Gasoline Additives and Public Health

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1. INTRODUCTION TO GASOLINE ADDITIVES

Since 1979, oxygenates as gasoline additives have been used in limited areas of the United States as octane enhancers to replace lead at levels around 2 to 8% by volume. During the 1980s, oxygenates came into wider use as some states implemented oxygenated gasoline programs for the control of carbon monoxide air pollution in cold winter. Oxygenates were added to conventional gasoline nationally at higher percentages with the passage of the 1990 Clean Air Act (CAA), which required that oxygenates be added either seasonally (15% MTBE by volume) or year-round (11% MTBE by volume) to gasoline in specific parts of the country where carbon monoxide in the winter or concentrations of ozone in the summer exceed their respective National Ambient Air Quality Standards (NAAQS). Title II of the 1990 CAA addresses mobile sources and mandates the following two types of oxygenated fuel programs:

- Section 211 (m) of the CAAA of 1990 directed the EPA to mandate that states establish a wintertime oxygenated fuel program in 42 geographic areas designated as moderate or serious CO nonattainment areas (i.e., areas with CO concentrations exceeding the CO NAAQS) by November 1, 1992. The oxygenated fuel program was mandated during the winter months of November through February based on the fact that gasoline combustion is less efficient at colder temperatures, resulting in increased CO emissions, and that pollutants stay closer to ground level in winter. During these months, the oxygen content requirement for gasoline sold in the designated areas is a minimum of 2.7 percent.
- Title II of the 1990 CAA under Section 211(k) specified that only reformulated gasoline (*RFG*) with a 2% oxygen weight requirement can be sold in metropolitan areas with populations more than 250,000, classified as extreme or severe for ozone pollution. These included Los Angeles, New York, Baltimore, Chicago, Milwaukee, Houston, San Diego, Sacramento, Philadelphia, and Hartford. Less-polluted nonattainment areas for ozone opted to implement the RFG program since its initiation in January 1995. During Phase I of the RFG program, refiners were required to reduce vehicle emissions of ozone-forming volatile organic compounds (VOCs) and air toxics by 15 to 17% annually, compared to 1990 baseline averages. The benzene and the aromatic content of RFG could not exceed 1.0% and 25% by volume, respectively. Nitrogen oxides (NO_x) emissions were not allowed to increase relative to conventional "baseline" gasoline. During Phase II, a 25 to 29% reduction in VOC was required, as well as a 20 to 22% reduction in air toxics and a 5 to 7% reduction in NO_x emissions from the 1990 baseline.

Among the available oxygenates in the marketplace, methyl tertiary butyl ether (MTBE) is the most widely used because of its low vapor pressure, compatibility with the blending and distribution system for gasoline, high octane rating, availability and ease of production, and low cost. MTBE had the second highest volume of all chemicals produced in the United States in 1997.

On the other hand, ethanol is the predominant oxygenate used in gasoline in some areas, particularly in the Midwest. Other fuel oxygenates that are in use or may potentially be used to meet the 1990 CAA oxygenated fuel requirements include ethyl tertiary butyl ether (ETBE), tertiary-amyl methyl ether (TAME), diisopropyl ether (DIPE), tertiary-butyl alcohol (TBA), and methanol. This article assesses the human health effects of MTBE, ETBE, TAME, DIPE, and ethanol based on potential for exposure to these compounds as a result of using oxygenates in the U.S. gasoline supply. The priority is given to human studies in analyzing health effects information related to each of these compounds in gasoline.

In the 1992–1993 CO season, MTBE-blended gasoline accounted for approximately two-thirds of the demand, with ethanol providing the remainder. According to the EPA, ethanol is the predominant oxygenate used in the oxyfuel program (about 7.5% and 15% by volume for ethanol and MTBE, respectively) to meet the 2.7% by weight oxygen requirement. On the other hand, MTBE at 11% by volume is the primary oxygenate used in RFG to meet the 2% by weight oxygen requirement. The EPA's Office of Mobile Sources estimated in 1994 that approximately 30 million people live in areas using wintertime oxygenated gasolines and about 45 million live in high ozone RFG areas. Later estimates by SRA Technologies suggest that 70 and 57 million people live in areas using oxyfuel and RFG, respectively. It is also reported that about 109 million Americans live in counties where MTBE is used as oxygenate in gasoline. There is some overlap between the areas implementing the winter oxyfuel program and the areas implementing the year-round RFG program. Estimated oxygenated volume consumed in RFG areas in the United States is 237 (MTBE), 0.3 (ETBE), 14.6 (TAME), and 24.2 (ethanol) thousand barrels per calendar day. These estimates suggest that a large fraction of the U.S. population may get exposed to oxygenates on a daily basis.

2. *HUMAN HEALTH EFFECTS OF METHYL TERTIARY-BUTYL ETHER (MTBE)*

Acute health symptoms attributed to methyl tert-butyl ether (MTBE) were reported in various parts of the United States soon after the addition of oxygenated compounds to gasoline during the winter of 1992–1993. Such complaints were not anticipated but have subsequently focused attention on possible health risks due to oxygenated gasoline. The health complaints were accompanied by complaints about reduced fuel economy and engine performance and by controversial cancer findings in long-term animal studies.

2.1 Epidemiological Evidence for Air Exposures

Following the introduction of MTBE-oxygenated gasoline in Fairbanks, Alaska, in November 1992, about 200 residents reported headaches, dizziness, irritated eyes, burning of the nose and throat, coughing, disorientation, nausea, and other acute health symptoms. The Alaska Department of Health and Social Services and the Center for Disease Control (CDC) conducted a number of field epidemiology studies to investigate the potential relationship between MTBE oxyfuel exposure and acute health symptom responses. A two-phase study was performed in Fairbanks, with Phase I occurring while MTBE-oxyfuel was in use and Phase II occurring 6 weeks after MTBE-oxyfuel use had been terminated. In this study, the relationship between MTBE oxyfuel exposure and blood levels of MTBE and a major metabolite of MTBE, tertiary butyl alcohol (TBA), was also investigated. The occupational and non-occupational exposure groups answered a questionnaire inquiring about the presence of certain symptoms, including the seven key complaints of headache, eye irritation, burning of nose/throat, cough, nausea, dizziness, and spaciness. Occupationally exposed individuals reported a greater prevalence of health complaints during Phase I compared to Phase II. Overall, the CDC's analysis of Fairbanks data showed that there was a statistically significant difference between the number of cases among the individuals who were exposed to higher concentration of MTBE (e.g., taxi drivers) compared to people exposed to lower exposure levels (e.g., students). The CDC cautioned that the results did not provide definitive evidence that the use of MTBE oxyfuels caused the reported symptoms due to potential confounding factors (e.g., negative publicity about MTBE-oxyfuel effects, small sample size, strong odor associated with MTBE, and lack of controls) and called for further research to determine whether there actually is an increase in acute health symptoms and, if so, whether they are causally associated with MTBE-oxyfuel. However, the governor of Alaska suspended the program in Fairbanks within 2 months of the introduction of oxyfuel and a switch from MTBE-oxyfuel to ethanol-oxyfuel occurred in following years.

A desire to conduct a study similar to the Fairbanks study in the absence of confounding factors observed in Alaska (especially negative publicity) led to a field study in another part of the country. The CDC compared the prevalence of acute health symptom reports in Stamford, Connecticut, in April 1993 (where MTBE-oxyfuel was used) and Albany, New York, in May 1993 (with no oxyfuels). There were no known consumer health complaints in either location. For the Stamford study, CDC in cooperation with the State of Connecticut Health Department selected 221 individuals from four groups of workers and administered a questionnaire similar to that used in Fairbanks. The CDC reported that the 11 individuals with the highest blood MTBE levels were statistically significantly more likely to report one or more key symptoms than the other 33 people with lower blood levels. However, there was no apparent relationship between symptom prevalence by occupational category and the median blood MTBE or the TBA concentrations associated with each category. CDC again cautioned that the small numbers of subjects studied, the wide range of blood MTBE and TBA levels within each category, and the wide variability of response prevented a definitive conclusion. For the Albany study, 264 individuals were nonrandomly selected and categorized into three groups presumed to have tiered levels of exposure. Overall, the results indicated that the Albany residents with no MTBE-oxyfuel exposure had symptom prevalence as high as those in Stamford residents with MTBE-oxyfuel exposure. It was suggested that this outcome could potentially be attributed to the high prevalence of symptoms due to allergies and viruses at the time of the study in Albany.

In New Jersey, the EOHSI evaluated 237 state-employed garage workers from two groups in 1993: (1) 115 northern New Jersey workers sampled during the wintertime oxyfuel program and (2) 122 southern New Jersey workers sampled 10 weeks after the phase-out of the program in that area. All participants were asked to complete questionnaires about symptoms and their severity over the previous 30 days and about preshift and postshift symptoms. Essentially no differences in symptom reports were found between the northern (high-exposure) and southern (low-exposure) groups. In a separate study, 11 workers who pumped MTBE-oxyfuel for more than 5 hours per day were matched with 11 workers from the south who had low or nondetectable exposures to MTBE. No differences in symptom prevalence were found between the groups.

Another EOHSI study attempted to identify a sensitive subpopulation for the effects of MTBE-oxyfuel exposure. This involved 13 subjects with multiple chemical sensitivities (MCS), five subjects with chronic fatigue syndrome (CFS), and six healthy controls. Through a symptom questionnaire, these subjects were asked to assess symptoms associated with situations in which they could be exposed to MTBE such as refueling and driving. On a total symptom score range of 0 (no discomfort) to 28 (severe discomfort), the MCS subjects scored 5.3, compared to 4.8 for the CFS subjects and 1.2 for the healthy subjects. It was not possible to draw any definitive conclusions from this study due to (1) lack of evidence to support that an unusually high rate of symptoms or an increase of symptoms was occurring uniquely where MTBE was most prevalent, (2) small sample sizes, and (3) inability to distinguish between those subjects using and not using MTBE oxyfuel.

In response to variety of health concerns of Milwaukee citizens after the beginning of the RFG program in January 1995, the state of Wisconsin conducted a random-digit-dial telephone survey of 500 residents of the Milwaukee metropolitan area and equal numbers of residents in Chicago and in non-RFG areas of Wisconsin. In Milwaukee, oxygenates in the RFG samples were 49% MTBE, 38% ethanol, and 14% ETBE. Symptom prevalence was significantly higher in Milwaukee than in either Chicago or elsewhere in Wisconsin (23% compared to 6%). In Milwaukee, persons were more likely to report symptoms if they had experienced a cold or flu, smoked cigarettes, or were aware that they had purchased RFG. Because overall symptom prevalence was essentially equivalent in Chicago and non-RFG areas of Wisconsin, the authors concluded that factors other than RFG use such as an increase in price of gasoline, odors of MTBE, and negative media coverage significantly contributed to the differences in symptom prevalence between Milwaukee and the other two areas. However, due to study design limitations, the study could not "rule out subtle effects of RFG exposure, or the possibility that a relatively small number of individuals may have a greater sensitivity to RFG mixtures."

Hakkola and his coworkers investigated neurological effects reported by 101 Finnish male tank drivers with exposure to gasoline containing 10%

MTBE. Drivers with longer exposure scored higher for fatigue and hostility changes as compared to drivers with shorter exposure. In addition, 20% of drivers reported the following symptoms in the order of decreasing frequency: headache, nausea, increased salvation, dizziness, and dyspnea.

2.2 Controlled Human Inhalation Exposure Chamber Studies

Assessment of humans exposed directly in a chamber to MTBE was hoped to answer whether there was a direct causal relation between MTBE exposure and acute health symptoms, particularly in view of the inconclusive evidence gathered from the field epidemiology studies. In an EPA investigation, 37 healthy nonsmoking individuals were exposed for 1 h to both clean air and 1.4 ppm (5 mg/m^3) "pure" MTBE in air at 75° F and 40% humidity. The endpoints selected, based on observations from Alaska, were the types of symptoms associated with organic solvent exposure: (1) nonspecific symptoms including headache, nasal irritation, throat irritation, cough, eye irritation, odor quality, and dizziness; (2) measures of behavioral response (neurobehavioral evaluation system test battery); (3) indicators of upper airways inflammation (nasal lavage); and (4) indicators of eye irritation. The study found that MTBE exposure had no statistically significant effects on any of the endpoints. Yale University researchers replicated the EPA study, with few minor modifications—that is, 43 subjects, slightly higher MTBE concentration of 1.7 ppm (6 mg/m^3), and an additional experiment involving a 1-h exposure to a complex mixture of 16 VOCs commonly found in gasoline at a concentration of 7.1 ppm without MTBE. Similar to the EPA study, it was found that MTBE exposure had no statistically significant effects on any of the endpoints studied as compared to clean air exposure. The VOC exposure caused an increase in inflammatory cells in the nasal lavage on the day following exposure when the VOC exposure compared to clean air exposure. Taken together, the EPA and Yale investigations showed that controlled exposure of a small number of healthy humans to MTBE in air under the conditions studied did not cause increased symptoms or measurable responses. Exposure concentrations utilized in these controlled exposure studies (1.4 and 1.7 ppm) did not represent the worst-case exposure conditions based on measurements from the customer breathing zone samples taken in air during refueling (median exposure range: 0.3 to 6 ppm, occasionally higher). Nor were subjects chosen who were seemingly susceptible to MTBE based on their complaints.

Another controlled exposure chamber study exposed normal subjects to much higher concentrations of MTBE (5, 15, and 25 ppm compared to 1.4 and 1.7 ppm) and a longer exposure duration (2 hours) than the EPA or the Yale study (1 hour). This study did not include neurobehavioral assessments. No effects associated with MTBE exposure were identified. In a separate study, 13 healthy male subjects were exposed to 25 and 75 ppm MTBE in air in an exposure chamber. Subjects with 75 ppm exposure developed irritation of mucous membranes and nonspecific symptoms indicative of effects on mood.

A controlled exposure study was conducted at the EOHSI to investigate the symptoms, psychophysiologic and neurobehavioral effects of exposure to the MTBE. The exposures were conducted at concentrations similar to those found while refueling a vehicle using both control subjects and those individuals self-described as sensitive to MTBE. In the double-blinded repeated-measures controlled exposure study, subjects were exposed for 15 min each to clean air, gasoline alone, gasoline with 11% MTBE, and gasoline with 15% MTBE. Relative to the control group ($n = 19$), sensitive individuals ($n = 12$) reported significantly more total symptoms only when exposed to gasoline with 15% MTBE and not to gasoline with 11% MTBE or clean air. However, the sensitive group did not exhibit significant differences in psychophysiologic responses from the control group at any exposure level. This study did not identify a dose-response relationship for MTBE exposure and symptoms were specific to MTBE. The EOHSI research group also studies the driving habits and vehicle maintenance patterns of these two study groups. Results showed that the individuals who had self-reported heightened sensitivity to oxygenated gasoline vapors drove their vehicles more often and fueled their vehicles more frequently than the control group. In addition, sensitive individuals more frequently drove their vehicles with compromised body integrity that could lead to higher exposures.

2.3 Health Effects Associated with Oral Exposure to MTBE

In the mid-1990s, the focus on MTBE began to shift from questions about air quality-related health risks and benefits to questions about water quality risks. The change was triggered by a number of factors including the USGS studies demonstrating contamination of the nation's water supply with MTBE, and discovery of underground storage tank (UST) leaks resulting in high concentrations of MTBE in water causing the closure of drinking water wells in Santa Monica, South Tahoe, and San Jose, California. The emergence of widespread reports of MTBE-impacted drinking water resources in other states (e.g., New Jersey, Maine, Vermont, New York, Virginia) heightened interest in protection of water resources from MTBE. The presence of MTBE in ground water and in reservoirs used for drinking water in other parts of the country is now relatively widespread.

Faced with an acute potential public health problem and degradation of water quality (e.g., strong odor and taste associated with MTBE) resulting in loss of water supplies for consumer consumption, the California legislature enacted a number of bills calling to address issues pertaining to oxygenates including risks and benefits to human health and the environment of MTBE and its combustion byproducts in air, water, and soil and alternate oxygenates like ethanol and ETBE. In response to these legislative bills, the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency proposed a Public Health Goal (PHG) of 14 ppb for MTBE in drinking water in June 1998 to protect consumers against health risks over a lifetime of exposure. The proposed PHG for MTBE was based on carcinogenic potency of 1.7×10^{-3} (mg/kg-day)$^{-1}$, which is the geometric mean of the cancer slope factor estimates obtained from three cancer sites: combined male rat kidney adenomas and carcinomas in the 1992 inhalation study of Chun *et al.*, the male rat Leydig cell tumors and the leukemia, and lymphomas in female rats in the 1995 oral study by Belpoggi *et al.* In July 1998, the Department of Health Services (DHS) adopted a secondary maximum contaminant level (SMCL) for MTBE of 5 ppb based on available data on odor and taste thresholds. Another product was a University of California (UC) report on "Health and Environmental Effects of MTBE," submitted to the governor and legislature of the state of California on November 12, 1998. The UC report states "For the general population, the risk of exposure to MTBE through ingestion of MTBE-contaminated water is currently low." However, because MTBE is highly soluble in water, poorly adsorbs to soil, readily transfers to groundwater from LUSTs, and pipelines, travels much further than plumes commonly associated with gasoline spills, and is highly resistant to biodegradation, the report concluded that "There are significant risks and costs associated with water contamination due to the use of MTBE." Most importantly, the UC scientists recommended phasing out MTBE over an interval of several years instead of an immediate ban. Based on significant risk to California's environment associated with the continued use of MTBE in gasoline, Governor Davis, on March 25, 1999, directed appropriate state regulatory agencies to devise and carry out a plan to begin immediate phase out of MTBE from California gasoline, with 100% removal achieved no later than December 31, 2002.

Faced with another MTBE problem, in 1996, the EPA began working on revising the 1992 drinking water lifetime health advisory for MTBE of 20–200 ppb to meet the needs of states that were struggling to endorse safe levels that ensure both consumer acceptability of MTBE-laden drinking water and public health protection against potential adverse health effects of ingested MTBE. Meanwhile, in the absence of enforceable federal drinking water standards, individual states began to adopt action levels or cleanup levels for MTBE in water. In December 1997, the EPA's Office of Water published "Drinking Water Advisory: Consumer Acceptability Advise and Health Effects Analysis on Methyl Tertiary-Butyl Ether (MTBE)." The advisory recommended that keeping MTBE levels in the range of 20 to 40 ppb or below to protect consumer acceptance of the water resource would also provide a large margin of safety from potential adverse health effects. The EPA could not develop a RfD for MTBE due to the persisting limitations of health effects data (e.g., lack of a pharmacokinetic model for converting inhalation exposure data for MTBE to oral exposure, limited reported pathology and historical tumor incidence, no toxicity studies with oral exposure to water). A blue-ribbon panel convened by the United States Environmental Protection Agency (EPA) recommended that Congress should act to provide clear federal and state authority to regulate or eliminate the use of MTBE and other gasoline additives that threaten drinking water supplies.

2.4 Carcinogenic Effects of MTBE

There are no human data on which carcinogenicity of MTBE can be evaluated. However, the evidence from chronic exposure by inhalation and oral exposure routes demonstrate that MTBE is carcinogenic in rats and mice. Two chronic animal cancer bioassays with inhalation exposure to MTBE resulted in rare kidney tumors and testicular tumors in the mid- and high-dose groups of male rates, and liver tumors in mice at the high-dose group. Sprague-Dawley rats exposed to MTBE in olive oil as the vehicle for oral gavage for 2 years showed dose-related increases in lymphomas and leukemias in females and in interstitial cell tumors of the testes in males. The biological mechanism responsible for MTBE cancer production in animals is not known. The lack of mechanistic information limits our ability to determine whether the MTBE bioassay results are relevant to humans. In 1998, IARC found insufficient evidence to establish that MTBE poses cancer risks to humans. The EPA has also concluded that potential for MTBE's carcinogenicity for humans is of concern and requires further study.

3. HUMAN HEALTH EFFECTS OF OTHER ETHER COMPOUNDS

The other aliphatic ethers, ethyl tertiary butyl ether (ETBE), tertiary amyl methyl ether (TAME), and diisopropyl ether (DIPE) are proposed as potential alternatives to MTBE as an oxygenate in gasoline. In particular, TAME was considered to be an attractive alternative due to its lower vapor pressure as compared to MTBE despite its lower octane content. These compounds are being used in varying percentages in gasoline in the United States (e.g., 19.90% TAME in Sussex County, Delaware, 1.6% TAME in San Diego, California, in 1999).

Although a number of toxicity studies in animal models for other ether oxygenates of ethyl tertiary butyl ether (ETBE), tertiary amyl methyl ether (TAME), and diisopropyl ether have been conducted and published, human relevance of these findings is not known. There appears to be qualitative similarities to the MTBE health effects, with kidney and liver being the most sensitive target organs. Biotransformation and pharmacokinetics of these compounds in animals and human volunteers have been studied except DIPE. A summary of animal studies and pharmacokinetic studies in animals and humans can be found in Ahmed's 2001 research.

The EPA has not been able to establish any quantitative cancer potency factor or noncancer toxicity values (i.e., reference dose [RfD] or reference concentration [RfC]) to date due to inability to establish dose-response relationships from the animal data in a scientifically defensible manner. To fill this data gap, the EPA mandated the manufacturers to perform toxicity testing of evaporative emissions of these compounds under the CAA Section 211(b) by 2004. The EPA also called for "comprehensive evaluation of multimedia, life-cycle environmental impacts" of different fuels to assess viability of TAME, ETBE, and DIPE to be a safe replacement for ethanol or MTBE. A number of scientific bodies convened to evaluate health effects of oxygenated gasolines more than two decades also repeatedly called for more research into understanding the health effects of these compounds alone and in combination with gasoline. The California DHS proposed to add ETBE and TAME to the list of unregulated chemicals for which monitoring is required by public water systems.

4. HUMAN HEALTH EFFECTS OF ETHANOL

Ethanol used as oxygenate in gasoline is produced from grains or other renewable agricultural and forestry feedstocks. The U.S. Congress has approved a 5.4 cents/gallon federal subsidy for this biomass-based source of fuel in nations' gasoline supply. Ethanol production in 2000 was 1.5 billion gallons. Approximately 30% of this amount is used in RFG during the summer in ozone nonattainment areas. About 20% is used in the winter oxygenate program to control CO air pollution. The remainder 50% is used in conventional gasoline in the United States to enhance octane and extend fuel supplies. Ethanol is highly volatile when spilled; it will evaporate five times faster than MTBE. However, it is commonly used in many modern day products including pharmaceuticals, mouthwash products, alcoholic beverages, and cleaning products. Because humans frequently ingest fermented beverages containing 12% ethanol by volume, ingestion-related health effects of ethanol are well known. The Health Effects Institute (HEI) in its assessment of health effects of oxygenates stated that our knowledge on health effects of ethanol emanates from ingestion exposures. Ethanol was shown to be associated with increased rates of tumors of digestive track with oral exposure to moderate levels of alcohol when other carcinogens were present. Ethanol is classified as a Class I carcinogen by IARC based on human data for alcoholic beverage consumption. There is no data of such association for inhalation exposures. However, ethanol, when blended in gasoline increases volatility of other compounds, results in an increase in evaporative emissions of VOCs, including benzene. Many of these VOCs are known or suspected carcinogens and also have adverse health effects associated with noncancer health endpoints. Ethanol exposure is also associated with cancers in the liver, esophagus, oral cavity, pharynx, and larynx. There have been reports of adverse reproductive and developmental effects of associated with exposure to ethanol in animal and human studies. Irvine analyzed the relevance of the developmental toxicity of ethanol in occupational settings and concluded that while developmental toxicity may result from drinking alcoholic beverages for which threshold levels have yet to be determined there was no evidence for developmental toxicity in occupational environment.

With the executive order to phase out of MTBE in gasoline distributed in California by December 31, 2002, Governor Davis also directed CARB and the State Water Resources Board to conduct an environmental fate and transport analysis of ethanol in air, surface water, and groundwater and the OEHHA to prepare an analysis of health risks associated with exposure to ethanol in gasoline. In terms of air quality effects, the substitution of ethanol for MTBE in CA's fuel supply was found to have not significantly impact air quality as long as RFG regulation in CA addressed the potential for ethanol to increase evaporative emissions and to cause more rail and truck traffic to bring ethanol to the state. The CA analysis found no substantial differences in the air-related public health impacts of different non-MTBE fuel formulations including ethanol. Although the replacement of MTBE by ethanol is expected to have some benefits in terms of water contamination due to ethanol's relative toxicity and rapid biodegradation, these could not be quantified. The overall estimated health risks for exposure scenarios with ethanol, MTBE, and nonoxygenated fuel did not differ between fuel formulations, but showed a significant improvement for 2003 in comparison to 1997.

The Northeast States for Coordinated Air Use Management (NESCAUM) also prepared an analysis in response to potential phase-out of MTBE in Northeast States due to adverse water quality impacts of MTBE and the need to protect environmental resources. The NESCAUM estimated that the use of ethanol instead of MTBE would increase emission rates of acetaldehyde, a combustion by-product, into the atmosphere in the Northeast by 50 to 70%. Acetaldehyde is also a probable human carcinogen. Ambient levels of acetaldehyde in the Northeast exceed the health-protective levels of acetaldehyde at majority of the air monitoring locations throughout the northeastern states. NESCAUM estimates that ethanol at 10% by volume in conventional gasoline would increase the VOC emissions significantly. Therefore, NESCAUM stressed the importance of studying health effects of ethanol alone, in combination with gasoline, but importantly, its lifecycle, its degradation products, and concurrent VOC emission increases. Schifter *et al.* also estimated an increase of about 80% in acetaldehyde emissions with 6% by volume ethanol as a substitution for 5% by volume MTBE accompanied by 16% decrease in CO and a 28% decrease in formaldehyde motor vehicle emissions in Mexico City. However, according to the CARB analysis on impact of use of ethanol-containing gasoline on air quality in Denver, Colorado, Albuquerque, New Mexico, Brazil, and other areas, acetaldehyde levels were substantial only in Brazil, where the fuels contained either pure ethanol or 22% ethanol, much greater than the maximum 10% ethanol allowed in CA gasolines.

There are no EPA toxicity values established for cancer (cancer slope factor) or noncancer (RfD or RfC) health endpoints for ethanol. There is also no safe drinking water standard for ethanol. The lack of toxicity values for ethanol for various exposure routes and lack of exposure information in various exposure media do not enable us to quantitatively estimate health risks associated with exposure to ethanol under different exposure conditions for public exposed to ethanol due to its circulation in the environment related to its widespread use in gasoline. Such analysis should not only include ethanol, but also all environmental degradation products of ethanol, and health risks and benefits analysis focusing on multimedia exposures is essential for not repeating the history of MTBE episode.

5. CONCLUSIONS AND RECOMMENDATIONS

There have been significant air quality benefits since the implementation of the oxygenated fuels program. Although some of the improvement in air quality indices may be simply due to fleet turnover, increase in fuel efficiency over time, and improvements in vehicle testing and maintenance programs, the oxygenates have also been credited for air quality benefits. For example, 10 to 14% reduction in ambient CO concentrations has been attributed to use of oxygenated in winter months in CO non-attainment areas. Although the National Research Council concluded that little air quality impact in terms of ozone reduction can be gained from the use of oxygenates in RFG, the EPA's blue ribbon panel acknowledged major reductions in VOCs, especially, some of the carcinogenic air toxics (e.g., benzene, 1,3-butadiene) in many urban environments where RFG is used during the summer months. However, health complaints associated with exposure to MTBE containing gasoline and discovery of degradation in water quality in national scale with contamination of groundwater, surface water, and drinking water resources with MTBE overshadowed the potential air quality benefits and associated air-quality-related health benefits in the decade since the enactment of the oxygenated fuel programs by the Congress. The course of the national debate on oxygenates has shifted to potential alternatives to MTBE. We know more about the potential human health effects associated with exposure to MTBE alone or in combination with gasoline than about its potential substitutes. Quantitative assessment of the public health inhalation risks of MTBE-oxyfuel in comparison to conventional gasoline has been difficult, in part due to uncertainties and data deficiencies in toxicity combined with the paucity of the population-specific human exposure data. Although both short-term field epidemiological studies and a few controlled human laboratory studies of healthy adults provide a better understanding of human exposures to MTBE and MTBE-oxyfuel, the large differences in terms of confounding parameters, study design, exposure conditions, and exposure parameters greatly complicate the interpretation of the results of these few studies. Although more animal toxicity data for MTBE have become available and have increased our scientific understanding of the toxicity of MTBE (especially the pharmacokinetics of MTBE), there are insufficient data to answer questions about the relevance of these animal data to humans. Additionally, in the absence of oral toxicity studies, health effects of ingested MTBE cannot be determined. Although neither the epidemiological studies nor the controlled human exposure studies of normal and sensitive subjects have been, in majority, inconclusive, they cannot rule out the possibility that for a small percentage of the population, those claiming that they were affected by MTBE, there is a causal relationship between their exposure and their symptoms. In conclusion, the human health effects of MTBE are still unclear. For some other oxygenates, animal testing has not been thoroughly conducted and published yet. Any alternatives to MTBE, including TAME, ETBE, DIPE, and ethanol, should be studied with well-designed experiments to assess potential environmental and public health implications of using these compounds in large scale. This requires a substantial commitment and well-coordinated research effort by government and industry. The EPA scientists have evaluated retrospectively the governmental decision making with MTBE and concluded that

> *The most valuable lesson to be gained from the MTBE experience may be the importance of obtaining comprehensive understanding of the many and varied risks and benefits potentially offered by any given fuel option. This should entail a consideration of all facets of the life cycle of a fuel or additive, including the environmental fate of any emissions or releases, because the by-products of a chemical may be of greater toxicological or environmental significance than the parent compound itself.*

Given the fact that ethanol has increasingly gained oxygenate market share in the absence of such comprehensive evaluation should remind the EPA and the scientific community about the importance of critical findings gleaned through the MTBE experience.

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