report one or more of the key symptoms on the day of testing than were other workers. Workers with the highest exposures to MTBE in gasoline, however, were also more highly exposed to other components of gasoline.

In New Jersey, researchers interviewed state garage workers in two parts of the state: 115 workers in northern New Jersey, where oxygenated fuel was still in use, and 122 workers

in the southern New Jersey, where use of oxygenated fuels had been discontinued 10 weeks earlier (Mohr *et al.*, 1994). This investigation did not report major differences in symptom reporting between these two groups of workers in New Jersey who presumably had different levels of exposure to MTBE. Because some of the highest exposures to gasoline were likely to occur during vehicle refueling, comparisons were made between a small subset of 11 workers in the north who pumped gasoline more than 5 h per day, and 11 workers in the south matched by age, sex, and education for whom some air-monitoring data indicated that exposures to MTBE were likely to be low. At the beginning of the workshift, a composite "MTBE-symptom" score was similar between both groups, but by the end of the workshift, the gasoline pumpers in the north were reporting more symptoms, whereas the comparison workers were reporting fewer symptoms. This difference was not statistically significant but the study had low statistical power because of the small number of workers in each group.

Acute Health Effects at Lower Exposure Levels

In November 1992, public concern and media attention over oxygenated fuels in Fairbanks, AK, began almost immediately after the start of the oxygenated fuel program. In both Fairbanks and Anchorage, the only oxygenate added to gasoline that winter was MTBE. In December 1992, the Alaska Department of Health and Social Services conducted surveys of taxicab drivers, health care workers, and university students at different locations in Fairbanks and Anchorage, AK (Beller and Middaugh, 1992; Chandler and Middaugh, 1992). This survey documented that people in both cities were reporting a perceived increase in certain symptoms after the introduction of oxygenated fuels but provided little information to judge the true prevalence of such symptoms in the broader population or whether such symptoms were actually caused by oxygenated gasoline.

During the winter of 1994-95, the Alaska Department of Health conducted a weekly random telephone survey of 100 adult residents in Anchorage for 16 consecutive weeks to identify possible health problems related to using ethanol as an oxygenate in fuels (Egeland and Ingle, 1995). The results indicated a much lower prevalence of symptoms than had been reported 2 yrs earlier when MTBE was used in gasoline, and the reported prevalence of symptoms remained fairly similar during periods when ethanol-containing gasoline was either not in use, was in use, or was being phased in or phased out.

Considerable media coverage and public concern about oxygenated fuel containing MTBE also occurred in Missoula, MT, during the 1992-93 winter season; the symptoms reported included many of the same acute effects that had been reported in Alaska, as well as others, including an exacerbation of symptoms among people with asthma. The next winter, the oxygenate used was ethanol rather than MTBE, and public concern over this issue essentially disappeared (E. Leahy, Missoula City-County Health Department, personal communication, 1995).

Several other state health departments have also received some health complaints related to oxygenated gasoline from citizens that are similar to those received in Alaska. State health departments, however, do not routinely conduct surveillance for complaints related to gasoline or other environmental exposures. In addition, citizens would not necessarily report health complaints of a nonspecific and noninfectious nature, such as a headache, to the health department, even if they believed symptoms were caused by gasoline or some other environmental agent. Although information on the number and nature of complaints

received by different health departments has been collected, analyses of this data are difficult to interpret (Livo, 1995; McCoy *et al.*, 1995)

Motorists who had no occupational exposures to gasoline had also been included among the people interviewed in both the investigations in Stamford, CT, where oxygenated gasoline was in use (CDC, 1993a), and in Albany, NY, where oxygenated gasoline was not in use (CDC, 1993b). Because both investigations relied on convenience samples rather than on random samples of motorists, the people interviewed may not have been representative of the larger population in either city. In both cities, the most common symptoms were headaches and cough, and the reported prevalence of these and other symptoms was fairly similar among motorists in both cities.

In response to public concern over reformulated gasoline (some of which contained MTBE, but at lower concentrations than is used in oxygenated gasoline), the Department of Health in Wisconsin conducted, during the winter of 1994-95, a random telephone survey of symptoms among approximately 500 residents in Milwaukee, WI, Chicago, IL, (which also used reformulated fuels but had not experienced the same intense media coverage of the issue), and areas in Wisconsin that did not use reformulated fuels (Anderson *et al.*, 1995). Overall, the survey found that people in Milwaukee reported a higher prevalence of unusual symptoms than did residents of other areas of the state or of Chicago. Several other findings are of relevance in evaluating this increase. First, every symptom was elevated in Milwaukee, not just symptoms that had previously been associated with gasoline or chemical solvents. Second, the symptom prevalence figures were not elevated in Chicago compared with such figures in areas of Wisconsin where reformulated gasoline was not used, although Chicago was also using reformulated gasoline. Third, although people were asked to report unusual symptoms, the symptoms reported in Milwaukee were more likely to be associated with having had a cold or the flu, smoking cigarettes, or being aware of reformulated gasoline than were symptoms reported by people in Chicago or the rest of Wisconsin. This survey had limitations, including lower participation rates than desired (especially in Chicago), imprecise classification of exposure to reformulated fuels based on questionnaire responses, and potential problems with the respondents' characterization of symptoms as unusual.

Summary of Findings and Conclusions

The Interagency Health Assessment had concluded that, "taken together, these studies suggest that most people do not experience adverse health effects from MTBE in gasoline, but the studies cannot rule out the possibility that some people do experience more acute symptoms from exposure to oxygenated gasoline than to conventional gasoline. Many basic questions, such as the relative importance of individual characteristics, exposure situations, and factors other than oxygenates for the occurrence of various health symptoms remain" (NSTC, 1996, p. 34). After a re-examination of the available data, we agree with the thrust of the NRC committee's findings that greater attention should be given to the potential health risks from oxygenated gasoline among occupationally exposed workers. Exposure to high concentrations of conventional gasoline can cause headaches and other acute health effects, but some evidence suggests that higher blood concentrations of MTBE were associated with a greater likelihood of acute health symptoms among persons exposed to oxygenated gasoline. However, we believe that the NRC committee's conclusion that "there is enough consistency among various studies to suggest that the levels of exposure to gasoline containing MTBE in certain occupational settings are associated with increased

rates of symptom reporting" overstates the strength and quality of the available data, which we found to be quite limited.

The Interagency Health Assessment also concluded that "a causal association between acute health effects and exposure to MTBE or other oxygenates in gasoline in a relatively smaller proportion of persons has not been demonstrated but cannot be ruled out on the basis of the limited epidemiologic studies that have been conducted to date" (NSTC, 1996, p. 34). The largely anecdotal reports of acute health symptoms among some individuals at sometimes fairly low levels of exposure to oxygenated fuel cannot be adequately explained, but also cannot be dismissed. Several factors could have a role in contributing to these reported symptoms. The HEI Oxygenates Evaluation Committee discussed the potential contribution of odor in the development of symptoms (HEI, 1996). It also has been suggested that many of the acute health symptoms that have been reported in areas using oxygenated gasoline may have been caused by the by-products of the atmospheric chemistry of MTBE (Joseph, 1995). Heightened public awareness resulting from intense media attention may also contribute to increased symptom reporting (Anderson *et al.*, 1995). Another hypothesis put forth in both the Interagency Health Assessment (NSTC, 1996) and the report of the HEI Oxygenates Evaluation Committee (HEI, 1996) was that certain people may be more sensitive to the effects of evaporative or combustion emissions of oxygenated gasoline containing MTBE. This suggestion was not intended to imply that effects would be confined to "sensitive" individuals or that everyone who experienced acute symptoms suffered from some unique condition comparable to multiple chemical sensitivity. The NRC committee agreed that "some people may indeed have greater sensitivity than others to MTBE" (NRC, 1996, p. 105), and commented that the development of objective criteria for determining sensitivity "would not seem out of place" (NRC, 1996, p. 106). The NRC committee also suggested that demographic or medical characteristics, such as sex, allergies, and history of exposure, could be studied as predisposing factors. We agree that an examination of possible predisposing factors might be useful to better understand the occurrence of various symptoms in the general population following exposure to MTBE-containing gasoline.

NEUROTOXIC POTENTIAL OF MTBE

In experimental animal models, the characteristic response of the nervous system to MTBE at high levels is sedation with a domination of anesthetic effects seen at very high levels of exposure. The sedative effects, which manifest as alterations in activity and reactivity levels, are transient and usually dissipate within an hour following cessation of exposure. While MTBE displays neuroactive properties at sufficiently high concentrations in animals, there is no conclusive evidence that exposure to MTBE at air concentrations from 100 ppm to 3000 ppm will produce neurotoxicity (for reviews: Burbacher, 1993; Costantini, 1993).

The effects of acute exposure to MTBE on the nervous system have been studied in rats following a single 6-h exposure by inhalation to 0, 800, 4000, and 8000 ppm MTBE (Gill, 1989). Labored respiration and lacrimation occurred during exposure to 8000 ppm MTBE. Using a systematic neurological assessment, the Functional Observational Battery (FOB), a mild level of ataxia was evident in 20% of the animals at 4000 ppm and 50% at 8000 ppm immediately following cessation of exposure. Measurements of fore- or hindlimb grip strength and righting reflex were not altered at any exposure level nor was treadmill performance altered at levels of 4000 ppm or below. No effect was seen at the 6-h

post-exposure evaluation period. In animals exposed to 8000 ppm, there was an initial decrease in automated measurements of motor activity during the first 10 min immediately following exposure. This was followed by a brief period of increased motor activity. Animals exposed to 800 or 4000 ppm showed increased activity levels during the first 10 min following cessation of exposure, reflecting either a low-dose stimulant effect or an exaggerated recovery from anesthetic effects.

Following 13 days of repeated exposure, a decreased level of activity and mild ataxia were observed in both rats and mice during the 6-h exposure session at levels of either 4000 or 8000 ppm (Dodd and Kintigh, 1989). Immediately following the 13th day of exposure, motor activity was observed to be decreased in 20% of the animals exposed to 8000 ppm. In this same exposure group, 70% showed signs of mild (30%) or moderate (40%) ataxia. Both effects dissipated within the first hour following cessation of exposure. In animals exposed to 2000 or 4000 ppm, no exposure related behavioral alterations were observed following cessation of exposure. In a 13-week exposure paradigm, Dodd and Kintigh (1989) imposed a time delay between exposure and testing in order to minimize the influence of sedation associated with acute exposure. Male rats exposed to 8000 ppm showed decreased activity levels at 8 weeks, which dissipated by 13 weeks. In addition, female rats exposed to lower concentrations showed an increase in activity levels at 8 weeks with no effect seen at 13 weeks. Other measurements of motor function, such as gait, hindlimb splay, hindlimb grip strength, or performance on a treadmill were not altered by exposure to MTBE. Given the limited accuracy of brain parameter measurements and the relationship to body weight, it is unlikely that the reported changes of less than 5% actual brain weight or 2% brain length were a significant alteration attributable to MTBE at exposures as high as 8000 ppm (Dodd and Kintigh, 1989) and exposure times as long as 24 months (Chun *et al.*, 1992). Histological evaluation of various brain regions and peripheral nerves failed to indicate evidence of morphological alterations in nervous system tissue following 13 weeks of exposure (Dodd and Kintigh, 1989).

Examination of the original data sets from each of these studies (Gill, 1989; Dodd and Kintigh, 1989) found extremely high levels of motor activity and high variability in both controls and exposed animals, suggesting that the specific apparatus used to record activity was not solely measuring ambulatory locomotor activity. Furthermore, although multiple statistical comparisons were conducted for the activity measurements, the FOB measurements, and the brain parameters, the original statistical analysis contained no correction for the number of comparisons performed within each data set. This would increase the likelihood of type 1 statistical errors and inflate the level of significance. Thus, caution is required in drawing conclusions from isolated points in these data sets prior to an appropriate statistical re-analysis.

Based upon altered motor activity levels in experimental animals as reported in two relatively short-term exposure studies (Gill, 1989; Dodd and Kintigh, 1989), the HEI review concluded that MTBE has neurotoxic potential (HEI, 1996). The Interagency report (NSTC, 1996) evaluated data from these same acute exposure studies, and from longer exposure studies of 13 weeks (Dodd and Kintigh, 1989; Robinson *et al.*, 1990) and 24 months (Chun *et al.*, 1992). This report concluded that the transient effect of MTBE on activity and reactivity were evidence of the neuropharmacological properties of MTBE at high levels of exposure rather than overt neurotoxicity. Any effects seen occurred only during exposure and within the first few minutes following cessation of exposure. In

addition, during longer exposure periods, animals appeared to adapt to the neuropharmacological actions of MTBE and sedation was no longer evident. Although exposure to neat MTBE vapor did not produce toxicologically significant neurobehavioral changes in these animal studies, task oriented performance could be hindered due to sedation during actual exposure to sufficiently high levels of MTBE. While measurements of motor activity and evaluations by the FOB do not assess more complex behaviors such as learning and memory or subtle alterations in sensory functioning, the experimental animal data currently available do not suggest the need for additional animal testing of neat MTBE vapors at lower doses.

The HEI report identified the need for additional short-term animal studies on MTBE to determine blood levels and correlate levels with altered CNS function. In contrast, given the transient neuropharmacological effect of MTBE, the NSTC report did not identify additional testing for CNS effects at low levels of exposure as a critical research need. Occurrence of sedation during actual MTBE exposure was reported in standard clinical observations. It is likely that existing pharmacokinetic studies may include clinical observations for sedation and ataxia and provide information concerning blood levels and sedation. The adaptation to sedation with continued exposure, however, would suggest that any such correlation would be limited to acute exposure.

GENETIC TOXICITY

Oxygenated Fuel Additives

MTBE has been extensively tested for genetic toxicity (NSTC, 1996; HEI, 1996). In vitro, MTBE was not toxic or mutagenic in the *Salmonella* mutation (Ames) test, and did not produce gene conversion in yeast, or chromosome aberrations (ABS) or sister chromatid exchanges (SCE) in Chinese hamster ovary cells. MTBE was not mutagenic in cultured Chinese hamster V79 cells, but was mutagenic in mouse lymphoma L5178Y cells with, but not without, exogenous metabolic activation. This positive response was presumed to be the result of the production of formaldehyde during the in vitro metabolism of MTBE. MTBE did not damage DNA in primary rat hepatocytes in culture.

Inhalation of MTBE at 800, 3000, or 8000 ppm did not produce ABS in bone marrow cells of rats exposed 6 h/day for 5 days or micronuclei in the bone marrow cells of mice exposed to 400, 3000, or 8000 ppm, 6 h/day for 2 days. Intraperitoneal injections of up to 0.4 mL MTBE/kg body weight given to rats in single acute doses or in five consecutive doses did not produce an increase in ABS in bone marrow cells. Oral administration of MTBE to male and female mice for 3 weeks at doses of 1, 10, 100, or 1000 mg/kg did not produce mutations at the *hprt* locus in lymphocytes. MTBE did not induce sex-linked recessive lethal mutations in the fruit fly, *Drosophila melanogaster*.

ETBE was neither mutagenic nor toxic in *Salmonella*; and TAME was not mutagenic or toxic in *Salmonella* and did not induce micronuclei in bone marrow cells of mice that had received intraperitoneal injections.

Ethanol has been extensively tested for genetic toxicity in vitro and in vivo (NSTC, 1996; HEI, 1996). With one exception, which may be the result of the generation of oxygen radicals, ethanol was not mutagenic in *Salmonella*. Ethanol induced genetic crossing over and aneuploidy in fungi, mutations in yeast without an exogenous metabolic activation

system, and ABS and SCE in cultured mammalian cells in the presence, but not the absence, of exogenous metabolic activation. These positive results are likely due to the presence of the metabolite, acetaldehyde, that can be formed from the in vitro metabolic activation system. With few exceptions, there was no induction of ABS or SCE in cultured human lymphocytes when tested without an exogenous metabolic activation system; ethanol was not tested with metabolic activation. Ethanol produced cell transformation in a mouse cell line, but not in a Syrian hamster cell line.

In vivo studies in rodents showed mixed results for the induction of SCE, and there was no induction of ABS or micronuclei in bone marrow cells of mice. There are conflicting studies of the induction of micronuclei in rats. Ethanol was active in the mouse dominant lethal test and it induced aneuploidy in vivo.

Metabolites and Photoxidation Products

TBA was not toxic or mutagenic in *Salmonella* or in L5178Y mouse lymphoma mutagenicity tests. No increase in ABS or SCE was seen in Chinese hamster ovary cells in culture.

Formaldehyde has been extensively tested for genetic toxicity, with generally positive results. It produced DNA strand breaks and mutations in bacteria, yeast, fungi, and human and rodent cells, ABS and SCE in cultured human and rodent cells, and sex-linked recessive lethal mutations and reciprocal translocations in *Drosophila.*

Formaldehyde produced DNA damage in monkey and rat cells treated in vivo. Mutations were detected in the *p53* gene isolated from nasal tumors of rats after inhalation exposure to 15 ppm formaldehyde for 2 years. Mixed results were obtained in other genetic tests in rodents and humans. ABS, SCE, and micronuclei were induced in rat and mouse cells treated in vivo in some studies but not in others. Increases in ABS were seen in pulmonary macrophages but not in bone marrow cells of rats exposed by inhalation to 0.5, 3, or 15 ppm formaldehyde for 6 h/day, 5 days/week, for 1 or 8 weeks. In rats treated by inhalation for 6 h/day for 5 days, no increase in ABS or SCE was seen in peripheral blood lymphocytes. Similarly, ABS, SCE, and micronuclei were found in humans exposed to formaldehyde in work environments in some studies but not in others. Many of these differences could be the result of different exposure regimens and test protocols or of differences in the performance of the test laboratories. Formaldehyde produced sperm morphology changes in rats but not in mice or humans.

Acetaldehyde has been extensively tested in vitro. With few exceptions, acetaldehyde was not mutagenic in *Salmonella.* It produced ABS, SCE, micronuclei, and DNA damage in cultured mammalian cells and in cultured human lymphocytes. There was induction of SCE in rodent bone marrow cells after in vivo exposure.

Summary of Genetic Toxicity Data

MTBE has been extensively tested for genetic toxicity with generally negative results. The only positive result was in an in vitro test. This effect was attributed to the mutagenicity of the putative metabolite, formaldehyde. Although TAME was tested only in *Salmonella* and for micronuclei in mouse bone marrow cells, these two tests are generally considered sufficient to define a nongenotoxic chemical. There are insufficient data from which to evaluate the genetic toxicity of ETBE. Ethanol has been extensively tested in vitro and in vivo in rodents. It appears to be genotoxic in mammalian cells in vitro through its

metabolite, acetaldehyde. The in vivo test results are mixed, but ethanol is clearly mutagenic in some endpoints.

Among the metabolites, formaldehyde has been studied extensively and was mutagenic in a wide range of in vitro and in vivo test systems. Acetaldehyde has been studied extensively in vitro. It is generally mutagenic, with the exception of *Salmonella*; there are insufficient data from in vivo studies. There are insufficient data for TBA, and no test data for *tertiary*-butyl formate (TBF).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

There are only two published studies on the reproductive effects of MTBE and one unpublished study on TBA, all three in rats, and two published studies on the developmental effects of MTBE, one involving rats and mice and a second involving mice and rabbits. There are no reproductive or developmental toxicity studies on ETBE or TAME.

Neeper-Bradley *et al.* (1991) conducted a two-generation rat reproductive study using 6 h/day, 5 days/week inhalation exposures of males and females, at vapor-target concentrations of 400, 3000 and 8000 ppm. Adult toxicity in the form of a slight increase in relative liver weights was observed at 3000 ppm, along with slight reductions in P_0 adult weight gain and in pup weight gain postnatally for both the F_0 and F_1 generations. At 8000 ppm, toxicities were more severe for both the adults and pups, including a four-fold increase in pup deaths between birth and postnatal day four. There was no significant histological change noted in any generation. In a single-generation rat inhalation study, Biles *et al.* (1987) reported no biologically significant changes in body weight or effects in any reproductive or fertility endpoint measured following MTBE exposures of 300, 1300 and 3400 ppm, 6 h/day, 5 day/week. Thus, MTBE appears to be a reproductive toxicant only at concentrations that also reduce adult weight gain and increase relative liver weight.

Neeper-Bradley *et al.* (1989; 1990) conducted developmental toxicity studies in pregnant female CD1 mice and New Zealand white rabbits, exposed to MTBE on gestation days (Gd) 6-15 and 6-18 respectively, at vapor-target concentrations of 1000, 4000 and 8000 ppm. Maternal toxicity was reported for mice and rabbits in the 4000 and 8000 ppm exposure groups. Fetuses of the CD1 mice in these two exposure groups exhibited weight reductions and skeletal variations which were attributed to this maternal toxicity. The number of viable implants of CD1 mice was also decreased in the 8000 ppm exposure group. For the rabbits, however, there was no significant decrease in the number of corpora lutea, implants or dead and live fetuses, or increases in malformations or resorptions in any exposure group. Based upon these results, no-observed-adverse-effect levels (NOAELs) were reported as 1000 ppm for developmental and maternal toxicities in mice and maternal toxicity in rabbits, and 8000 ppm for developmental toxicity in rabbits. In addition, Conaway *et al.* (1985) reported no maternal toxicity and no significant change in fetal weights or frequency of fetal malformations following MTBE inhalation exposures of pregnant female CD1 mice and Sprague-Dawley rats on Gd 6-15 at vapor-target concentrations of 250, 1000 and 2500 ppm.

Tertiary-butyl alcohol (TBA) was assessed in the Sperm Morphology and Vaginal Cytology Evaluation by the National Toxicology Program (NTP, 1995). F344 male and female rats and B6C3F$_1$ male and female mice were exposed to TBA in drinking water for 90 days at concentrations of 2.5, 5.0, 10, 20, or 40 mg/mL. There was no change in caudal, epididymal or testis weights, sperm motility, sperm density, or percent abnormal sperm of male rats or mice, and there was no change in estrual cyclicity or average estrous length in female rats or mice. Determinations of reproductive function were not made. Nelson *et al.* (1985) exposed pregnant rats to ethanol vapors of 10,000, 16,000, or 20,000 ppm for 7 h per day on Gd 1-19. In the highest exposure group, where dams were severely narcotized and food consumption was reduced, mean fetal weights were reduced by about 8%. There was no increase in skeletal or soft tissue malformations at any exposure level.

In summary, MTBE caused reproductive and developmental toxicity in rodents only at exposures that produce significant liver effects or body weight reduction in the exposed adult. Considering the magnitude and duration of exposures used, MTBE is not expected to pose a reproductive or developmental health hazard under the intermittent, low-level exposures experienced by humans. There were no reproductive or developmental toxicity data on TBA, ETBE or TAME.

CARCINOGENICITY

Although there are no published studies on the carcinogenicity of MTBE in humans, there are multiple carcinogenicity studies in animals. Experimental studies show that MTBE is carcinogenic in rats and mice by the inhalation route of exposure and carcinogenic in rats by the oral (gavage) route, with tumor responses seen at multiple organ sites. TBA and formaldehyde, the primary metabolites of MTBE, also show evidence of carcinogenic activity in animals exposed directly to these substances. Several papers related to the health effects of MTBE were published subsequent to the preparation of this report. These are listed following the references cited in this chapter.

Ingestion of ethanol in relatively large quantities increases the risks for several forms of human cancer. In animals, ingestion of ethanol enhances the carcinogenic effects of other agents. No studies have been reported on the carcinogenicity of ETBE, TAME, or TBF. Unresolved at this time is whether the cancer risk of oxygenated gasoline is different from that of nonoxygenated gasoline.

Carcinogenicity of MTBE

Inhalation exposure of F344 rats to 0, 400, 3000, or 8000 ppm MTBE (6 h/day, 5 days/week, for up to 2 years) produced increased incidences of renal tubular adenomas and carcinomas and of interstitial cell adenomas (Leydig cell tumors) of the testes in male rats (Chun *et al.,* 1992). Whereas kidney tumors are uncommon in control rats, testicular tumors occur at a high spontaneous rate in this strain. The severity of chronic nephropathy was increased in exposed male and female rats, although no carcinogenic response was observed in females. Excessive mortality of male rats in the 3000 and 8000 ppm dose groups was due mainly to chronic progressive nephropathy and these dose groups had an early sacrifice. CD-1 mice were exposed to the same concentrations of MTBE as were rats,

but for only 18 months. Exposure to 8000 ppm MTBE produced increased incidences of hepatocellular carcinomas in male mice and hepatocellular adenomas and carcinomas in female mice (Burleigh-Flayer *et al.,* 1992). The high-dose male mice had decreased survival. Because of the shortened duration of this study, it is not possible to determine whether MTBE induces late developing tumors in the low or mid-exposure groups in mice or whether more hepatocellular adenomas would have progressed to carcinomas. The tumor data from the rat and mouse inhalation studies were not analyzed using statistical methods that adjust for differences in survival between the control and exposed groups. These studies were conducted under an EPA TSCA Section 4 Test Rule Consent Agreement with the fuel industry and are documented by detailed technical reports submitted to EPA.

Administration of MTBE by gavage in olive oil to Sprague-Dawley rats, four times per week for 104 weeks, at doses of 0, 250, or 1000 mg/kg body weight produced a dose-related increase in lymphohematopoietic tumors (lymphomas and leukemia) in female rats, but not in male rats, and an increased incidence of interstitial cell tumors of the testes in the high-dose group of males (Belpoggi *et al.,* 1995). The animals were allowed to live out their normal lives, rather than being sacrificed at 104 weeks. Dysplastic proliferation of lymphoreticular tissue was also increased in treated female rats; no other toxicity was reported. The authors used statistical methods that adjust the tumor incidence for intercurrent mortality. A detailed technical report for this bioassay is not available.

Carcinogenicity of MTBE Metabolites

Administration of TBA in drinking water to F344 rats for 2 years produced increased incidences of renal tubular hyperplasias and renal tubular adenomas or carcinomas in male rats but not in female rats. As with MTBE by inhalation, TBA increased the severity of nephropathy in both male and female rats. Exposure of $B6C3F_1$ mice to TBA in drinking water for 2 years produced increased incidences of follicular cell hyperplasias and follicular cell adenomas or carcinomas of the thyroid gland (Cirvello *et al.,* 1995; NTP, 1995). NTP concluded that the responses in male rats and female mice constitute "some" evidence of carcinogenicity while the responses in male mice constituted "equivocal" evidence.

Inhalation exposure of F344 rats and $B6C3F_1$ mice to formaldehyde (a genotoxic metabolite of MTBE) for 2 years at concentrations up to 14.3 ppm induced squamous cell carcinomas of the nasal cavity in rats (at concentrations greater than 5.6 ppm), but not in mice (Kerns *et al.,* 1983). A dose-related increase in incidence of leukemia was observed in a lifetime drinking water study of formaldehyde in Sprague-Dawley rats (Soffritti *et al.,* 1989), however, a 2-year drinking water study using Wistar rats (Til *et al.,* 1989) at doses ranging up to 82 mg/kg/d in males and 109 mg/kg/d in females showed no evidence of carcinogenicity. Both EPA and IARC view formaldehyde as a "probable" human carcinogen.

Relevance of the Rat Kidney Tumor Response for Human Risk Assessment

When male and not female rat kidney tumors are seen in bioassays and the presence of the α2u-globulin protein is also observed in the kidney, it is EPA's practice to determine whether that tumor occurrence will or will not be used as an indicator of potential human hazard.

The Interagency report (NSTC, 1996) concluded that the available data do not support the view that the male kidney tumor response was due solely to accumulation of α2u-globulin. The HEI report (HEI, 1996) indicated that the mechanisms are not understood; it was possible that other proteins related to α2u-globulin, or having similar characteristics, might be involved. They stated, "although it appears that the hyaline droplet nephropathy in the male F344 rats may be rightfully implicated as a potential factor in the pathogenesis of the renal tumor response, other factors may also be involved", and "it is conceivable that the MTBE and TBA induced renal tumor response may involve similar pathogenic mechanisms, however, not all findings are consistent with this interpretation". During 1996, research conducted at Chemical Industry Institute of Toxicology (CIIT) on MTBE and α2u-globulin (i.e., Prescott-Mathews *et a.l*, 1996; Poet *et al.*, 1996) became available in abstract or poster form. The NRC panel took the position of relying on these, and concluded that the research conducted at CIIT appears to have "fulfilled the EPA criteria for causation" with respect to α2u-globulin and that "the data for MTBE induced kidney tumors in male rats should not be used for human risk assessment until the recently reported data on mechanism of action are reviewed and evaluated. If the new data support the view that α2u-globulin nephropathy is involved in the response, as this committee now believes, then this endpoint should be discounted for human risk assessment". The NRC report did not discuss how the available data matched with the EPA criteria.

EPA (USEPA, 1991) established risk assessment criteria for examining male rat kidney α2u-globulin evidence. The three criteria are: (1) increased number and size of hyaline droplets in renal proximal tubule cells of treated male rats; (2) accumulating protein in the hyaline droplets is α2u-globulin; and (3) additional aspects of the pathological sequence of lesions associated with α2u-globulin nephropathy are present; if the response is mild all of the typical lesions may not be observed, however, some elements consistent with the pathological sequence must be demonstrated to be present. EPA specifies that if experimental data do not meet the criteria in any one of these three categories, then the α2u-globulin process alone is not considered to be responsible and the kidney tumor response may be used for both hazard identification and quantitative risk estimation. If experimental data reasonably fulfill the criteria yet some tumors are attributable to other carcinogenic processes, then EPA's cancer risk assessment policy is to include the tumor response for hazard identification but to only engage in quantitative risk estimation if the non α2u potency can be estimated. If the tumor response is solely attributable to α2u nephropathy, then EPA does not use that response in human hazard identification or quantitative risk estimation.

Based on a review of the NRC report and of all currently available data, including the newer abstract and poster information, we conclude that, of the three EPA criteria for causation of an α2u-globulin effect, the first criterion has been satisfied but not the second and third. The discussion in the following paragraphs supports this judgment. The evaluation of the MTBE inhalation kidney tumor response is difficult because the evidence is showing mild α2u-globulin accumulation and symptomatic nephropathy, with some of the nephropathy being intermingled with a background of non α2u rat nephropathy in both males and females.

Previously cited immunohistochemical studies for α2u-globulin in kidney sections from male rats exposed to MTBE for 13 weeks did not show an exposure-related increase in staining of this protein (Swenberg and Dietrich, 1991). Because staining was equivalent after exposure to 400, 3000, or 8000 ppm MTBE, yet only the two higher concentrations

produced kidney tumors, a clear relationship between α2u-globulin accumulation and kidney carcinogenesis could not be established. Furthermore, proteinaceous casts localized at the junction of the proximal tubules and the thin loop of Henle did not stain positively for α2u-globulin. Thus, classical effects of α2u-globulin nephropathy-inducing agents are not evident in rats exposed to MTBE (Swenberg and Dietrich, 1991), suggesting that other factors are involved in MTBE-induced nephropathy and renal carcinogenicity in male rats.

Unpublished data from CIIT indicate that 10-day exposures to MTBE (at 0, 400, 1500, or 3000 ppm) produce exposure-related increases in protein droplet accumulation and in renal epithelial cell proliferation in proximal tubules of male F344 rats but not in female rats (Prescott-Mathews *et al.,* 1996). Unlike other chemicals that induce α2u-globulin nephropathy, only a mild increase in the concentration of α2u-globulin was observed in the kidney of male rats exposed to 3000 ppm MTBE, as measured by an enzyme-linked immunosorbent assay. The authors concluded, in their abstract, that the mild α2u-globulin increase in male rats exposed to MTBE was not totally responsible for the increase in protein droplet accumulation. A comparison between the renal effects of unleaded gasoline and MTBE further illustrates this point. In a previously published study from this same laboratory (Borghoff *et al.,* 1992), treating male F344 rats with unleaded gasoline for 10 days produced dose-related increases in protein droplets, α2u-globulin accumulation, and renal epithelial cell proliferation. At exposures to unleaded gasoline and MTBE that produced comparable increases in protein droplets and cell proliferation, male rats treated with unleaded gasoline had much greater increases in α2u-globulin (300%) than those treated with MTBE (40%). Further, the slope of plots of cell proliferation rate versus concentration of α2u-globulin in the male rat kidney is much steeper for MTBE than it is for unleaded gasoline. The disconnect between increases in protein droplets or cell proliferation after exposure to MTBE and α2u-globulin accumulation suggests that the second EPA criterion has not been met and that other factors contribute to the protein droplet and cell proliferation responses in rats exposed to MTBE. In addition, a 10-day cell proliferation study is not of sufficient duration to demonstrate a sustained response.

Poet et al. (1996) found that the interaction between kidney proteins and MTBE did not withstand dialysis in buffer or anion exchange chromatography and suggested that binding between MTBE and kidney proteins was either very weak or nonspecific. For other chemicals that induce α2u-globulin accumulation in the male rat kidney, approximately 20-40% of the ligand remains bound after dialysis in buffer. This finding is true even for chemicals such as 1,4-dichlorobenzene and its metabolite 2,5-dichlorophenol (Charbonneau *et al.,* 1989), which have weak binding affinities for α2u-globulin (Borghoff *et al.,* 1991). Thus, interactions between MTBE and α2u-globulin appear to be different from those of other chemicals that induce the accumulation of this protein. A binding constant for MTBE with a α2u-globulin had not been reported. Other than necrosis in short-term studies and hyaline droplet accumulation, the typical sequence of pathological lesions associated with α2u-globulin nephropathy have not been observed after 10-day or 13-week inhalation exposures to this chemical. Renal tubular necrosis and accumulation of hyaline droplets containing small amounts of α2u-globulin can occur by mechanisms that do not necessarily involve binding to this protein (Melnick *et al.,* 1996).

Finally, EPA 1993 notes that a nephrotoxic response in the female rat suggests the possibility of other processes leading to or influencing the kidney tumor response.

Nephropathy was increased in female rats exposed for 13 weeks to TBA, a metabolite of MTBE, which is also carcinogenic to the male rat kidney; and exposure of female rats to MTBE in the 2-year inhalation study increased the severity of chronic nephropathy. We conclude that currently available information does not support the NRC's contention that the kidney tumor response in male rats exposed to MTBE has met the EPA criteria of causation due to α2u-globulin accumulation. Because the NRC did not specify how they arrived at their conclusion, we cannot determine where the difference in judgment lies.

Depending on the judgments involved in using the EPA decision criteria, the evidence for an α2u-globulin role in the rat kidney tumor response may be considered to be borderline or lacking, but as yet it does not reasonably fulfill the criteria in our judgment. Based on available experimental data, it is reasonable to believe that other modes-of-action are operating. Because evidence of an actual influence of α2u-globulin on the rat kidney tumor response is not established, the prudent public health approach is to use this tumor response for both hazard identification and quantitative estimation of cancer risk, yet we acknowledge that other views have been expressed on this subject. Users of this risk information should be cautious to recognize that the cancer potency value based on male rat kidney tumors shown later in this assessment could be substantially lower in magnitude if α2u-globulin is having a meaningful influence.

Several key issues need to be resolved to better understand the possible involvement of α2u-globulin in the male rat kidney response; these include: (1) the basis for accumulation of moderate to large protein droplets in proximal tubular epithelial cells of male rats exposed to MTBE when there is only a mild increase in kidney α2u-globulin concentration, (2) a determination of whether the weak interaction between MTBE and α2u-globulin is sufficient to account for the hyaline droplet nephropathy observed in male rats exposed to MTBE, (3) characterization of the role of TBA in MTBE-induced kidney nephropathy, and (4) an evaluation of the impact of non α2u-globulin nephropathy in the kidney of male and female rats exposed to MTBE or TBA.

Risk Assessment Relevance of Lymphoma/Leukemia Response in Female Rats and Testicular Tumors in Male Rats in the Oral-Gavage Study

Belpoggi *et al.,* (1995) using olive oil gavage, reported a dose-related increase in lymphoma-leukemia in female rats as well as increased dysplastic proliferation of the lymphoreticular tissue; there was no corresponding response in males. High dose male rats showed an increase in interstitial cell tumors of the testes. The Belpoggi study is the only lifetime oral exposure bioassay for MTBE and it is the first report of a lymphoma/leukemia response with this chemical. The reported increase in testicular tumors, is the second such report for this tumor response, as the rat inhalation study also showed increases in benign testicular tumors with a positive trend across dose groups. The high-dose testicular tumors in the Belpoggi study are of some interest for determining human hazard potential but may be less useful for low-dose risk characterization compared to other tumor types that show increased incidence at lower doses. An oil gavage bioassay such as this one provides a perspective on ingestion risks, is a study by another route of exposure, and contributes to the overall evidence for human hazard potential. However, this type of exposure introduces uncertainties for drinking water risk assessment because of dose-rate and vehicle issues.

The Belpoggi *et al.* study was published in the peer reviewed literature. However, no detailed technical report of the bioassay is available. Lacking a detailed report about the

bioassay, the NRC panel (NRC, 1996) identified a number of issues and questions which reflect upon the risk assessment use of these data. The NRC noted that the morphological criteria used to classify histopathological findings for both the lymphoma-leukemia and interstitial cell tumor responses were not adequately described and that the study did not adequately address the impact on tumor outcomes of differences in survival between controls and dosed groups. NRC went on to say that "because of the importance of this study for eventual use in risk assessment, the superficial reporting of the data and the nature of the observed lesions, the committee felt strongly that an independent in-depth review of the data, especially the pathology (microscopic slides) of the critical lesions is warranted (as was done with the inhalation studies) before the data are used for risk assessment". While the NRC raised questions about survival differences and the tumor outcome, it should be noted that Belpoggi *et al.* included statistical analyses that adjusted for intercurrent mortality. Several attempts by the Interagency Oxygenated Fuels Assessment Steering Committee to arrange for a pathology review of the Belpoggi *et al.* study have not been successful, hence, the underlying concerns raised by the NRC review cannot yet be resolved.

The lack of a detailed technical report of the Belpoggi *et al.* study, including data on the individual animals, is a limitation of this study, as is the lack of an independent peer review of the histopathology. The model for carcinogenesis study conduct and reporting is the NTP Carcinogenesis Bioassay Program. However, independent peer review of pathological findings are not routinely performed in many carcinogenesis studies used by the risk assessing community and EPA. Such a review was not conducted for the MTBE inhalation studies, though NRC (1996) indicated such. Even in the absence of the Belpoggi *et al.* study, MTBE would be considered to pose a potential risk from oral exposure pathways due to the fact that pharmacokinetic data and neoplastic effects from the inhalation study indicate systemic exposure in both rats and mice.

Questions about the combining of the lymphoma-leukemia incidence, as done by Belpoggi *et al.,* were discussed by HEI (1996) and by NSTC (1996). HEI noted that a panel of pathologists assembled by the National Toxicology Program recommended that lymphomas and leukemias in F344 rates be analyzed separately. If the neoplastic lesions in the Belpoggi *et al.* study were composed of similar cell types (e.g., mononuclear cells) and the lymphomas were interpreted as extravascular invasions of leukemic cells, (i.e., as is commonly observed in F344 rats with mononuclear cell leukemia), then combining the lymphomas and leukemias may be an appropriate approach (HEI 1996). While not verifiable at this time, the combining of the tumor incidences in the Belpoggi *et al.* study may be defensible but should be reevaluated as further information on the study pathology becomes available. The lack of a full technical report or the lack of an independent pathology review should not be an *a priori* condition for excluding the results in a hazard characterization. The use of the data to generate risk estimates is a choice that depends on judgments about the value of estimating potency as part of risk characterization compared to the limitations and uncertainties of such estimates. Regulatory agencies have historically used data from reports like that of Belpoggi *et al.* in performing risk assessments and will continue to consider such data in order to characterize the full body of available information, recognizing that the added influence should be viewed cautiously.

Consistency of Findings

Consistency of findings across studies contributes to the weight-of-evidence in evaluating carcinogenicity data. Thus, the increased incidence of interstitial cell tumors of the testis

in high-dose Sprague-Dawley rats that were administered MTBE by gavage, supports the finding of an exposure-related increase in F344 rats that were exposed to MTBE by inhalation, even though the latter strain exhibits a high spontaneous rate of these benign tumors. The lack of a tumor response in the testes of rats that were given TBA in their drinking water suggests that exposure to the parent compound, rather than to this metabolite, may be the cause of this effect. The finding of kidney tumors in male F344 rats exposed to MTBE by inhalation is supported by a similar response in male F344 rats treated with TBA. The lack of a kidney tumor response in Sprague-Dawley rats treated with MTBE by olive oil gavage at doses that were lower than those used in the inhalation study may be due to differences in target organ dosimetry of the causal agent. Pharmacokinetic studies may help explain this difference in response.

The reported increase in lymphomas and leukemia in female rats given MTBE by gavage is supported by the increase in these tumors in Sprague-Dawley rats administered formaldehyde via their drinking water and suggests a possible involvement of this metabolite in the leukemogenic effect of MTBE. In addition to the reported positive response in Sprague-Dawley rats, there is also a negative drinking water study of formaldehyde in Wistar rats. It should be noted that the contribution of formaldehyde, produced metabolically from MTBE, may be different than a drinking water study of formaldehyde in terms of target organ dosimetry. The lack of a lymphoma-leukemia response in F344 rats exposed to MTBE by inhalation may be clouded by the high spontaneous rate of mononuclear cell leukemia in this strain of rat and early mortality in males.

Weight-of-Evidence for Human Hazard

Although there are no published human carcinogenicity studies for MTBE, there are multiple animal studies showing carcinogenic activity and there is supporting animal carcinogenicity data for the MTBE metabolites. With the multiplicity of MTBE tumor responses in two animal species, and by two routes of exposure, one can conclude there is sufficient evidence that MTBE is an animal carcinogen. HEI (1996) concluded "the possibility that ambient levels of MTBE may pose some risk of carcinogenic effects in human populations cannot be excluded". NRC (1996) considered the animal evidence to be positive but "weak" for the purpose of assessing human hazard. Different parties can support more than one conclusion about weight-of-evidence depending on how information about metabolites, pharmacokinetics, mode-of-action hypotheses and the lack of background information for the oral MTBE bioassay is incorporated. We believe the weight-of-evidence supports regarding MTBE as having a carcinogenic hazard potential for humans. The risk assessing community should monitor the ongoing research to see what evolves regarding new studies and modes-of-action research and what these indicate about the likelihood of a human hazard.

Cancer Potency

Once a hazard potential has been established the follow-on task is frequently to characterize the possible impact of exposure on humans. For animal evidence this is done through a dose-response-extrapolation analysis to produce an estimate of possible human risk (i.e., potency) using assumptions and procedures which are not likely to understate the risk. The presentation of estimated cancer potency values in this section provides a crude estimate of possible risk. The act of performing the calculations does not add more certainty to the original hazard weight-of-evidence position or debate. Risk managers must be very cautious about using the estimates for regulatory decision-making purposes and

must consider the uncertainties in determining the appropriate use of these potency estimates.

Based on carcinogenicity data from the inhalation and oral studies of MTBE in rats or mice, upper-bound unit cancer risk estimates for lifetime human exposure to MTBE were calculated using the linearized multistage model (NSTC, 1996). These estimates are based on the assumptions that dose-response relationships are linear and that the mechanisms of tumor induction by MTBE in rats and mice can also occur in humans. In the absence of compelling scientific information showing otherwise, these assumptions are made as a policy choice for ensuring the protection of public health. Estimates were also made of the human cancer ED_{10} benchmark dose (i.e., the estimated dose associated with an increased cancer risk of 10% converted to a human equivalent dose) for comparison with other carcinogenic agents (see Table 4.1).

Table 4-1. Cancer potency estimates for MTBE based on rat and mouse tumor data using linear multistage extrapolation[a]

Species, sex	Tumor site	Exposure route	Upper bound unit cancer risk	ED_{10}
mouse, female	liver	inhalation	$3x10^{-4}$ per ppm[b]	480 ppm[b] 500 mg/kg/d[b]
rat, male	kidney	inhalation	$6x10^{-4}$ per ppm[b]	330 ppm[b] 350 mg/kg/d[b]
rat, female	lymphoma/ leukemia	oral (gavage)	$4x10^{-3}$ per mg/kg/d[b,c]	38 mg/kg/d[b,c]

[a]In the absence of appropriate human data or definitive information on the mode-of-action of carcinogenicity findings in animals, public health conservative risk estimation techniques are used. These techniques yield estimates which are not likely to underestimate risk for the general population. True risk for most individuals in the population is likely to be lower and for some may even be nearly zero. The ability to calculate such an estimate does not imply greater confidence in potential cancer hazard. There are uncertainties inherent in these values and they should be used cautiously.

[b]Additional understanding of the mode-of action of this response could substantially alter these estimates or possibly make them irrelevant for characterizing potential human risk. See text for additional comment about limitations and cautions regarding their use.

[C]The use of oil-gavage (i.e. bolus dosing) as a surrogate for inhalation or drinking water exposure has inherent limitations due to differences in dose-rate and possible vehicle effects. In addition, the lack of a detailed report for the oral study in rats, including morphological criteria used to classify the histopathology findings and the lack of individual animal data, limit the use of the findings for estimating risk. The NRC panel, for example, raised strong cautions about using the oral female rat tumor incidence in risk estimation until these questions can be answered.

In terms of quantitative risk estimation (i.e. potency), the oral Belpoggi *et al.* study has no direct influence on inhalation risk estimation, unless route extrapolation is contemplated for comparison with the inhalation based estimates. In the absence of a chronic drinking

water study, the use of an oil gavage (bolus dose) tumor dose-response as a surrogate for a drinking water exposure carries inherent limitations because of dose-rate and possible vehicle influences on the tumor response. Likewise, extrapolating from an inhalation dose-response as a surrogate for a drinking water exposure has limitations. This report provides, for informational purposes only, an oral risk estimate (potency-unit risk as well as ED_{10}) based on the Belpoggi lymphoma-leukemia incidence, using identified assumptions and noted caveats.

The inhalation upper-bound cancer unit risks for MTBE are six to seven times lower than those of fully vaporized conventional gasoline (2×10^{-3} per ppm based on induction of liver tumors in mice and 4×10^{-3} per ppm based on induction of kidney tumors in rats, using the linearized multistage model). For comparison, cancer ED_{10} benchmarks for 80 other Clean Air Act hazardous air pollutants range from 0.0000015 mg/kg/d (most potent) to 80 mg/kg/d (least potent). Estimates for MTBE ED_{10} fall at the low end of the range.

Limitations in Estimating Human Cancer Risk

Estimations of human cancer risks using animal study data are influenced by the exposure estimates, extrapolation models, and estimates of cancer potency. Ideally, human exposures to MTBE would be estimated from measurements of MTBE in ambient air, measurements of MTBE concentrations in specific micro environments (e.g., inside automobiles), and estimates of the distribution of time spent in each environment. At this time, estimates of low-dose human cancer risk associated with lifetime exposure to MTBE are complicated by several scientific uncertainties, including (1) the adequacy of the exposure characterizations (especially with respect to the distribution of exposures in the environment and the workplace), (2) potential differences in sensitivity between laboratory animals and humans, (3) the assumption that the mechanisms that caused tumors in rodents under the bioassay conditions operate in humans at ambient exposures, (4) the adequacy of the models that were used to perform low-dose extrapolations and estimate cancer potency, and (5) inter-individual differences in sensitivity among the exposed human population. The use of tumor data from the gavage study of MTBE to estimate cancer risk for inhalation exposure involves additional assumptions (e.g., that equivalent total exposures by inhalation and gavage administration result in similar internal doses of MTBE and that differences in dose rate and metabolism from gavage and inhalation exposures do not affect the tumor response). An oil gavage bioassay provides a perspective on potential oral risks, however, it may introduce important uncertainties for use in drinking water risk assessment because of dose-rate and vehicle issues. Further research in this area should help to clarify these issues.

Overall Evaluation

Inhalation exposure to MTBE produced increased incidences of kidney and testicular tumors in male rats and liver tumors in mice. Oral administration of MTBE produced an increased incidence of leukemia and lymphomas in female rats and testicular tumors in male rats. Two metabolites of MTBE, TBA and formaldehyde, show carcinogenic activity in animals, with some responses paralleling those seen with MTBE (rat kidney and perhaps leukemia) and some responses being at different sites (thyroid gland and nasal cavity). Epidemiological studies suggest a causal relationship between exposure to formaldehyde and nasopharyngeal cancer (IARC, 1995). The mechanisms by which MTBE causes cancer in rodents are not understood, nor is the relative role of the parent compound and its metabolites known. Consequently, the possibility of a low-dose hazard cannot be

excluded. It is unlikely that carcinogenic effects of ethanol would result from inhalation exposure to ambient air concentrations associated with use of ethanol in gasoline.

Based on the weight-of-evidence on MTBE carcinogenicity (positive in two species, by two routes of exposure, and at multiple organ sites), other supporting factors (e.g., one metabolite is a "probable" human carcinogen and the other also induces male rat kidney tumors), and considering various uncertainties, it is reasonable to regard this alkyl ether oxygenate as posing a potential carcinogenic hazard and risk to humans. At the same time, it should be recognized that the estimated upper-bound cancer unit risks for MTBE are similar to or slightly less than those for fully vaporized conventional gasoline; substantially less than that for benzene, a constituent of gasoline that is classified as a known human carcinogen; and more than 100 times less than that for 1,3-butadiene, a carcinogenic emission product of incomplete fuel combustion. More important is whether the cancer risk from using oxygenated gasoline containing MTBE is significantly different than the cancer risk attributed to using conventional gasoline. Meaningful predictions of human cancer risk from the wintertime use of oxygenated gasoline versus nonoxygenated gasoline require much more knowledge of the relative ambient concentrations and personal exposure to the air toxicants that are present in both the evaporative and exhaust emissions from both types of fuels. Exposure to mobile-source air toxicants may be affected by the composition of the gasoline, the engine, the emissions control technology, and atmospheric conditions.

Comparing Potential Cancer Risks of Conventional Gasoline and Oxygenated Gasoline

The NRC concurred with the Interagency view that the interpretation of any cancer risks related to the addition of MTBE to gasoline requires a comparison to the cancer risks associated with the use of conventional gasoline (NRC, 1996). The NRC also agreed with the opinion of the Interagency assessment (NSTC, 1996) and the HEI report (HEI, 1996) that large data gaps on exposures and health effects of the mixture of compounds to which people are exposed through the use of oxygenated and nonoxygenated fuels prevent the development of a definitive comparative risk assessment. However, the NRC believes that sufficient data are available to bound a quantitative assessment of the cancer risks associated with use of oxygenated gasoline and nonoxygenated gasoline, and recommended the development of a framework for conducting a comparative risk assessment of these two types of fuels. The NRC claims that even an assessment with uncertain data is justified as long as uncertainties are specified and thoroughly characterized. EPA had previously developed a research strategy and framework for conducting comparative risk assessments on conventional and alternative fuels (USEPA, 1992).

A comprehensive comparative risk assessment on oxygenated and nonoxygenated fuels requires information on the level and distribution of human exposure to toxic compounds in each of these fuels and those present in evaporative and combustion emissions, as well as atmospheric transformation products. Assessments of potential health risks should account for multipathway exposures (including drinking water and inhalation) and potential interactive effects among this complex mixture of compounds. However, because there are no data that address the mixture issue, because information on general population exposures via drinking water are very sparse, and because it is likely that not all toxic compounds have been identified, a narrower assessment of relative cancer risk from inhalation exposure performed at this time would have to be limited to additive effects of MTBE and the small number of confirmed carcinogenic air pollutants that have been

identified in fuels and/or in combustion emissions (e.g., benzene, 1,3-butadiene, formaldehyde, acetaldehyde). For the latter compounds, reliable estimates of cancer potency are available. However, even with this highly restricted approach, the human exposure assessment still presents an enormous challenge. Emission studies on test vehicles found that fuel oxygenates decrease the emissions of benzene and 1,3-butadiene and increase the emissions of aldehydes (formaldehyde from use of MTBE and acetaldehyde from use of ethanol or ETBE). The effects of low temperatures on toxic emissions are not well characterized. It is not certain whether results from emission studies are directly applicable to the ambient air effects of the on-road fleet (see Air Quality chapter of this report). Quantifying vehicle emissions and exposures that occur during refueling and when operating motor vehicles fueled with oxygenated or nonoxygenated gasoline must account for actual changes in fuel composition beyond the addition of the oxygenate (e.g., differences in levels of aromatics and olefinic hydrocarbons in the fuel), fleet composition with respect to the type of emission control system, vehicle maintenance condition, vehicle operation, meteorology (including effects of ambient temperature), and altitude of different geographical sites. Information on emissions from vehicles operating on oxygenated fuels under varied conditions is very fragmentary. However, even if suitable emissions data were available, translation of quantitative evaluations of differences in emissions resulting from use of oxygenated versus nonoxygenated gasoline to realistic estimates of ambient air and microenvironment concentrations of these toxic air pollutants are needed. The ambient and microenvironment estimates should be compared to the limited data on actual concentrations. Assessments of human exposure and health risks also need to account for effects of meteorology (e.g., wind, temperature, and precipitation during the oxygenated fuels season) and differences in human activity patterns, since these factors can have a substantial effect on individual and population exposures. Inconsistent accounting of the numerous variables that impact on exposure could result in a mistaken differential effect of the two fuels.

EPA and other agencies are analyzing available data, collecting new data, and developing better models to reduce uncertainties in the exposure and health effects assessments. The Interagency Oxygenated Fuels Assessment Steering Committee shares the desire of the NRC to assess the health risks and benefits associated with the use of oxygenated gasoline compared to those resulting from use of nonoxygenated gasoline; however, the Steering Committee believes that a quantitative comparative risk assessment would not be useful at this time because large data gaps in human exposure could result in considerable overestimation or underestimation of the actual risks associated with use of either or both of these types of fuels. Information on cancer risks associated with evaporative and combustion emissions from use of nonoxygenated gasoline are not adequate to serve as a baseline against which changes in risk associated with use of oxygenated fuels could be measured. Excessive reliance on hypotheses and assumptions would not likely yield a useful health assessment. The feasibility of preparing a quantitative comparative risk assessment will be reexamined periodically, particularly after EPA has conducted an inventory of existing data and models for their usefulness in producing meaningful evaluations. This step should be reached even before new data become available that will more definitively fill some of the critical information gaps. EPA is taking steps to obtain data that would allow a comprehensive comparative risk assessment. Existing health effects testing requirements for fuels and fuel additives, promulgated under section 211(b) of the Clean Air Act, have led to discussions between EPA and representatives of a consortium of fuel and additive manufacturers that are expected to result in the

performance of bioassay and exposure studies and will help fill some of the critical information gaps.

CONCLUSIONS

Exposures to MTBE in various occupational and nonoccupational settings have been examined in a limited number of studies. Available data indicate that the highest potential for acute inhalation exposure to oxygenates for the general population occurs during refueling at gasoline stations. Based on several qualitative assumptions about various exposure scenarios, high-end, time-weighted annual average exposure to MTBE in the general population was estimated to be on the order of about 0.01 to 0.02 ppm. The exposure data were too limited to make quantitative estimates of the range and distribution of MTBE exposure. Less information is available on exposures to other oxygenates.

MTBE is rapidly absorbed by humans or rats after inhalation exposure. Studies in rats also show rapid absorption after oral exposure. Metabolism and elimination of MTBE and its metabolites proceed rapidly regardless of the route of exposure. Studies in rats indicate that MTBE is metabolized by cytochrome P450 enzymes to TBA and formaldehyde. Measurements of blood levels of TBA in humans exposed to MTBE show a rapid rise after exposure begins and a slow elimination rate.

Complaints of acute health symptoms, such as headaches, nausea, dizziness, and breathing difficulties, were reported in various areas of the country after the introduction of oxygenated gasoline containing MTBE. The limited field investigations conducted to date suggest that greater attention should be given to the potential for increased symptom reporting among workers exposed to high concentrations of oxygenated gasoline containing MTBE. At the lower concentrations that are experienced by the general population, the limited epidemiological studies and controlled exposure studies conducted to date do not support the contention that MTBE as used in the winter oxygenated fuels program is causing significant increases over background in acute symptoms or illnesses. The anecdotal reports of acute health symptoms among some individuals cannot yet be explained or dismissed.

The assessment found that chronic non-cancer health effects, including neurotoxic, developmental, or reproductive effects, would not likely occur at environmental or occupational exposures to MTBE. The observation of acute and reversible neurobehavioral changes in rats exposed to relatively high levels of MTBE is indicative of a neuroactive effect that could hinder performance during periods of high exposure.

MTBE has been tested for genotoxicity with generally negative results, whereas its metabolite formaldehyde is genotoxic in a variety of experimental systems. Experimental studies indicate that MTBE is carcinogenic in rats and mice at multiple organ sites after oral or inhalation exposure. The mechanisms by which MTBE causes cancer in animals are not well understood. *Tertiary*-butyl alcohol and formaldehyde, the primary metabolites of MTBE biotransformation, are also carcinogenic in animals. While there are no studies on the carcinogenicity of MTBE in humans, there is sufficient evidence to indicate that MTBE is an animal carcinogen and to regard MTBE as having a human hazard potential. However, estimates of human risk from MTBE contain large uncertainties in both human exposure and cancer potency.

The estimated upper-bound cancer unit risks for MTBE are similar to or slightly less than those for fully vaporized conventional gasoline; substantially less than that for benzene, a constituent of gasoline that is classified as a known human carcinogen; and more than 100 times less than that for 1,3-butadiene, a carcinogenic emission product of incomplete fuel combustion. The interpretation of any acute or chronic health risks associated with the addition of MTBE to gasoline requires a comparison to the health risks associated with conventional gasoline. Meaningful predictions of human cancer risk from the wintertime use of oxygenated gasoline versus nonoxygenated gasoline require much more knowledge on human exposures to oxygenates, as well as quantitative evaluations on how exposures to the toxic compounds in both evaporative and exhaust emissions of fuels are altered with use of oxygenated gasoline.

REFERENCES

American Petroleum Industry (API), 1995, Petroleum industry data characterizing occupational exposures to MTBE 1983-1993. Washington, DC: API #4622.

Anderson, H.A., Hanrahan, L., Goldring, J., and Delaney, B., 1995, An investigation of health concerns attributed to reformulated gasoline use in southeastern Wisconsin: final report. Madison, WI: Wisconsin Department of Health and Social Services, Bureau of Public Health; May 30.

Beller, M. and Middaugh, J., 1992, Potential illness due to exposure to oxygenated fuels, Fairbanks, Alaska. Anchorage, Alaska: State of Alaska Department of Health and Social Services, December 11.

Belpoggi, F., Soffritti M., and Maltoni, C., 1995, Methyl-tertiary-butyl ether (MTBE)—a gasoline additive—causes testicular and haematopoietic cancers in rats. Toxicol. Ind. Health 11:119-149.

Biles, R.W., Schroeder, R.E., and Holdsworth, C.E., 1987, Methyl tertiary butyl ether inhalation in rats: a single generation reproduction study. Toxicol. Ind. Health 3:519-534.

Bio-Research Laboratories, 1990a, Pharmacokinetics of methyl tert-butyl ether (MTBE) and tert-butyl alcohol (TBA) in male and female Fischer-344 rats after administration of ^{14}C-MTBE by intravenous, oral, and dermal routes. Bio-Research Laboratories Report #38842, Senneville, Quebec, Canada.

Bio-Research Laboratories, 1990b, Mass balance of radioactivity and metabolism of methyl tert-butyl ether (MTBE) in male and female Fischer-344 rats after administration of ^{14}C-MTBE by intravenous, oral, and dermal routes. Bio-Research Laboratories Report #38843, Senneville, Quebec, Canada.

Bio-Research Laboratories, 1990c, Pharmacokinetics of methyl tert-butyl ether (MTBE) and tert-butyl alcohol (TBA) in male and female Fischer-344 rats after single and repeat inhalation nose-only exposure to ^{14}C-MTBE. Bio-Research Laboratories Report #38844, Senneville, Quebec, Canada.

Bio-Research Laboratories, 1990d, Disposition of radioactivity and metabolism of methyl tert-butyl ether (MTBE) in male and female Fischer-344 rats after nose-only inhalation exposure to ^{14}C-MTBE. Bio-Research Laboratories Report #38845, Senneville, Quebec, Canada.

Borghoff, S.J., Miller, A.B., Bowen, J.P., and Swenberg, J.A., 1991, Characteristics of binding to α2u-globulin in vitro–evaluating structure-activity relationships. Toxicol. Appl. Pharmacol. 107:228-238.

Borghoff, S.J., Youtsey, N.L., and Swenberg, J.A., 1992, A comparison of European high test gasoline and PS-6 unleaded gasoline in their abilities to induce α2u-globulin nephropathy and renal cell proliferation. Toxicol. Lett. 63:21-33.

Borghoff, S.J, Murphy, J.E., and Medinsky, M.A., 1996, Development of a physiologically based pharmacokinetic model for methyl tertiary-butyl ether and tertiary-butanol in male Fischer-344 rats. Fundam. Appl. Toxicol. 30:264-275.

Brady, J.F., Xiao, F., Ning, S.M., and Yang, C.S., 1990, Metabolism of methyl tertiary-butyl ether by rat hepatic microsomes. Arch. Toxicol. 64:157-160.

Burbacher, T.M., 1993, Neurotoxic effects of gasoline and gasoline constituents. Environ. Health Perspect. 101(Suppl. 6):133-141.

Buckley, T.J., Wallace, L.A., Prah, J.D., Ashley, D., and Zweidinger, R.A., 1995, Breath and urine measurements to assess environmental inhalation exposure to methyl tertiary butyl ether (MTBE) - draft, U.S. Environmental Protection Agency, National Exposure Research Laboratory, Research Triangle Park, NC.

Burleigh-Flayer, H.D., Chun, J.S., and Kintigh, W.J., 1992, Methyl tertiary butyl ether: vapor inhalation oncogenicity study in CD-1 mice. Export, PA: Bushy Run Research Center; OPTS-42098.

Cain, W.S., Leaderer, B.P., Ginsberg, G.L., Andrews, L.S., Cometto-Muniz, J.E., Gent, J.F., Buck, M., Berglund, L.G., Mohsenin, V., Monahan, E., and Kjaergaard, S. , 1996, Acute exposure to low-level methyl tertiary-butyl ether (MTBE): human reactions and pharmacokinetic responses. Inhal. Toxicol. 8:21-48.

Cederbaum, A.I. and Cohen, G., 1980, Oxidative demethylation of tertiary-butyl alcohol by rat liver microsomes. Biochem. Biophys. Res. Comm. 97:730-736.

Centers for Disease Control and Prevention (CDC), 1993a, An investigation of exposure to methyl tertiary butyl ether among motorists and exposed workers in Stamford, Connecticut. Atlanta, GA: U.S. Department of Health and Human Services, National Center for Environmental Health; September 14.

Centers for Disease Control and Prevention (CDC), 1993b, An investigation of exposure to MTBE and gasoline among motorists and exposed workers in Albany, New York [draft]. Atlanta, GA: U.S. Department of Health and Human Services, National Center for Environmental Health; August 4.

Chandler, B. and Middaugh, J., 1992, Potential illness due to exposure to oxygenated fuels, Anchorage, Alaska. Anchorage, AK: State of Alaska Department of Health and Social Services, December 23.

Charbonneau, M., Strasser, J., Lock, E.A., Turner, M.J., and Swenberg, J.A., 1989, Involvement of reversible binding to α2u-globulin in 1,4-dichlorobenzene-induced nephropathy. Toxicol. Appl. Phamacol. 99:122-132.

Chun, J.S., Burleigh-Flayer, H.D., and Kintigh, W.J., 1992, Methyl tertiary butyl ether: vapor inhalation oncogenicity study in Fischer 344 rats. Export, PA: Bushy Run Research Center; Report 91N0013B.

Cirvello, J.D., Radovsky A., Heath, J.E., Farnell, D.R., and Lindamood, C., 1995, Toxicity and carcinogenicity of t-butyl alcohol in rats and mice following chronic exposure in drinking water. Toxicol. Ind. Health 11:151-165.

Conaway, C.C., Schroeder, R.E., and Snyder, N.K., 1985, Teratology evaluation of methyl tertiary butyl ether in rats and mice. J. Toxicol. Environ. Health 16:797-809.

Costantini, M.G., 1993, Health effects of oxygenated fuels. Environ. Health Perspect. 101 (Suppl. 6):151-160.

Dodd, E.E. and Kintigh, W.J., 1989, Methyl tertiary butyl ether (MTBE): repeated (13-week) vapor inhalation study in rats with neurotoxicity evaluation. Export, PA: Bushy Run Research Center; Report 52-507.

Egeland, G.M. and Ingle, D., 1995, Ethanol-blended fuel in Anchorage, 1994-1995: residents may smell the difference but have no health complaints. Anchorage, AK: Alaska Department of Health and Social Services, State of Alaska Epidemiology Bulletin, August 17, 1995.

Gill, M.W., 1989, Methyl tertiary butyl alcohol: single exposure vapor inhalation neurotoxicity study. Export, PA: Bushy Run Research Center; Report no. 52-533.

Health Effects Institute (HEI), 1996, The potential health effects of oxygenates added to gasoline. A review of the current literature. Health Effects Institute, Cambridge, MA.

International Agency for Research on Cancer (IARC), 1995, Formaldehyde. In: IARC monographs on the evaluation of carcinogenic risks to humans: wood dust and formaldehyde. Lyon, France: IARC 62:217-362.

Johanson, G., Nihlen, A., and Lof, A., 1995, Toxicokinetics and acute effects of inhaled MTBE and ETBE in male volunteers. Toxicol. Lett. 82-83:713-718.

Joseph, P., 1995, Letter to the Editor. Arch. Environ. Health 50:395-396.

Kerns, K.D., Pavkov, K.L., Donofrio, D.J., Gralla, E.J., and Swenberg. J.A., 1983, Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. Cancer Res. 43:4382-4392.

Livo, K.B., 1995, Overview of public's perspective of health effects from oxygenated gasolines in Colorado. Presented at the HEI Workshop on Acute Health Effects on Oxygenates and Oxygenated Gasolines, Chicago, July 27.

McCoy, M. Jr, Abernethy, J., and Johnson, T., 1995, Anecdotal health-related complaint data pertaining to possible exposures to methyl tertiary butyl ether (MTBE): 1993

and 1994 follow-up surveys (1984-1994). American Petroleum Institute; Publication No. 4623. Washington, DC.

Mehlman, M.A., 1995, Dangerous and cancer-causing propoerties of products and chemicals in the oil refining and petrochemical industry, Part XV, Health hazards and health risks from oxygenated automotive fuels (MTBE): Lessons not heeded. Int. J. Occup. Med. Toxicol. 4:1-16.

Melnick, R.L., Kohn, M.C., and Portier, C.J., 1996, Implications for risk assessment of suggested nongenotoxic mechanisms of chemical carcinogenesis. Environ. Health Perspect.104 (Suppl. 1):123-134.

Mohr, S.N., Fiedler, N., Weisel, C., and Kelly-McNeil, K., 1994, Health effects of MTBE among New Jersey garage workers. Inhal. Toxicol. 6:553-562.

Moolenaar, R.L., Hefflin, B.J., Ashley, D.L., and Etzel, R.A., 1994, Methyl tertiary butyl ether in human blood after exposure to oxygenated fuels in Fairbanks, Alaska. Arch. Environ. Health 49:402-409.

National Research Council (NRC), 1996, Toxicological and performance aspects of oxygenated motor vehicle fuels. National Academy Press, Washington, DC.

National Science and Technology Council (NSTC), 1996, Interagency assessment of potential health risks associated with oxygenated gasoline. NSTC, Washington, DC.

National Toxicology Program (NTP), 1995, Toxicology and carcinogenesis studies of t-butyl alcohol (CAS No. 76-65-0) in F344/N rats and B6C3F1 mice (drinking water studies). Research Triangle Park, NC: National Institutes of Health; Technical Report Series No. 436, NIH Publication No. 94-3167.

Neeper-Bradley, T.L., Tyl, R.W., Fisher, L.C., Tarasi, D.J., Fait, D.L., Dodd, D.E., Pritts, I.M., Panson, R.S., and Ridlon, S.A., 1990/1989, Developmental toxicity study of inhaled methyl tertiary butyl ether (MTBE) in New Zealand White rabbits and CD-1 mice [abstract] Society of Toxicology, 1990; and Bushy Run Research Center Project Reports 51-628 and 52-526,1989.

Neeper-Bradley, T.L., 1991, Final report: Two-generation reproduction study of inhaled methyl tert-butyl ether in Sprague-Dawley rats. Bushy Run Research Center, Export, PA.

Nelson, B.K., Brightwell, W.S. MacKenzie, D.R., Khan, A., Burg, J.R., Weigel, W.W., and Goad, P.T., 1985, Teratological assessment of methanol and ethanol at high inhalation levels in rats. Fundam. Appl. Toxicol. 5:727-736.

Poet, T.S., Murphy, J.E., and Borghoff, S.J., 1996, In vitro uptake of methyl t-butyl ether (MTBE) in male and female rat kidney homogenate: solubility and protein interactions. Toxicologist 30:305 (abstract).

Prah, J., Goldstein, G., Devlin, R., Otto, D., Ashley, D., House, D., Cohen, K., and Gerrity, T., 1994, Sensory, symptomatic, inflammatory and ocular responses to and the metabolism of methyl tertiary butyl ether in a controlled human exposure experiment. Inhal. Toxicol. 6:521-538.

Prescott-Mathews, J.S., Wolf, D.C., Wong, B.A., and Borghoff, S.J., 1996, Methyl tert-butyl ether (MTBE)-induced protein droplet nephropathy and cell proliferation in male F-344 rats. Toxicologist 30:304 (abstract).

Robinson, M., Bruner, R.H., and Olson, G.R., 1990, Fourteen- and ninety-day oral toxicity studies of methyl tertiary-butyl ether in Sprague-Dawley rats. J. Am. College Toxicol. 9:525-540.

Soffritti, M., Maltoni, C., Maffei, F., and Biagi, R., 1989, Formaldehyde: an experimental multipotential carcinogen. Toxicol. Ind. Health 5:699-730.

Swenberg, J.A. and Dietrich, D.R., 1991, Immunohistochemical localization of α2u-globulin in kidneys of treated and control rats of a 13-week vapor inhalation study undertaken with methyl tertiary butyl ether (MTBE). Report to the MTBE Health Effects Testing Task Force.

Til, H.P., Woutersen, R.A, Feron, V.J., Hollanders, V.H.M., Falke, H.E., 1989, Two-year drinking water study of formaldehyde in rats. Food Chem. Toxicol. 27:77-87.

U.S. Environmental Protection Agency (USEPA),1991, Alpha 2u-globulin: association with chemically induced renal toxicity and neoplasia in the male rat. Risk Assessment Forum. EPA/625/3-91/019F. USEPA, Washington, DC.

U.S. Environmental Protection Agency (USEPA), 1992, Alternative fuels research strategy. Office of Research and Development. EPA/600/AP-92/002. USEPA, Washington, DC.

U.S. Environmental Protection Agency (USEPA), 1995, Workshop panel report on developing guidelines on the feasibility and design of epidemiologic studies among populations exposed to MTBE. Research Traingle Park, NC: National Health and Environmental Effects Research Laboratory; December 1995.

White, M.C., Johnson, C.A., Ashley, D.L., Buchta, T.M., and Pelletier, D.J., 1995, Exposure to methyl tertiary butyl ether from oxygenated gasoline in Stamford, Connecticut. Arch. Environ. Health 50:183-189.

SUPPLEMENTAL REFERENCES

(The following papers related to the health effects of MTBE were published subsequent to the preparation of this report and may be of interest to the reader.)

Bird, M.G., Burleigh-Flayer, H.D., Chun, J.S., Douglas, J.F., Kneiss, J.J., Andrews, L.S., April, 1997, Oncogenicity studies of inhaled methyl tertiary-butyl ether (MTBE) in CD-1 mice and F-344 rats, J. Appl. Toxicol. 17(S1): S45-S55.

Casanova, M., Laethem, C., d'A Heck, H., 1997, Lack of evidence for the involvement of formaldehyde in the hepatocarcinogenicity of methyl-t-butyl ether (MTBE), Fund. Appl. Toxicol., 36:339 (abstract).

Hutcheon, D.E., Arnold, J.D., ten Hove, W., Boyle, J. 3rd, 1996, Disposition, metabolism, and toxicity of methyl tertiary-butyl ether, an oxygenate for reformulated gasoline, J. Toxicol. Environ. Health 47:453-464.

Mackerer, C.R., Angelosanto, F.A., Blackburn, G.R., Schreiner, C.A., 1996, Identification of formaldehyde as the metabolite responsible for the mutagenicity of methyl tertiary-butyl ether in the activated mouse lymphoma assay. Proc. Soc. Exp. Biol. Med. 212:338-341.

Moser, G.J., Wong, B.A., Wolf, D.C., Fransson-Steen, R.L., Goldsworthy, T.L., 1996, Methyl tertiary butyl ether lacks tumor promoting activity in N-Nitrosodiethylamine-initiated B6C3F1 female mouse liver. Carcinogenesis 17:2753-2761.

Prescott-Mathews, J.S., Wolf, D.C., Wong, B.A., Borghoff, S.J., 1997, Methyl tert-butyl ether causes α2u-globulin nephropathy and enhanced renal cell proliferation in male Fisher-344 rats. Toxicol. Appl. Pharmacol. 143:301-314.

Abbreviations and Terms

ABBREVIATIONS AND TERMS

ABS	chromosome aberrations
A/F	air/fuel
AK	Alaska
API	American Petroleum Institute
AQIRP	Air Quality Improvement Research Program
AST	aboveground storage tank
ASTM	American Society for Testing and Materials. An independent organization with members from industry, government and academia, as well as private citizens.
Auto/Oil AQIRP	Auto/Oil Air Quality Improvement Research Program
BTEX	benzene, toluene, ethylbenzene, and xylenes
Btu	British thermal unit
CAA	Clean Air Act
CARB	carbureted
CARB	The California Air Resources Board
CFR	Code of Federal Regulations
CIIT	Chemical Industry Institute of Toxicology
CL	closed loop
CNS	central nervous system
CO	carbon monoxide
CO_2	carbon dioxide
Complex Model	EPA model developed for use by vehicle manufacturers and petroleum refiners to predict the effects of fuel formulations on primarily 1990 technology vehicle emissions
CT	Connecticut
CWA	Clean Water Act
DIPE	diisopropyl ether
DNA	deoxyribonucleic acid
EC_{50}	median effective concentration
Emission level	FTP measure of mass emission in grams per mile (g/mi)
EPA	The U. S. Environmental Protection Agency
ETBE	ethyl *tertiary*-butyl ether, a fuel oxygenate
EtOH	ethanol
exceedance	jargon, meaning an air pollution event in which the ambient concentration of a pollutant exceeds the EPA NAAQS
FOB	Functional Observational Battery
FTP	Federal Test Procedure, a standard procedure for measuring vehicle exhaust emissions at 75 °F
gal	gallon
gasoline	Fuel sold for use in spark ignition, internal combustion engines (including motor vehicles). It is a volatile mixture of liquid hydrocarbons that may or may not contain "oxygenates" and very small amounts of additives that are designed to preserve fuel quality and prevent engine deposits.

GC/MS	gas chromatography/mass spectrometry
Gd	gestation days
GM	General Motors
g/mi	grams of pollutant per vehicle mile
h	hour
HC	hydrocarbon
HEI	Health Effects Institute
IL	Illinois
I/M	Inspection and Maintenance
i.v.	intravenous
kg	kilogram
L	liter
LC_{50}	median lethal concentration
MeOH	methanol
µg	microgram
mg	milligram
mi	mile
min	minute
mL	milliliter
mph	miles per hour
MOBILE Model	EPA model developed for use by states for predicting vehicle emission inventories and the effects of emission control programs
MPFI	multi-port fuel injection
MT	Montana
MTBE	methyl *tertiary*-butyl ether, a fuel oxygenate
MY	model year (of vehicle)
NAWQA	National Water Quality Assessment
NY	New York
NAAQS	National Ambient Air Quality Standard
NO	nitric oxide
NPDES	National Pollution Discharge Elimination System
nonoxygenated gasoline	Gasoline that contains no measurable oxygenates or oxygenates at very low levels due to commingling during distribution and storage.
NO_x	nitrogen oxides (NO and NO_2)
NRC	National Research Council
NSTC	National Science and Technology Council
NTP	National Toxicology Program
OC	oxidation catalysts
OL	open loop
oxygenated gasoline	Gasoline that contains oxygenates. For oxygenated gasoline programs to reduce carbon monoxide (CO) pollution, the minimum oxygen content is typically 2.7 weight percent.

oxygenates	Compounds containing oxygen (alcohols and ethers) that are added to fuels to increase its oxygen content. Lawful use of these substances as components of gasoline requires that they either be "substantially similar" under section 211(f)(1) of the Clean Air Act or approved under a waiver granted under section 211(f)(4) of the Clean Air Act. Methyl tertiary butyl ether (MTBE) and ethanol are the most common oxygenates currently used, although there are a number of other possible oxygenates.
ppbv	parts per billion by volume
ppm	parts per million
ppmv	parts per million by volume
psi	pounds per square inch, pressure
RFG	Reformulated gasoline. Specially formulated fuels developed to minimize vehicle emissions of ozone-forming and toxic air pollutants and improve air quality. RFG contains, on average, a minimum of 2.0 weight percent oxygen.
rpm	revolutions per minute.
RVP	Reid vapor pressure, fuel vapor pressure (Psi) at 100 °F
SCE	sister chromatid exchange
TA	*tertiary*-butyl alcohol
TAEE	*tertiary*-amyl ethyl ether, a fuel oxygenate
TAME	*tertiary*-amyl methyl ether, a fuel oxygenate
TAP	toxic air pollutants (benzene, 1,3-butadiene, formaldehyde, acetaldehyde, and polycyclic organic matter)
TBA	*tertiary*-butyl alcohol
TBF	*tertiary*-butyl formate
TBI	throttle body fuel injection
TRI	Toxics Release Inventory
TWO	three-way catalysts
USEPA	United States Environmental Protection Agency
USGS	United States Geological Survey
UST	underground storage tank
VOC	volatile organic compound
WI	Wisconsin
wt	weight
yr	year

For additional copies or information contact:

Additional copies of the "Interagency Assessment of Oxygenated Fuels" can be requested through GCRIO User Services:

telephone:	517-797-2730
fax:	517-797-2622
e-mail	help@gcrio.org
www:	http://www.gcrio.org (see Document Request Form)

For additional information, please contact:

Environment Division
Office of Science and Technology Policy
Executive Office of the President
Washington, DC 20502
telephone: 202-456-6202
fax: 202-456-6025

Also available on the NSTC Home Page via link from the OSTP Home Page at:
http://www.whitehouse.gov/WH/EOP/OSTP/html/OSTP Home.html