

Health Risk Perspectives on Fuel Oxygenates

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Gasoline and Air Pollution

The Clean Air Act (CAA) directs the Administrator of the U.S. Environmental Protection Agency (EPA) to establish National Ambient Air Quality Standards (NAAQS) for several widespread air pollutants, based on scientific criteria and allowing for an adequate margin of safety to protect public health. The CAA establishes several programs for meeting these standards for allowable amounts of air pollutants. So many U.S. citizens potentially are exposed to two of these pollutants, ozone and carbon monoxide (CO), that Congress has made their reduction a national priority.

Because gasoline and its combustion by-products are major contributors to the problems of air pollution, Congress required oxygenated gasoline programs during the winter in areas that do not attain the CO NAAQS (beginning November 1, 1992) and reformulated gasoline programs in the nine worst ozone areas (beginning January 1, 1995). Some areas with less serious ozone problems have voluntarily elected to join the reformulated gasoline program, and others

may do so in the future. According to EPA's Office of Mobile Sources, reformulated gasoline is to be used year-round in high-ozone areas (where about 45 million people live) and will account for roughly one-third of the gasoline used nationwide as of January 1, 1995. Approximately 30 million people live in areas using oxygenated gasolines. There is some overlap of the areas where reformulated and oxygenated gasolines are used.

Gasoline Problems and Solutions— Past, Present, and Future

Gasoline-fueled cars and trucks are major sources of numerous air pollutants. People can be exposed to chemical combustion products from the tailpipe and to chemicals evaporated from fuels, such as happens during refueling or entry into a garage where a car has been parked. Some chemicals such as benzene and ethers are in both evaporative and tailpipe emissions. Carbon monoxide, formaldehyde, acetaldehyde, butadiene, and other air toxics are principally combustion products. In addition, some emissions are

What Are the General Differences Between Fuel Types?

- "Traditional" gasoline has over 1,000 components that have varied somewhat over the years.
- Oxygenated gasoline, also called oxyfuel, is traditional gasoline to which at least 2.7% oxygen (by weight) has been added; for example, mixing in 15% MTBE or 7.5% ethanol achieves this oxygen content. This fuel is designed to reduce CO and is used in the winter only.
- Reformulated gasoline has a significantly different chemical formulation than that of traditional gasoline. One of the major differences is that, according to the CAA Amendments of 1990, reformulated gasoline must contain at least 2.0% oxygen (by weight); for example, having 11% MTBE or 13% ETBE achieves this goal. In addition, the use of reformulated gasoline must result in a 15% decrease in emissions of hydrocarbons (including air toxics). This fuel is designed to reduce ozone and several air toxics and is used year-round.
- Various compounds can fulfill the fuel oxygen requirements and are collectively called "oxygenates". Currently, MTBE and ethanol are popular, but numerous other candidates exist, and their potential health risk must be considered.

chemically transformed in the air, creating new pollutants such as ozone and nitrogen dioxide. The EPA estimates that motor vehicle emissions account for roughly half of the ozone problem, 75 to 90% of the CO problem, and about half of the airborne toxics cancer risk. This is why cars and trucks have been a major focus of laws and regulations dealing with pollution prevention and control. For example, due primarily to emissions-control devices, cars coming off today's production lines typically emit roughly 90% fewer air toxics over their lifetimes than did cars of the 1960s.

In spite of this major achievement, increases in the number of cars and miles traveled per car have resulted in continuing vehicular-related pollution problems that require several approaches for solution. One such approach is to alter fuel composition, as noted in the previous section. The currently popular, available chemicals for this purpose are methyl-tertiary-butyl ether (MTBE) (about 65% of oxyfuels sold contain MTBE) and ethanol (about 35% of oxyfuels sold). Several other ethers are under consideration as alternatives and include ethyl-tertiary-butyl ether (ETBE), tertiary-amyl-methyl ether (TAME), diisopropyl ether (DIPE), and several others.

As is widely known from television and print reports, it is a national goal that other technologies for providing power to vehicles, such as those using electricity and natural gas, will assume a larger role in the future, making gasoline improvement programs an interim step. The health perspective taken must be comprehensive because the present petroleum-based technologies, interim fuel programs, and new technologies all involve some health risks as well as societal and economic contributions.

How Risk Is Assessed and Evaluated

To optimally evaluate the health impacts of a compound, that compound must be assessed, preferably in the context of the mixture with which it is associated, and should be compared to risks from other pollutants. For the oxygenates in particular, it would be desirable to assess the risks of the oxygenate-gasoline mixture and compare that to the risks of the gasoline mixture it is replacing.

Developing a risk assessment has three major phases, (1) a health assessment, (2) an exposure

What Is the Reformulated Gasoline Program?

- *The program requires numerous changes in fuel constituents to reduce ozone-forming hydrocarbons and air toxics. Air toxics, as defined in the CAA, are benzene, butadiene, formaldehyde, acetaldehyde, and polycyclic organic matter.*
- *Phase 1 (begins on January 1, 1995) is required to achieve a reduction of 15 to 17% of ozone-forming hydrocarbons during the high-ozone season and an annual reduction of 15 to 17% of air toxic emissions from vehicles fueled with reformulated gasoline. For example, with MTBE-reformulated gasoline, benzene and butadiene emissions decrease, whereas formaldehyde and MTBE emissions increase, all within the context of a net decrease in hydrocarbons. That is, the increases in formaldehyde and MTBE are more than offset by the decreases in other hydrocarbon emissions.*
- *Phase 2 (begins on January 1, 2000) is required to achieve an annual reduction of 25 to 29% in ozone-forming hydrocarbon emissions, a 5 to 7% reduction in ozone-forming nitrogen oxide emissions, and a 20 to 22% reduction in air toxic emissions.*
- *The exact changes in emissions from reformulated gasoline are dependent on numerous factors, including the specific fuel formulation, vehicle characteristics, and vehicular operating conditions (e.g., speed, temperature).*

How Are Concentrations of Chemicals Expressed?

Concentrations may be expressed by various units of measurement, but the one used here is "parts per million", or "ppm". This refers to the number of parts of the chemical per million parts of air. For example, 1 ppm of ozone equals 1 part of ozone per million parts of air. Alternatively, concentrations may be expressed in terms of the mass of a chemical per volume of air, as in milligrams (mg) per cubic meter (m^3). For example, 1 ppm of MTBE = $3.6 \text{ mg}/m^3$ of MTBE.

assessment, and (3) the linkage between them. The health phase begins with what is called hazard identification; that is the determination of what types of hazard a pollutant can cause. For example, does it cause cancer, damage to the nervous system, or both? Next is the quantitative evaluation of what is called the exposure-response relationship. For example, what exposure regimen (concentration and duration) causes a specific increase in the number of laboratory rats with tumors? Determining exposure-response relationships for humans can be very difficult because often it is necessary to extrapolate from animal data to humans and from very high laboratory exposures to low-level environmental exposures. Often, there are no or inadequate data on dose (the amount of the chemical that reaches sensitive tissue from an exposure and actually causes the response). Educated assumptions are used to overcome these difficulties, but they introduce uncertainty into the assessment process. Once "harmful" or "safe" exposures have been defined in the exposure-response assessment, the main question is what exposures do people encounter? Because acute and chronic exposures can cause profoundly different effects, both need to be assessed.

The health and exposure assessments are linked, forming the risk assessment. For actual health risk to occur, a susceptible person must be exposed to a sufficient pollutant concentration and exposure duration to cause effects. This principle is the basis

for assessing the effects of most noncarcinogens and some carcinogens. For example, if one were exposed for 1 hour to 1 ppm of a chemical that is only toxic after 100 hours of exposure to 100 ppm, a health risk would not exist. A contrasting viewpoint, used for most carcinogens, assumes that some risk is directly related to any exposure at all. This approach often considers the number of people likely to experience an effect in relation to each unit of exposure. For example, one might predict that if 1 million people were exposed for a lifetime to 1 ppm of a chemical, 10 of them might be at risk for cancer. The difficulty is that adequate quantitative information on health risks does not exist for many chemicals—especially for mixtures of chemicals.

People are usually exposed to mixtures of chemicals, but typically information is available on only a few of the many chemicals in a mixture. The effects of the mixture can be less than, equal to, or greater than the sum of the parts of the mixture. Thus, even if extensive information were available on the adverse effects of a few of the components, only a crude estimate could be made as to what might result from exposure to the components as a part of a whole fuel mixture. This is the case with fuels and MTBE. There is a significant amount of health information about MTBE, but very little information on its effects in combustion or evaporative mixtures with gasoline. The lack of data on complex mixtures is a common situation faced by risk assessors. In such a case, total risk often is estimated by evaluating the separate constituents.

It is not appropriate to compare the estimated risk of one chemical to a toxicologically unknown chemical. For example, in the context of fuel oxygenates, with no exposure or health data on other ethers such as ETBE or TAME, it is not possible to say whether they have greater, lesser, or equal health risks in comparison to MTBE, either alone or mixed in a fuel.

The world is replete with ever-present risks, ranging from the rather obvious, such as car accidents, to the very subtle, such as indoor exposures to gases. Use of "traditional" gasoline results in exposures to all sorts of pollutants (e.g., CO, ozone, benzene), with attendant risks for both cancer and noncancer effects. To reduce these risks, Congress mandated cleaner fuels. However, a "cleaner" fuel does not result in

zero risk, for there is no such thing as zero risk, only comparative risk. With decreases in some pollutants, there may be increases in others. The objective of using new fuels is to achieve a net decrease in existing health risk, essentially by substituting some chemicals in fuels for other chemicals in fuels. For example, with ethanol-oxygenated gasoline, CO emissions decrease, but ethanol and acetaldehyde emissions increase.

Effects of Key Pollutants from Traditional Gasoline

Although oxyfuels and reformulated gasolines are designed to reduce CO, ozone, and air toxics, there is not yet enough data to know exactly how well the programs will succeed. To appreciate trade-offs and impacts, it is necessary to understand the key pollutant-specific health information discussed below. The question is whether these trade-offs yield a net benefit to society and public health.

Ozone Health Effects

Because of the adverse health effects of ozone, EPA has set the NAAQS at 0.12 ppm, daily maximum 1-hour average, not to be exceeded more than once a year. From 1991 to 1993, the standard was exceeded in areas with a total population of about 100 million people. Although only a fraction of these people may actually be exposed to levels above the NAAQS, the classes of potential effects are of significant concern. They range from acute, transient effects on lung function to potentially irreversible structural changes in the lung from many years of high exposure.

Ozone is a highly reactive irritant gas that primarily affects the respiratory system, producing acute exposure effects such as coughing, shortness of breath, and soreness in the area of the breastbone or pain when taking a deep breath. These symptoms often accompany a reduction in the ability to take a deep breath and a switch to rapid, shallow breathing. Such reductions in inspiratory capacity are often referred to simply as "pulmonary function decrements". In children, pulmonary function decrements can occur in the absence of any symptoms such as cough or pain.

To illustrate, data from hundreds of human volunteers studied under short (1- to 3-hour) exposure conditions show that detectable pulmonary function

decrements occur at greater than 0.16 ppm, with exposure during very heavy exercise (competitive running). A prolonged 0.08-ppm ozone exposure for 6.6-hours, simulating a day of heavy outdoor work or play, can also cause pulmonary function decrements. A wide variability in individual responsiveness to ozone exposure exists, with about 5 to 20% of the general population being sensitive, healthy individuals ("responders") who consistently experience pulmonary function decrements and respiratory symptoms at distinctly lower ozone exposure levels than nonresponders. The lung function of children also can be decreased by ambient concentrations around 0.1 ppm, and these decrements may persist for a while (up to about 1 day) after exposure ceases, as shown in field studies conducted at several summer camps.

Of particular concern with regard to other, potentially more serious effects are such findings as (1) increased hospital admissions for respiratory causes related to summertime ozone concentrations in the Northeastern United States, even when the ozone standard is met; (2) increased physiological and biochemical signs of lung inflammation observed in humans exposed to ozone levels as low as 0.08 ppm while engaged in simulated strenuous work over a 6.6-hour period; (3) indications of decreased host defenses against bacterial respiratory infections observed in laboratory animals and humans exposed to 0.08 ppm ozone for several hours; and (4) laboratory animal studies showing that chronic ozone exposures can cause persistent changes in lung structure thought to be indicative of likely increased risk of chronic lung disease in humans. Unfortunately, however, it is not yet possible to specify with much certainty the exposure concentrations or periods of chronic exposure (months, years) necessary to produce seriously increased risk of altered lung structure or associated chronic lung disease in humans.

Ozone exposure is clearly of most concern when the health-based NAAQS for ozone is exceeded. The impacts of acute exposure effects, although transient, are of much more concern for ozone-sensitive asthmatics or individuals with other types of respiratory problems (e.g., chronic obstructive lung disease) than for otherwise healthy adults. Children also represent a group at special risk because they typically engage in higher levels of physical activity outdoors, often for longer periods than adults. The possible

What Major Air Pollutants Are Related to All Gasoline-Based Fuels, and What Types of Health Effects Can They Cause If Exposures Are Sufficiently Great?

For most of these pollutants, the general public is not expected to receive routine exposures to concentrations that will cause these effects.

Acetaldehyde ¹	Cancer, respiratory tract irritation
Benzene ¹	Cancer, ² effects on blood, ² reproductive/ developmental effects
Butadiene ¹	Cancer, reproductive/developmental effects
CO ¹	Effects on heart, ² neurotoxicity ²
Formaldehyde ¹	Cancer, respiratory tract irritation ²
Gasoline	Cancer neurotoxicity, ² respiratory tract irritation
Nitrogen Dioxide ¹	Respiratory illness, ² respiratory tract effects ²
Ozone ¹	Respiratory tract effects ²
Polycyclic Organic Matter ¹	Cancer
Toluene	Neurotoxicity, ² reproductive/developmental effects
Xylene	Neurotoxicity, ² reproductive/developmental effects

¹Specific legal requirements for reductions. ²Effects observed in humans.

effects of chronic exposures to ozone on lung structure and development, especially for young children, are of concern, although it is not yet possible to estimate with confidence the chronic ozone exposure levels or periods (months, years) necessary to cause persisting lung tissue damage or impaired lung development in humans.

Carbon Monoxide Health Effects

The EPA has documented the detrimental health effects that CO can have on populations and has set the CO NAAQS at 9 ppm for an 8-hour average and 35 ppm for a 1-hour average; neither is to be exceeded more than once per year. In 1992 and 1993, about 30 million people lived in areas that exceeded the CO NAAQS. Carbon monoxide is a colorless, odorless, and nonirritating gas that is readily absorbed from the lungs into the bloodstream, there forming a slowly reversible complex with hemoglobin, known as carboxyhemoglobin (COHb), within red blood cells. The presence of COHb reduces the oxygen-carrying capacity of the blood, thus reducing the oxygen available to vital tissues, such as the cardiovascular and nervous systems. Exposure to very high levels of

CO (well above environmental levels) can lead to death.

The effects of exposure to low concentrations of CO, such as the levels found in ambient air, are far more subtle and considerably less threatening than those occurring in frank poisoning from high CO levels. Maximal exercise performance in healthy individuals is affected at COHb levels of 2.3% and greater. The reductions in performance at these levels are small and are likely to affect only competing athletes rather than people engaged in the activities of daily life. Central nervous system effects, observed at peak COHb levels of 5% and greater, include reduction in visual perception, manual dexterity, learning driving performance, and attention level. Of most concern, however, are adverse effects observed in individuals with chronic heart disease at COHb levels of 3 to 6%. At these levels, such individuals are likely to have reduced capacity for physical activity because they experience chest pain (angina) sooner. Exercise-related heart problems (e.g., cardiac arrhythmias) also have been observed in some people with chronic heart disease at COHb levels of 6%, which may result in an increased risk of sudden death from

a heart attack. The COHb levels (3 to 6%) of concern for induction of cardiovascular effects among people with chronic heart disease would be expected, on average, at exposures during light exercise to CO ambient air concentrations of 60 to 100 ppm (1 hour) or 20 to 45 ppm (8 hours).

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

Health Effects of Whole Gasoline and Major Air Toxics

Gasoline has been around for many decades, and exposures to vehicular emissions have been commonplace. For some time, most gasoline pumps have carried a warning label indicating that "exposure to gasoline by inhalation has caused cancer in laboratory animals", and people are urged not to breathe vapors.

Laboratory animals exposed to wholly aerosolized gasoline by inhalation developed tumors, leading EPA to classify gasoline as a "probable human carcinogen" (Group B2). However, exposure to a wholly aerosolized mixture is not the same as being exposed to vapors. The chemical composition of vapors is quite different because of differences in vapor pressures among the numerous constituents. Thus, there is uncertainty about using the risk assessment based on whole-gasoline aerosols to describe risks from gasoline vapors.

Information is available on certain components of gasoline and its combustion products, but, as mentioned earlier, the net effects of the mixture could be different from the sum of several components. In terms of carcinogenicity, the primary constituents of concern are benzene, butadiene, formaldehyde, acetaldehyde, and a group of organic compounds (polycyclic organic matter). Of these five, benzene is an evaporative emission (also emitted from the tailpipe) and the others are predominantly combustion emissions.

What Are Cancer Classifications and Unit Risks?

The EPA traditionally has described the potential for a chemical to cause cancer in two ways—qualitatively and quantitatively.

Qualitatively, there are four key classes:

- A. Known human carcinogen, based on sufficient evidence from human population (epidemiological) studies;*
- B1. Probable human carcinogen, based on limited evidence from epidemiological studies, with or without evidence from animal studies;*
- B2. Probable human carcinogen, based on sufficient evidence from animal studies and inadequate data from epidemiological studies; and*
- C. Possible human carcinogen, based on limited evidence from animal studies.*

Quantitative cancer assessments are called unit risks. Cancer exposure-response data are mathematically modeled, creating an estimate of a theoretical risk to humans at the end of a lifetime of exposure. Unit risks facilitate comparisons of chemicals; a chemical with a higher unit risk is likely to cause cancer in more people at a given unit of exposure. Both approaches are directly related to the data available. For example, if there are no studies of human populations, by definition there can be no evidence of effects in humans required for a "Group A" or "Group B1" designation.

Benzene is classified by EPA as a "known human carcinogen" (Group A) because of its ability to cause leukemia in humans. Formaldehyde (Group B1), acetaldehyde (Group B2), and butadiene (Group B2) are classed as "probable human carcinogens", primarily because they cause tumors in animals. Of these four, butadiene is the most potent (i.e., it is calculated to cause more cases of cancer per unit concentration than the other chemicals).

Air toxics also can cause noncancer effects, especially to the respiratory and nervous systems and

to the fetus and child. In particular, low concentrations of formaldehyde can be irritating to the respiratory tract and affect pulmonary function. Other constituents of evaporative emissions, such as hexane, are neurotoxic, but the quantities of these emissions are unlikely to be affected by changes in other fuel constituents. As for risks to the developing fetus, a preliminary assessment using conservative assumptions and available, limited exposure estimates does not raise concern about developmental toxicity risks from hexane, xylene, or toluene, which also are key constituents of gasoline. For benzene, it appears that 1 ppm may be a level that is likely to be without appreciable risk of adverse effects on the developing fetus; however, refueling with traditional gasoline occasionally could result in benzene exposures above 1 ppm, raising concern about the potential for developmental effects. Routine public exposures to benzene are not well characterized, but are not expected to be of concern.

Health Effects of the Oxygenates

Methyl-tertiary-butyl ether has been used at low levels for several years as an octane enhancer in high-test fuels. Since wider utilization of MTBE in oxyfuels began in November 1992, some individuals and groups have expressed concern over the potential health effects of MTBE. Initially, people in a few areas (e.g., Fairbanks, AK) complained of acute symptoms, such as headaches and nausea, from breathing fumes associated with MTBE oxyfuels. The Office of Research and Development (ORD) of EPA evaluated the results of numerous health studies dating from 1987 and published a health risk assessment of MTBE and MTBE oxyfuels in November 1993. This risk assessment by ORD was based primarily on toxicological and clinical studies of pure MTBE, epidemiological studies related to MTBE oxyfuels, and exposure estimates based on certain assumptions and limited measurements of MTBE levels in environments where MTBE oxyfuels were used.

Since ORD's 1993 assessment, very little new information has come to light, so the major conclusions about pure MTBE and MTBE oxyfuels have not changed. The present evaluation is intended to provide a risk perspective of MTBE in both oxyfuels and reformulated gasoline. Although reformulated gasoline is different from oxyfuels (as discussed earlier), our

current conclusions are not significantly influenced by this difference. Basically, to detect differences between the fuels would require research on mixtures, which has not yet been conducted. Thus, the conclusions are based primarily on the likely similarities in MTBE exposure between the two fuel classes. For example, acute exposures to reformulated gasoline, with its smaller concentration of MTBE (11% versus 15%), will result in lower MTBE exposures and, hence, lower risks. Annual exposures to MTBE will be higher with reformulated gasoline because it will be used year-round, rather than just in the winter. For example, in the 1993 assessment, ORD estimated that highly exposed members of the general public living in areas with oxyfuels during the winter might receive annual exposures of about 0.02 ppm. Using similar information and assuming these same people lived in areas with reformulated gasoline the rest of the year, ORD estimated a high annual MTBE exposure of about 0.03 ppm. As will be discussed later, this difference in annual exposure estimates does not significantly influence the risk assessments of MTBE fuels.

Noncancer Health Effects of MTBE

The 1993 MTBE assessment by ORD concluded that there is not likely to be a substantial risk of acute health symptoms among healthy members of the public receiving "typical" acute environmental exposures under temperate conditions (i.e., not subarctic temperatures). These conclusions are based on two separate studies of volunteers exposed to pure MTBE in chambers and on field studies of people receiving exposures as part of their daily lives. Acute (1-hour) exposures to typically encountered high ambient levels of "pure" MTBE (1.4 and 1.7 ppm) did not appear to cause health symptoms, eye or nose irritation, or behavior changes in young, healthy adults under room temperature conditions (75 °F). However, it is possible that there are more sensitive members of the population who would respond.

Because people in Fairbanks complained about health symptoms after the introduction of MTBE oxyfuel, an epidemiological study was conducted to compare symptoms during the time MTBE-containing oxyfuel was used and after MTBE was removed. Symptom reports in Fairbanks clearly decreased when MTBE oxyfuels were removed. However, the

situation was confounded because the heightened public concern about the potential health effects, higher fuel costs (14¢/gal), and distinctive odor of MTBE oxyfuel also disappeared when MTBE oxyfuels were removed. Even so, the unique meteorology and topography of Fairbanks could influence exposure and prevents ruling out an association between MTBE oxyfuels and symptoms. The symptom prevalence data from Anchorage, AK, cannot be interpreted relative to MTBE oxyfuel use because no similar group without MTBE oxyfuel exposure was studied.

Preliminary reports of epidemiological studies in New Jersey did not indicate differences in symptoms reported by workers (drivers, mechanics, and refuelers) in northern New Jersey (when MTBE oxyfuels were in use) and southern New Jersey (when MTBE oxyfuels were not in use). Moreover, there were not large differences in symptom reports between a variety of worker and commuter subgroups with varying exposures in Stamford, CT (with MTBE oxyfuels), or between populations studied in Stamford and Albany, NY (without MTBE oxyfuels). However, it is possible that flu symptoms or other factors confounded the Albany results, making intercity comparisons difficult.

Studies of rats and mice have shown effects on the developing fetus from repeated exposures to high concentrations of MTBE. Using a very cautious assessment approach like that used for benzene, it appears that 13.3 ppm MTBE is likely to be without appreciable risks of adverse effects on the developing fetus. Infrequently, gasoline fill-up scenarios are at or above this level, but most public exposures to MTBE are well below this concentration and are not of concern. Other gasoline constituents also are capable of producing developmental effects in laboratory animals. Although it is beyond the scope of this report, the potential of the individual components of gasoline or of the mixture itself to cause developmental toxicity should be recognized and compared to the potential added risk from MTBE in order to provide a complete analysis. However, there are incomplete data for such a comparative evaluation.

Studies of other effects also have been assessed. Based on several studies of laboratory animals exposed chronically to MTBE and annual human exposure estimates, it does not appear that there is a significant risk for MTBE alone to cause chronic

noncancer effects. This finding is based on studies of rats and mice that inhaled very high concentrations of MTBE for a lifetime. Upon analysis, EPA concluded that 0.83 ppm MTBE should not cause adverse effects, even in susceptible people exposed for a lifetime. As noted above, ORD's highest annual exposure estimate that assumed use of oxygenated and reformulated gasoline was 0.03 ppm, which is well below the "safe" level of 0.83 ppm. The potential risk of noncancer health effects from chronic exposure to MTBE as part of a complex mixture with gasoline is not known.

Carcinogenic Effects of MTBE

There are no human studies to provide direct evidence about the potential human cancer hazard of MTBE. Inhalation carcinogenicity studies in mice and rats show evidence of three types of animal tumors. These particular studies are difficult to interpret because of some high-dose general toxicity. Nevertheless, ORD believes the inhalation carcinogenicity evidence would support placing MTBE in Group C as a "possible human carcinogen".

Additional laboratory animal carcinogenicity studies for MTBE have been conducted in Italy using oral exposure (by insertion of the chemical into the esophagus [i.e., gavage]). Anecdotal reports of these studies available to date indicate that tumors were observed in rodents. The results of this study cannot be included into a formal cancer assessment until they are peer reviewed and published. If the anecdotal reports are sustained after publication and a fuller evaluation, they may provide enough additional evidence to place MTBE in Group B2, a "probable human carcinogen". Even when the full oral-study report is published, it is not likely to significantly alter the worst-case risk estimate of inhaled MTBE.

Typically, a carcinogenicity characterization attempts to provide a quantitative perspective on what the impact of a chemical might be on an exposed population by providing an upper-bound unit risk (added risk per unit of dose). The unit risk is often an estimate of the highest plausible risk that a chemical may pose for humans, realizing that the true risk, which cannot be ascertained, could be lower, even so low as to be insignificant. For the MTBE cancer inhalation studies, the circumstances of the bioassays make the estimation of a quantitative unit risk very problematical. With three different tumor types (male

rat kidney and testicular tumors and mouse liver tumors), the theoretical worst-case unit risks span a 25-fold range. The ORD estimates that MTBE may have a cancer unit risk about the same or somewhat lower than benzene (a Class A "known human carcinogen"), which is also present in gasoline. If a comparison is made to the cancer unit risks of other fuel-related air toxics, MTBE's worst-case unit risk would be about half that of formaldehyde and 50-fold less than that of butadiene. Thus, from an individual chemical viewpoint, MTBE's carcinogenic properties are not that different from those of components already present in traditional gasoline emissions. Estimates of theoretical risk to a population are dependent on being able to estimate population exposure, which is discussed later.

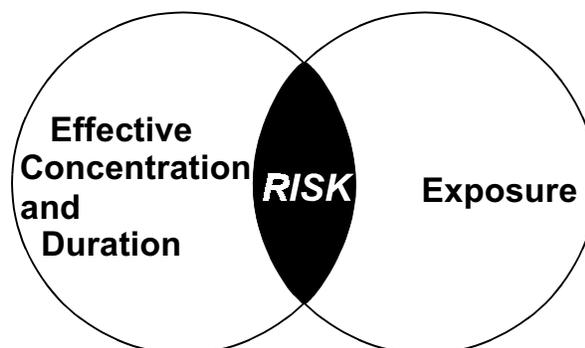
Effects of Other Ethers and Ethanol

No major toxicity or exposure studies of other ethers that may be used as fuel oxygenates (e.g., TAME, ETBE, DIPE) have been completed. Thus, their health risks are virtually unknown.

The health effects of oral exposure to ethanol have been extensively investigated. In addition to the rather familiar and often obvious effects of acute, high-level exposure to ethanol (e.g., staggered walking, visual impairment), chronic ethanol exposure is associated with a variety of health effects. Depending on the degree of exposure, ethanol may affect the central nervous system, endocrine and reproductive function, prenatal and postnatal development (including fetal alcohol syndrome), the immune system, the cardiovascular system, and the liver. The International Agency for Research on Cancer has declared alcoholic beverage exposure to be carcinogenic for humans. The vast majority of research on ethanol health effects has been concerned with ingested ethanol; very little attention has been devoted to inhaled ethanol. Therefore, insufficient evidence exists to determine whether, or at what levels of exposure, inhaled ethanol would produce significant adverse health effects. However, experimental animal studies using ethanol vapor suggest that rather high concentrations (hundreds or thousands of parts per million) are necessary to produce toxic effects.

When Does Health Risk Occur?

When susceptible people are exposed for sufficient durations to concentrations of chemicals that can cause health effects, risks exist. Some people may be more sensitive and affected by lower concentrations than others. Some people may have average sensitivity, but receive more exposure. Assessing health risks is a complex process involving expert judgments and assumptions.



Summary

Everyone in the United States is exposed to pollutants from motor vehicles at some time. To reach full understanding of the health risks of these pollutants, substantial data would need to be evaluated on the range of exposures to and health effects of whole combustion and evaporative emissions of traditional fuels and oxygenated fuels. Then, these health risk changes would need to be weighed with quantitative

health risk benefits of the fuels gained through lowering ozone, CO, and selected air toxics. However, there are and will always be inadequate data to define all risks precisely for all populations and exposure scenarios. Realistically, what can be done is to examine the available, limited evidence for risks and benefits and to attempt to stimulate research to elucidate key issues. *With the currently available information, there is no basis to expect that the use of*

MTBE-oxygenated gasoline or MTBE-reformulated gasoline will pose a greater public health risk than traditional gasoline. Additionally, no conclusions are drawn about major fuel formulations using oxygenates other than MTBE because of the lack of health or exposure data on them. Due to the widespread pattern of exposure, the possibility of susceptible subpopulations, and possible shifts in the market resulting in the use of other oxygenates, more research and testing are required to better understand the comparative risks of different fuels. More discussion of these points follows.

- Oxygenated and reformulated gasolines were mandated by Congress to help deal with serious air quality problems, namely excessive levels of CO, ozone, and toxic chemicals in ambient air.
- Currently, there is no scientifically established explanation for the symptom complaints of some members of the general public exposed briefly to MTBE-oxyfuels. Available human clinical studies show no such effects, and epidemiological studies are equivocal or show no effects. However, the possibilities of a subpopulation susceptible to pollutant mixtures related to the use of MTBE-fuels and of unique circumstances in Fairbanks cannot be ruled out.
- Although MTBE has the potential to cause developmental effects in animals, only some unusually high and infrequent human exposure scenarios (i.e., some refuelings) are of concern. Even then, exposures to other fuel components with the potential for developmental effects (e.g., benzene) also could be of concern. Prudent practices would call for pregnant women to avoid or reduce breathing any type of gasoline fuel fumes.
- Very long-term exposures to MTBE vapors are not expected to cause adverse noncancer health effects, but effects of the interaction of evaporative and combustion mixtures of gasoline and MTBE (or ethanol or other ethers) are unknown.
- From a cancer hazard perspective, both the liquid and vapors of traditional gasolines have a cancer hazard potential, resulting in the warning label on gas pumps. Newer gasolines with MTBE have a hazard potential that does not appear to be substantially different. Both the liquid and vapors of traditional and MTBE-blended gasolines contain Group

A, B, and C carcinogenic compounds. The ORD currently views MTBE itself as a Group C (possible human carcinogen), though formal peer review of this classification has not occurred. The amount of carcinogenic compounds in emissions changes somewhat with MTBE, but the overall hazard potential probably has not changed even with the addition of MTBE as a new emission constituent. A good quantitative estimate of differential population risks for various gasolines (with and without oxygenates) is essentially impossible to make because of the crudeness and variability of available exposure data. Nevertheless, it is noted that reformulated fuel with MTBE will result in lower net emissions (on a mass basis) of total hydrocarbons, some of which are "known or probable" human carcinogens (i.e., benzene and butadiene), even though emissions of MTBE and aldehydes increase.

- To improve understanding of the health trade-offs between different types of fuels, more research and evaluation is needed. A new EPA rule that requires testing to compare the emissions and health effects of complex mixtures of fuels, with and without additives such as oxygenates, will provide key information. Other testing being planned or conducted by EPA, industry, the State of Alaska, and the Centers for Disease Control and Prevention also is expected to be helpful. More information will need to be gathered and analyzed to quantitatively estimate the relationship between use of these fuels and improvements in ozone and CO air quality.

Selected References

U.S. Environmental Protection Agency (1993) Assessment of potential health risks of gasoline oxygenated with methyl tertiary butyl ether (MTBE). Washington, D.C.: Office of Research and Development; report no. EPA/600/R-93/206; November.

U.S. Environmental Protection Agency (1994) Reproductive and developmental effects from gasoline vapors: a screening evaluation for internal EPA consideration related to gasoline oxygenates. Washington, DC: Reproductive and Developmental Toxicology Branch, Office of Health and Environmental Assessment; November 7.

U.S. Environmental Protection Agency (1994) Summary of cancer risk derivations for MTBE: a screening evaluation for internal consideration related to gasoline oxygenates. Washington, DC: Cancer Assessment Statistics and Epidemiology Branch, Office of Health and Environmental Assessment; December 2.

U.S. Environmental Protection Agency (1994) Estimates of MTBE exposures related to reformulated gasoline. Research Triangle Park, NC: Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment; December 8.

December 8, 1994

ESTIMATES OF MTBE EXPOSURES RELATED TO REFORMULATED GASOLINE

By Environmental Criteria and Assessment Office, RTP, NC. These calculations have been internally reviewed and are based on a peer-review exposure assessment.

The following is a record of the calculations used to estimate human exposures to MTBE related to use of reformulated gasoline (RFG).

Objective - What are exposures if a person lives in an area with a 4- or 6-month oxyfuel season and RFG the remainder of the year?

1. Assume that previous exposure estimates (Table 5, p38 of ORD's MTBE assessment) for oxyfuels hold and that RFG has 11% MTBE. Thus, RFG has 11/15 (73.3%) MTBE compared to oxyfuel.

2. Perform calculations that essentially prorate the exposures, as follows:

	High (mg/m ³ MTBE)		Low (mg/m ³ MTBE)	
	4 mo oxy 8 mo RFG	6 mo oxy 6 mo RFG	4 mo oxy 8 mo RFG	6 mo oxy 6 mo RFG
oxy/mo ^a	0.01057	0.01057	0.00625	0.00625
x oxy season	(x4) 0.0423	(x6) 0.063	(x4) 0.025	(x6) 0.0375
73.3%/mo	0.00775	0.00775	0.00458	0.00458
x RFG season	(x8) 0.062	(x6) 0.0465	(x8) 0.0306	(x6) 0.0275
Oxy + RFG season	0.104	0.109	0.062	0.065
Round-off	0.10	0.11	0.06	0.06

^aFrom Table 5 of ORD's MTBE assessment add mg/m³·h for high and for low and divide by 8773.59 hr (the sum of time/year).

Conversions based on 1ppm = 3.6mg/m³. Therefore 0.11mg/m³ MTBE = 0.03 ppm.

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS FROM GASOLINE VAPORS
A Screening Evaluation for Internal EPA Consideration
Related To Gasoline Oxygenates

By

Reproductive & Development Toxicology Branch
Office of Health & Environmental Assessment

U.S. EPA, Washington, DC

November 7, 1994

The evaluation that follows has not been subjected to peer review and thus should not be construed as a final Agency position.

The currently available information shows that developmental toxicity is produced at high laboratory exposures of mice and rats to MTBE. Developmental toxicity, expressed as reduced offspring growth in rats, was observed at 10,800 mg/m³, but not at 1,440 mg/m³. A conservative preliminary estimate of a level at which no adverse developmental toxicity is likely to occur in humans (including sensitive subpopulations) is 48 mg/m³. Occasionally, MTBE concentration during gasoline fill-ups is likely to exceed that level if an effort is not made to avoid the maximum concentration of fumes. Therefore, because it must be assumed that even a short exposure has the potential to result in developmental toxicity if the exposure is sufficiently high, there is a possibility that worse-case exposures could exceed a level at which developmental toxicity could be induced.

With respect to other components of gasoline vapor, it appears that C4 to C6 saturated aliphatic hydrocarbons predominate. No evidence has surfaced from a quick and limited search to indicate that butane or pentane are likely to be of concern. Hexane is metabolized in rats to 2,5-hexanedione which is a testicular toxicant. It is unlikely that brief, intermittent exposures such as those experienced in fueling would result in human testicular toxicity from hexane. Hexane also has produced developmental toxicity in rats. The reported high end exposure concentration of 2.1 ppm (Clayton) appears to be below a level that would be of concern for developmental effects in humans.

Benzene is also present in gasoline vapor. A NOAEL of 10 ppm for reproductive/developmental effects has been determined in rats. That NOAEL has been represented as controversial (too low), but a recent study with rats sponsored by the API has resulted in a NOAEL of 30 ppm with rats that included a trend toward lowered birth weights from the significant LOAEL of 300 ppm. If 30 ppm were used as a NOAEL and an uncertainty factor of 30 applied, the resulting 1 ppm would be very close to the high end exposure measurements for humans made by Clayton.

Other aromatic hydrocarbons such as xylene or toluene can produce reproductive or developmental toxicity in laboratory species, but are not expected to be present in sufficient concentrations in the inhaled vapor to be a human health concern for reproductive or developmental effects.

**SUMMARY OF CANCER RISK DERIVATIONS FOR MTBE
A Screening Evaluation for Internal Consideration
Related To Gasoline Oxygenates**

Cancer Assessment Statistics & Epidemiology Branch
Office of Health & Environmental Assessment
U.S. EPA, Washington, DC
2 December 1994

The following information has not been peer reviewed and so should not be construed as a final Agency position

In some instances the Agency needs to understand worst case scenarios about possible cancer risks and in the context "what if" estimates of upper bound risk are developed. The "what if" setting means that we want to know "what" the worst case risk might be using the available data "if" the agent in question is, in fact, a human carcinogen. Assumptions are used to override uncertainties in development such estimates.

**SUMMARY OF RISK ESTIMATES FOR METHYL TERTIARY BUTYL ETHER (MTBE)
BASED ON MOUSE LIVER TUMORS**

inhalation unit risk: 2E-7 per ug/cu.m. (5E-4 per mg/kg/d)

extrapolation method: linearized multistage (GLOBAL86)

ED10: 500 mg/kg/d (2E+6 ug/cu.m.)

DOSE-RESPONSE DATA

tumor type: hepatocellular adenoma and/or carcinoma

test animal: CD-1 mouse

route: inhalation

reference: Bushy Run Research Center Report 91N0013A

female

administered <u>exposure (ppm)</u>	human equivalent <u>exposure (ppm)</u>	<u>tumor incidence</u>		
		<u>adenoma</u>	<u>carcinoma</u>	<u>combined</u>
0	0	2/50	0/50	2/50
400	70	1/50	1/50	2/50
3000	540	2/50	0/50	2/50
8000	1430	10/50	1/50	11/50

male

administered <u>exposure (ppm)</u>	human equivalent <u>exposure (ppm)</u>	<u>tumor incidence</u>		
		<u>adenoma</u>	<u>carcinoma</u>	<u>combined</u>
0	0	11/47	2/42	12/47
400	70	11/47	4/45	12/47
3000	540	9/46	3/41	12/46
8000	1430	12/37	8/34	16/37

COMMENTS

1. The unit risk is considered to be a plausible upper bound on the increased cancer risk from lifetime inhalation of MTBE.
2. Due to increased early mortality in the male mice, the denominators in the male mouse tumor incidences were corrected to include only those animals alive at the time of the first observed tumor, week 49 for adenomas and week 63 for carcinomas.
3. The inhalation unit risk estimate of $2E-7$ per ug/cu.m. reflects an averaging of the unit risk based on the combined tumor incidence in the females ($3.4E-4$ per ppm) and the unit risk based on the combined tumor incidence in the males ($7.7E-4$ per ppm), i.e. $5.5E-4$ per ppm, and a conversion of units from ppm to ug/cu.m.
4. These tumor incidences are from an 18-month study. The unit risk estimate was adjusted to reflect a full lifetime (24 months). The lifetime adjustment is less than a factor of 3.
5. The human equivalent exposures were calculated by adjusting for exposure 6 hours/day, 5 days/week, assuming ppm equivalence between species for exposure (i.e., scaling for respiration and metabolism are assumed to cancel out).
6. If the unit risk were estimated from only the hepatocellular carcinomas in male mice, the estimate would decrease by less than a factor of 2.
7. Anesthetic effects were observed in the mice at the 3000 and 8000 ppm exposure levels of this ether. Such a response would imply a decreased inhalation rate, and consequently a decreased dose. Without the necessary data to correct for this effect, the potency (unit risk) is underestimated by an unknown amount.
8. To compare the potency of a carcinogen with that of other carcinogens, the Agency has sometimes used "benchmark" methods, specifically, the effective dose associated with an increased cancer risk of 10 percent (the cancer ED10 benchmark). This method is used for ranking because comparisons can be based on estimates that are (1) within the range of experimental observation, (2) compatible with different dose-response models, and (3) central estimates rather than statistical bounds.

For MTBE, the cancer ED10 benchmark is 500 mg/kg/d, estimated by averaging ED10 benchmarks from the two data sets used for estimating the cancer unit risk. For comparison, cancer ED10 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).

Benchmark methods can also provide an integrated approach for cancer and noncancer risk assessment. As noncancer benchmarks for MTBE become available, they can be compared with the cancer ED10 benchmark of 500 mg/kg/d.

INHALATION RISK ESTIMATE FOR METHYL TERTIARY BUTYL ETHER (MTBE) BASED ON MALE RAT KIDNEY TUMORS

inhalation unit risk: $5E-6$ per ug/cu.m. ($2E-2$ per mg/kg/d)

extrapolation method: one-stage Weibul time-to-tumor model
(TOX_RISK)

ED10: 20 mg/kg/d ($8E+4$ ug/cu.m.)

DOSE-RESPONSE DATA

tumor type: renal tubular cell adenomas and carcinomas
test animal: F344 male rat
route: inhalation
reference: Bushy Run Research Center Report 91N0013B

<u>administered</u> <u>exposure (ppm)</u>	<u>human equivalent</u> <u>exposure (ppm)</u>	<u>tumor incidence</u>
0	0	1/50
400	70	0/50
3000	540	8/50
8000	1430	3/50

COMMENTS

1. The unit risk is considered to be a plausible upper bound on the increased cancer risk from lifetime inhalation of MTBE.
2. A time-to-tumor model was used to take into account increased early mortality (attributed to chronic progressive nephropathy) in the mid- and high-dose groups.
3. The human equivalent exposures were calculated by adjusting the exposure 6 hours/day, 5 days/week, assuming ppm equivalence between species for exposure.
4. Anesthetic effects were observed in the rats at the 3000 and 8000 ppm exposure levels of this ether. Such a response would imply a decreased inhalation rate, and consequently a decreased dose. Without the necessary data to correct for this effect, the potency (unit risk) is underestimated by an unknown amount.