AN ANALYSIS AND COMPARISON OF METHYL TERTIARY BUTYL ETHER'S (MTBE'S) USE AS A FUEL OXYGENATE AGAINST THE TENETS OF THE PRECAUTIONARY PRINCIPLE

by

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A Thesis: Essay of Distinction
Submitted in partial fulfillment
of the requirements for the degree
Master of Environmental Studies
The Evergreen State College
March 2011

This Thesis for the Master of Environmental Studies Degree

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ABSTRACT

An Analysis and Comparison of Methyl Tertiary Butyl Ether's (MTBE's) Use as a Fuel Oxygenate Against the Tenets of the Precautionary Principle

Diane R Fowler

Fuel oxygenates, such as methyl tertiary butyl ether (MTBE), are commonly added to gasoline to reduce air pollution by promoting more complete burning of fossil fuels in combustion engines. However, large-scale production and use of MTBE for this purpose has contaminated groundwater throughout the United States, primarily as a result of spills and leaking underground storage tanks. Shortly after MTBE's introduction as a fuel oxygenate, anecdotal reports of acute respiratory health symptoms surfaced, raising concerns about human health risks from exposure to inhaled MTBE during vehicle refueling and in occupational settings. The chemical structure and properties of MTBE suggest that its release into the environment would result in widespread groundwater contamination and that remediation might prove challenging. Once MTBE was discovered in groundwater, steps were taken to replace MTBE with another fuel oxygenate, even though there was uncertainty about MTBE's health impacts to humans or the environment.

There are at least two schools of thought governing how or if a chemical is introduced into the marketplace. The first, risk assessment, is the process of quantifying the probability a chemical will cause a harmful effect to individuals or populations. The other, the precautionary principle, states that with evidence of threats of significant harm, even in the face of scientific uncertainty, precautionary actions should be taken to protect public health. This thesis examines and compares the use of MTBE as a fuel oxygenate against the tenets of the precautionary principle. Variations in how precautionary principles are applied are described as strong, moderate, or weak.

After reviewing the scientific literature available for MTBE, I believe its use as a fuel oxygenate provides, at best, an example of the weak version of the precautionary principle. Although steps were taken to discontinue its use after it was found in groundwater, a strong version of the precautionary principle would have required proof of "no environmental harm" prior to MTBE's introduction as a fuel oxygenate.

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ACKNOWLEDGEMENTS

I would like to thank my family for their love, support, and patience while writing this thesis. It took longer than I ever could have imagined.

Specifically, I would like to thank my husband Chris for his encouragement, and even his concern, during the course of this work. It all helped to motivate me to finish this project. And to my two beautiful and amazing sons, Ian and Ryan, I love you more than you could ever know.

To Harry, Dorothy, and Dave McAbee – You are always in my thoughts. I hope you know how much you're missed.

And to my reader and advisor Maria Bastaki, I greatly appreciate your guidance, your willingness to share your toxicology expertise, and your encouragement to continue my writing in spite of obstacles. You might be almost as glad as I am to see this project completed.

CHAPTER 1 – INTRODUCTION AND BACKGROUND

INTRODUCTION

Fuel oxygenates, such as methyl tertiary butyl ether (MTBE), are commonly added to gasoline to reduce air pollution by promoting more complete burning of fossil fuels in combustion engines. However, large-scale production and use of MTBE for this purpose has contaminated groundwater throughout the United States, primarily as a result of spills and leaking underground storage tanks. This thesis examines and compares the use of MTBE as a fuel oxygenate against the tenets of the precautionary principle.

AIR POLLUTION AND THE CLEAN AIR ACT

Gasoline-fueled engines are a major source of carbon monoxide (CO), a colorless, odorless, and poisonous gas produced by the incomplete combustion of carbon-containing fuels (EPA, 2011a). Elevated levels of CO have been shown to be a human health hazard (National Science and Technology Council, 1997; EPA, 2011b). While motor vehicles built today emit fewer pollutants (60% to 80% less, depending on the pollutant) than those built in the 1960s, cars and trucks still account for almost half the emissions of the ozone precursors volatile organic compounds (VOCs) and nitrogen oxides (NOx), and up to 90% of the CO emissions in urban areas (EPA, 1970; EPA, 2011c).

The purpose of the Clean Air Act, originally passed by the United States Congress in 1963, is to reduce air pollution in order to protect the environment and human health. Under this law, the U.S. Environmental Protection Agency (EPA) set limits on certain air pollutants and implemented a variety of programs intended to reduce outdoor concentrations of air pollutants that cause smog, haze, acid rain, and other problems (EPA, 2008a). The law was also intended to reduce emissions of toxic air pollutants known to, or suspected of, causing cancer or other serious health effects; and to phase out production and use of chemicals that destroy stratospheric ozone (EPA, 2008a). These pollutants come from both stationary sources, such as chemical plants, and mobile sources, such as cars and planes. This federal legislation has undergone several amendments, most recently in 1990 (EPA, 1990). Three major threats specifically addressed in this latest amendment are acid rain, urban air pollution and toxic air emissions (EPA, 2008b). Two of these threats, urban air pollution and toxic air emissions, are addressed in part by the addition of fuel oxygenates to vehicle fuel.

The 1990 Clean Air Act Amendments (1990 CAAA) created two programs, administered by the EPA, requiring the use of fuel oxygenates (EPA, 1990). These provisions address the continuing problem of urban air pollution, particularly with regard to ozone (smog), carbon monoxide (CO) and particulate matter (PM-10), the major components of urban air pollution.

The first program, the Winter Oxyfuel Program, began in the fall of 1992 with the objective of reducing carbon monoxide emissions in several areas of the country where air pollutant monitoring demonstrated a persistent pattern of high CO levels during winter months (EPA, 2008c). (Note: Denver, Colorado implemented a winter oxyfuel program in 1988, prior to the 1990 CAAA.) During cold weather, temperature inversions tend to trap pollutants near the ground and inhibit dispersion. The buildup of CO is further aggravated in cold climates by longer engine idling times from cold vehicles (National Science and Technology Council, 1997). Under this program, the 1990 Clean Air Act Amendments required the sale of gasoline with an oxygen content of 2.7% by weight during the cold weather season in areas that failed to attain national ambient air quality standards (NAAQS) for carbon monoxide. Although the 1990 CAAA does not require the use of a specific fuel oxygenate, this level of oxygen is typically achieved by the addition of about 15% methyl tertiary butyl ether (MTBE) or about 7.5% ethanol (by volume) (National Science and Technology Council, 1997). Other fuel oxygenates that are used to a lesser extent or that may potentially be used include ethyl tertiary-butyl ether (ETBE), tertiary-amyl methyl ether (TAME), diisopropyl ether (DIPE), and tertiary-butyl alcohol (TBA). As shown in Table 1, twenty three states were required to implement the Winter Oxyfuel Program, but by January 2008 only six states had continued the program (EPA, 2008d). The number of states participating in the Winter Oxyfuel Program decreased over time as air quality improved. Once

wintertime air quality standards were met, the use of gasoline oxygenate was no longer required in these areas.

Table 1. States participating in the Winter Oxyfuel Program as of January, 2008

State	Winter Oxyfuel Program Required, 1992	Implementing Winter Oxyfuel Program, 2008
Alaska	✓	
Arizona	✓	✓
California	✓	✓
Colorado	✓	
Connecticut	✓	
District of Columbia	✓	
Maryland	✓	
Massachusetts	✓	
Minnesota	✓	
Montana	✓	✓
Nevada	✓	✓
New Jersey	✓	
New Mexico	✓	✓
New York	✓	
North Carolina	✓	
Ohio	✓	
Oregon	✓	
Pennsylvania	✓	
Tennessee	✓	
Texas	✓	✓
Utah	✓	
Virginia	✓	
Washington	✓	

Source: EPA, 2008d

The second program mandated by the 1990 Clean Air Act Amendments required year-round use of reformulated gasoline (RFG) containing a minimum of

2.0% oxygen by weight, beginning in 1995, in selected areas having the highest levels of tropospheric ozone. RFG is specially blended to have fewer polluting compounds than conventional gasoline. In addition to reducing emissions of ozone precursors, the RFG program was also intended to help reduce the emissions of certain toxic organic air pollutants. The RFG program was initially mandated in nine metropolitan areas with “severe” ozone problems (EPA, 2008d):

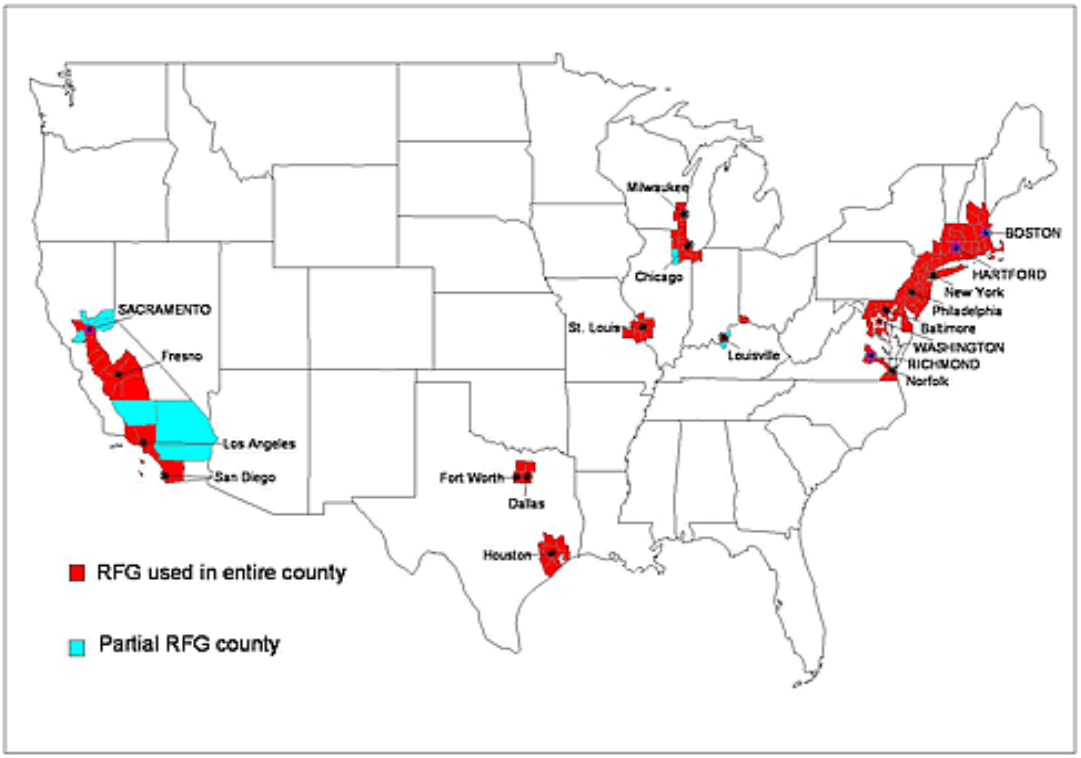
- Los Angeles and San Diego, California;
- Chicago, Illinois;
- Houston, Texas;
- Milwaukee, Ohio;
- Baltimore, Maryland;
- Philadelphia, Pennsylvania;
- Hartford, Connecticut; and
- New York City, New York.

Since then, five other areas have been classified with ‘severe' air quality (EPA, 2008d):

- Baton Rouge, Louisiana;
- Atlanta, Georgia;
- Sacramento and San Joaquin Valley, California; and
- Washington, DC.

The map below (Map 1) shows the counties of nineteen states and the District of Columbia that used RFG, either because of Clean Air Act requirements or on a voluntary basis to achieve air quality standards. Table 2 is similar, but shows greater detail about the voluntary or required use of RFG for each state.

Map 1. Areas of the United States requiring the use of reformulated gasoline (RFG) as of May 1, 2007



Source: EPA, 2008d

Table 2. Use of reformulated gasoline (RFG) in the United States as of May 1, 2007

State	Required (at least in certain areas) to use RFG under 1990 Clean Air Act Amendment	Opted to use RFG (voluntary use) (Some states required to use RFG in specified areas may also voluntarily use RFG in other areas.)
California	✓	
Connecticut	✓	✓
Delaware	✓	✓
District of Columbia	✓	
Georgia	✓	
Illinois	✓	✓
Indiana	✓	
Kentucky		✓
Louisiana	✓	
Maryland	✓	✓
Massachusetts		✓
Missouri		✓
New Hampshire		✓
New Jersey	✓	✓
New York	✓	✓
Pennsylvania	✓	
Rhode Island		✓
Texas	✓	✓
Virginia	✓	✓
Wisconsin	✓	

Source: EPA, 2008d

In the summer of 1996, about 11 percent of the RFG sold contained ethanol while virtually all the remainder contained MTBE (EPA, 1998a). By the late 1990s, MTBE contamination was shown to be widespread in groundwater throughout the United States (Squillace *et al.,* 1999). Concerns about the unknown health risks posed by drinking water containing MTBE prompted the Clinton administration in

2000 to ask the U.S. Congress to change a provision in the Clean Air Act that set the standard for oxygen content in reformulated gasoline. The intent of this provision was to eliminate or at least reduce the amount of MTBE in gasoline. By the summer of 2005, the ethanol share had increased to about 53 percent, with corresponding decreases in MTBE (EPA, 2008c).

In late 2005, the U.S. Congress passed the Energy Policy Act which amended the 1990 Clean Air Act Amendments to remove the oxygen content requirement and associated compliance requirements for reformulated gasoline (EPA, 2005). Although the requirement to use fuel oxygenates has been removed, many states continue to use oxygenates to meet air quality standards (EPA, 2008d). All states still using fuel oxygenates now use 100% ethanol.

EXTENT OF MTBE CONTAMINATION IN THE UNITED STATES

The presence of MTBE in groundwater has been observed at least since the mid-1980s. The 1990 Clean Air Act Amendments led to a rapid expansion in the production and use of MTBE starting in the late 1980s (ATSDR, 1996), and it has been used by refiners since the 1970s to increase octane when lead was banned for this use (McCarthy & Tiemann, 2006). The first national survey on the occurrence of volatile organic compounds (VOCs) analyzed samples of untreated ambient groundwater collected between 1985 and 1995 (Squillace *et al.,* 1999). It was noted that MTBE was one of the most frequently detected VOC in both urban and rural areas. Routine monitoring of ambient ground water between 1993 and 1998

noted the frequent occurrence of MTBE, typically at low levels, in shallow urban ground water in the northeastern United States (Grady, 2001). The occurrence of MTBE and other VOCs were also noted in surveys of community drinking water sources in the United States between 1999-2001 (Clawges *et al.,* 2001; Delzer & Ivahnenko, 2003).

More recently (2006), the U.S. Geologic Survey (USGS) National Water Quality Assessment (NAWQA) Program performed a national assessment of 55 VOCs in ground water to provide a general characterization of water-quality conditions in the United States (Zogorski *et al.,* 2006). The assessment of ground water included analyses of about 3,500 water samples collected between 1985 and 2001 from various types of wells. Samples were collected at the well head, before any treatment or blending, from 2,401 domestic wells and 1,096 public wells. Almost 20 percent of the water samples from aquifers contained one or more of the 55 VOCs, at a detection limit of 0.2 microgram per liter (µg/L). This detection frequency increased to slightly more than 50 percent for the subset of samples analyzed with a low-level analytical method and for which an order-of-magnitude lower assessment level (0.02 µg/L) was applied. The finding that most VOC concentrations in ground water are less than 1 µg/L is important because many previous monitoring programs did not use low-level analytical methods and therefore would not have detected such contamination. MTBE was the third most frequently detected VOC (behind chloroform and perchloroethene, see Table 3 for a complete list) and was found to have a regional or local occurrence pattern

(Zogorski *et al.,* 2006). The greatest detection frequency of MTBE was in areas: (1) with high population density; (2) where MTBE was used as an oxygenate in reformulated gasoline, and (3) with high rates of ground-water recharge, such as in the highly populated New England and Mid-Atlantic States. In general, MTBE did not occur frequently with other gasoline components in ground water except when detected at high concentrations. The detection of MTBE without other common gasoline hydrocarbons likely is the result of MTBE's higher solubility and greater persistence in ground water relative to common gasoline hydrocarbons. The study noted that the relatively frequent detections of MTBE in aquifers were not anticipated due its relatively short and recent use (a period of approximately 10 years at the time of this study) (Zogorski *et al.,* 2006).

Table 3. Most frequently detected volatile organic compounds (VOCs) in U.S. aquifer samples

(VOCs found in about one percent or more of aquifer samples, at an assessment level of 0.2 µg/L. Compounds are listed by decreasing detection frequency.)

Compound name	VOC group
Chloroform	trihalomethane
Perchloroethene	solvent
Methyl *tert*-butyl ether	**gasoline oxygenate**
Trichloroethene	solvent
Toluene	gasoline hydrocarbon
Dichlorodifluoromethane	refrigerant
1,1,1-Trichloroethane	solvent
Chloromethane	solvent
Bromodichloromethane	trihalomethane
Trichlorofluoromethane	refrigerant
Bromoform	trihalomethane
Dibromochloromethane	trihalomethane
trans-1,2-Dichloroethene	solvent
Methylene chloride	solvent
1,1-Dichloroethane	solvent

Source: Zogorski *et al.,* 2006

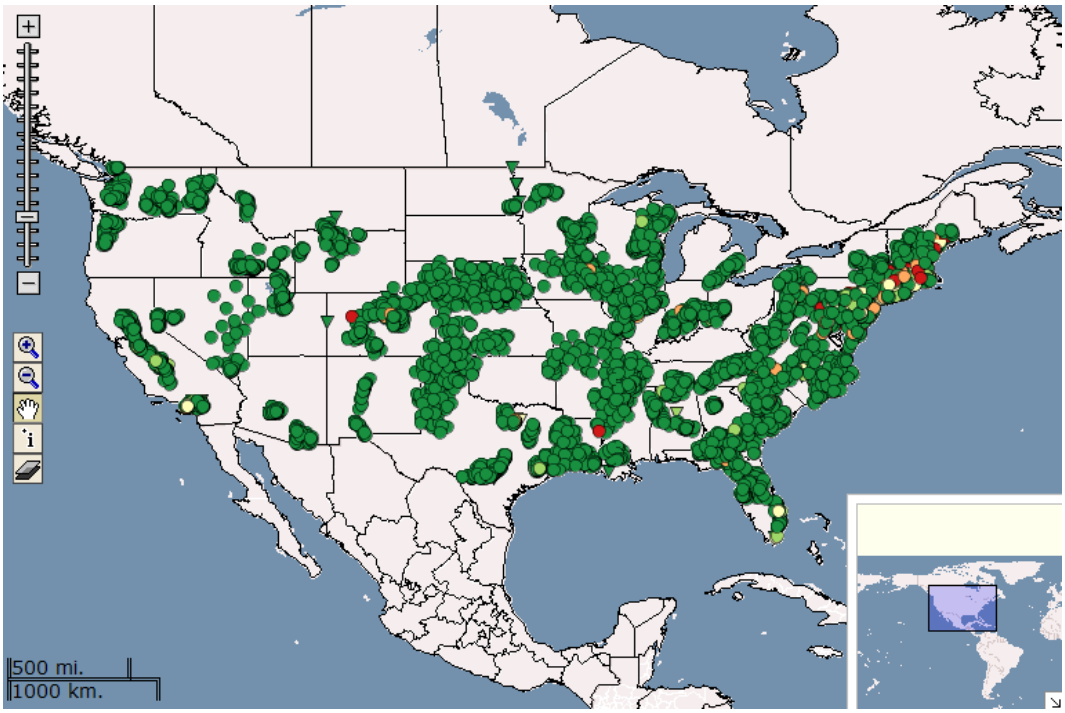
Because of known or suspected human-health concerns, the EPA has established Maximum Contaminant Levels (MCLs) that apply to 29 VOCs in drinking water supplied by public water systems. In addition, some States have set MCLs for additional VOCs and in some cases have established more stringent standards than EPA's values. To set an MCL for a contaminant, EPA first determines how much of the contaminant may be present with no adverse health effects. This level is called the Maximum Contaminant Level Goal (MCLG) and is basically a non-enforceable public health goal. The MCL is then set as close as possible to the MCLG standards and is the legally enforceable limit on the amount of a hazardous substance that

can be delivered to any user of a public water system (EPA, 2006). While the MCLG considers only public health, the MCL considers other factors, such as the use of best available technology, treatment techniques, and cost. The human-health consequences of exposure to VOCs in drinking water at concentrations less than MCLs are uncertain. Concentrations of MTBE were typically less than the lower limit of the EPA drinking-water consumer concentration range of 20-40 parts per billion, which is based on taste and odor thresholds. Only one drinking-water sample, which was from a domestic well, had a concentration of MTBE equal to the lower limit of the drinking-water consumer advisory. No Federal drinking-water standard (MCL) currently exists for MTBE. Health-based Screening Levels (HBSLs) have been calculated for unregulated contaminants (those with no MCLs) analyzed by the NAWQA Program. HBSLs are estimates of benchmark concentrations of contaminants in water that may be of potential human-health concern and are based on health effects alone. Although HBSLs have been calculated for 15 of the 26 unregulated VOCs in this assessment, they were not calculated for the remaining 11 VOCs, which include MTBE, due to a lack of toxicity information. The NAWQA Program also analyzed samples for three other gasoline oxygenates – tert-amyl methyl ether (TAME), diisopropyl ether (DIPE), and ethyl tert-butyl ether (ETBE). These VOCs were detected infrequently in samples from domestic and public wells (Zogorski *et al.,* 2006).

Although most detections of MTBE contamination are found in areas where MTBE has been used as a fuel oxygenate, it is not limited to these areas. The map

below (Map 2), created using the NAWQA Data Warehouse Mapper, shows areas of the United States where MTBE has been detected in groundwater samples between 1990 and 2009. Comparisons to the previous map of RFG areas illustrate MTBE contamination is found in areas where MTBE has not been used as a fuel oxygenate.

Map 2. MTBE detections in groundwater in the United States, 1990-2009



Source: USGS, 2009

Possibilities for how this contamination spread beyond the RFG-use areas include point sources such as leaking underground storage tanks, tank overflow spills, leaks from transport pipelines, vehicle accidents, and improper disposal. Potential nonpoint sources of MTBE include evaporative losses from tanks or pipelines, incomplete combustion in automotive engines, urban storm water runoff, exhaust from motorized watercraft, and leaks from watercraft tanks (Zogorski *et al.,*

2006). Since the contribution of leaking underground storage tanks, or LUSTs, towards MTBE contamination is likely substantial, it is worth exploring in greater detail.

LEAKING UNDERGROUND STORAGE TANKS

Leaking underground storage tanks (LUSTs) that contain gasoline are believed to be the primary source of localized releases of MTBE in high concentrations. The EPA defines an underground storage tank as "a tank (or a combination of tanks) and connected piping having at least 10 percent of their combined volume underground" (EPA, 2008e). Until the mid-1980s, most underground storage tanks (USTs) were made of bare steel, which is likely to corrode over time and allow UST contents to leak into the environment. Faulty installation or inadequate operating and maintenance procedures also can cause USTs to release their contents into the environment. According to the EPA, as of March 31, 2009, there were 616,613 active underground storage tanks (at approximately 235,000 sites) nationwide which are regulated by the UST technical regulations (EPA, 2009a).

In order to prevent leaks from occurring, all regulated tanks and piping are required by the EPA to have release detection (often called leak detection) so that leaks are discovered quickly before contamination spreads from the underground storage tank site. Leak detection methods include manual tank gauging (on tanks 2,000 gallons or less), automatic tank gauging systems, vapor monitoring, ground

water monitoring, and statistical inventory reconciliation (SIR). SIR uses computer software to conduct a statistical analysis of inventory, delivery, and dispensing data collected over a period of time to determine whether or not a tank system is leaking. Another method is secondary containment, which involves placing a barrier between the underground storage tank and the environment, such as a vault, liner, or outer wall of a double-walled structure.

Despite federal and state programs to improve handling of gasoline and other fuels in pipelines, underground and above ground storage tanks, and other transport modes, gasoline spills and leaks still occur. Improper installation is a significant cause of fiberglass-reinforced plastic (FRP) and steel UST failures, particularly piping failures (EPA, 2009b). Many releases at UST sites come from spills made during delivery and usually result from human error (EPA, 2008e). Additionally, not all UST systems are regulated and not all components of regulated systems are regulated (EPA, 2009c).

As of March 31, 2009, there were 482,166 confirmed releases at underground storage tanks (EPA, 2009a). The actual number of releases is likely much higher as not all tank leaks are reported. Although 456,677 cleanups have been initiated and nearly 381,000 cleanups have been completed, there is a cleanup backlog of 101,190 tanks (EPA, 2009a). Nearly all LUSTs at these sites contain petroleum (EPA, 2008e).

CHAPTER 2 – TOOLS FOR PROTECTING HUMAN HEALTH: RISK ASSESSMENT AND THE PRECAUTIONARY PRINCIPLE

INTRODUCTION

There are at least two schools of thought governing how or if a chemical is introduced into the marketplace. The first, risk assessment, is the process of quantifying the probability a chemical will cause a harmful effect to individuals or populations. The other, the precautionary principle, states that with evidence of threats of significant harm, even in the face of scientific uncertainty, precautionary actions should be taken to protect public health. These two methods of protecting human health are discussed below.

RISK ASSESSMENT

In the context of public health, risk assessment is the process of quantifying the probability of a harmful effect to individuals or populations. A goal of risk assessment is to estimate the extra risk caused by a toxic or carcinogenic chemical over that which exists when exposure to the chemical does not exist (Rodricks, 2007).

For all non-carcinogenic chemicals, there is a dose threshold under which no effects of toxicity are observed in animal studies or expected in exposed individuals. Toxic effects are observed in a dose-dependent manner above this threshold. As

the dose increases above the threshold, the frequency and seriousness of those effects also increase. This relationship is referred to as the dose-response. According to Rodricks (2007), if for every chemical in the environment we knew the range of 'no-effect' doses and the point at which toxicity begins to appear – the point at which the threshold of toxicity is passed – we could then act to prevent exposures from ever reaching the level at which harmful doses are created. The problem is that data on toxicity and dose-response are only available for a small fraction of the chemicals to which people are exposed.

Risk is the likelihood, or probability, that the toxic properties of a chemical will be produced in populations of individuals under their actual conditions of exposure (Rodricks, 2007). Risk assessment involves four steps: (1) hazard identification; (2) dose response assessment; (3) exposure assessment; and (4) risk characterization.

First, in hazard identification, all available epidemiology and experimental toxicity data are gathered and critically evaluated in order to assess the types of toxicity the chemical can produce. These may include acute or chronic effects, various organs and tissues (dermal, respiratory, etc), and a variety of biological endpoints from the most overt (death) to molecular level effects (enzyme inhibition).

Next, a dose-response assessment quantifies the relationship between exposure and the response observed in studies. This analysis considers the range of

doses where the chemical's toxicity can be produced and the threshold of no effect. The challenge in this step is extrapolating results from experimental animals (such as mice or rats) to humans, and/or from higher to lower doses. There are also differences between individuals due to genetics or other factors, which may mean that the hazard may be higher for particular groups, often referred to as susceptible populations. There may also be missing data. To account for uncertainties, the lowest no-observed-effect-level (NOEL) from all available studies is assumed to be the threshold of toxicity for the groups of subjects (human or animal) in which toxicity data were collected. Safety factors (typically a factor of ten) are built in to further account for uncertainties. For example, for humans, the threshold is estimated by dividing the NOEL derived from animal studies by a factor of ten for each reason of uncertainty, and typically is 1/100th of the animal threshold value.

Then, in exposure assessment, the condition (dose, timing and duration) under which humans may be exposed to the chemical is evaluated. Since different locations, lifestyles, and other factors likely influence the amount of contaminant that is received, a range or distribution of possible values are generated. Particular care is taken to determine the exposure of susceptible populations.

Finally, risk assessment, or risk characterization, uses the results of the previous three steps to produce an estimate of overall risk. Because of the different susceptibilities and exposures, this risk will vary within a population. The decisions based on the application of risk assessment are sometimes based on a standard of

protecting those most at risk. If an identifiable sub-population is more susceptible due to inherent genetic or other factors, policies are often set to protect such groups. This is currently done under the Clean Air Act for populations such as asthmatics.

It is important to note that the final calculated risk is still only an estimate. Because of the approach of ten-fold safety factors, risk is more likely to be overestimated (so the resulting estimates are more likely to be greater than the actual risk) but some detailed analyses have shown that for specific chemicals it is still possible that risk can be underestimated.

In summary, risk assessment is a process of estimating risk. It takes into account all available scientific information and uses the most conservative adjustments for uncertainties to offer as safe an estimate of risk as possible. The information gathered in the risk assessment should identify hazards, identify the populations potentially at risk from those hazards, and estimate the risks involved.

The products of risk assessment are typically used in efforts to reduce, limit or eliminate the risks, also referred to as risk management. The problem with risk management is that the techniques and approaches used are intended to minimize the risks of the proposed activity but not to question whether the harm is necessary, or if there might be alternatives that would avoid harm altogether. Questioning whether the risks are necessary or if there are alternatives falls under a

larger decision making process that may directly or indirectly affect regulatory change.

Risk assessment is intended to be used as a regulatory tool to show, for example, dangerous products that should be removed from the market. At times, it appears to have had the opposite effect. Risk assessment has been used by industry groups to insist that harm must be proven scientifically before action is taken to stop a process or product. There are many examples where "certainty" about the absence of harm delayed preventative actions with potentially disastrous results.

For example, Bovine Spongiform Encephalopathy (BSE, or more commonly, Mad Cow Disease) was first recognized in the United Kingdom (UK) in November 1986 (DEFRA, 2008). When it was first noticed that the illness observed in cows might be passed to humans, adequate preventative actions were not taken based on this suspicion. Instead, it was argued that to act would cause economic hardship among the country's producers of beef. The result was the spread of BSE and a subsequent ban by other countries against the importation of beef from the UK. The BSE epidemic in the United Kingdom peaked in January 1993 at almost 1,000 new cases per week (CDC, 2010). By the end of 2008, more than 184,500 cases of BSE had been confirmed in the UK in more than 35,000 herds (CDC, 2010). BSE was eventually brought under control by culling all suspect cattle populations. However, human health is still impacted by the BSE outbreak. A new variant of

Creutzfeldt-Jakob disease (nvCJD), a form of brain damage that leads to a rapid decrease in mental function and movement, is linked to eating BSE-contaminated beef products (USDA Food Safety Research Info Office, 2009). nvCJD is believed to result from a protein called a prion. Although suspect cattle have been culled, new cases of nvCJD occur because of the long incubation time for prion diseases, which are typically measured in years or decades.

According to Myers (2002), global warming is another example where insistence on "scientific certainty" and focus on monetary costs has delayed protective action. In the United States, one of the heaviest users of fossil-fuel and where risk assessment has been widely used, little was done to move away from fossil fuels even when there was mounting evidence that the burning of fossil fuels was a primary cause of global warming. Priority was given to protecting national economic interests over environmental protection as the United States signed but did not ratify the 1997 Kyoto protocol, an international agreement that sought to decrease human activities that contribute to ozone depletion and global warming. Along with the United States, international trade organizations and agreements like the World Trade Organization (WTO) and the North American Free Trade Agreement (NAFTA) have institutionalized a non-precautionary approach to environmental controls (Myers, 2002).

In contrast to the typical risk assessment process and perhaps as a result of its shortcomings, an alternative approach based on precaution has been developed

and articulated as the precautionary principle. The goal of the precautionary principle is to prevent harmful chemicals from ever entering the marketplace, eliminating exposure and therefore risk.

THE PRECAUTIONARY PRINCIPLE

The precautionary principle is believed to have evolved in the early 1970s out of the German socio-legal tradition centering on the concept of good household management. In German, the concept is Vorsorgeprinzip, which translates into English as precaution principle. However, it was not until the 1992 United Nations Conference on Environment and Development that the principle received broad international recognition. It has been evoked in a number of multilateral agreements, international laws, and domestic laws and policies dealing with climate change, biodiversity, endangered species, fisheries management, wildlife, trade, food safety, pollution controls, chemicals regulation, exposure to toxics, and other environmental and public health issues (Peterson, 2006). Table 4 highlights a few of these agreements and policies.

Table 4. Examples of the precautionary principle in environmental laws and policy

Year	Name of Conference	Main Topic Addressed
1984	International Conferences on the Protection of the North Sea (The North Sea Conferences) (OSPAR Commission, 1984)	Pollution in the North Sea
1987	Montreal Protocol on Substances that Deplete the Ozone Layer (United Nations, 1987)	Greenhouse gases, climate change
1990	Second World Climate Conference (United Nations, 1990)	Climate change
1992	Rio Declaration on Environment and Development (The Rio Earth Summit) (United Nations, 1992a)	Sustainable development
1992	United Nations Framework Convention on Climate Change (United Nations, 1992b)	Greenhouse gases, climate change
1992	Maastricht Treaty (European Union, 1992)	Established the European Union (EU), named the precautionary principle as a guide to EU environment and health policy
1994	United Kingdom Biodiversity Action Plan (Department of the Environment (UK), 1994)	Protect threatened species and habitats by protecting and restoring natural systems
1997	Kyoto Protocol (United Nations, 1997)	Greenhouse gases, climate change
1998	Wingspread Statement on the Precautionary Principle (Wingspread Conference, 1998)	How to implement the precautionary principle in environmental regulation
2000	Cartagena Protocol on Biosafety (United Nations, 2000)	Genetically modified organisms
2000	Earth Charter (Earth Charter Commission, 2000)	Environmental protection, human rights
2001	Stockholm Convention on Persistent Organic Pollutants (United Nations, 2001)	Certain toxic chemicals
2007	Registration, Evaluation, Authorisation, and Restriction of Chemical Substances (REACH) (European Parliament, Council, 2007)	Burden of proof placed on industry to collect or generate the data necessary to ensure the safe use of chemicals (both new and existing)

There are many definitions of the precautionary principle, but the most widely quoted is from the 1992 Rio Declaration (United Nations, 1992a), which states that:

> "where there are threats of serious or irreversible damage, lack of full scientific evidence shall not be used as reason for postponing cost-effective measures to prevent environmental degradation."

While most definitions of the precautionary principle share common features, there are some key areas of difference (Peterson, 2006). These differences include:

- The level of threat or harm that is sufficient to trigger application of the principle (the threshold of harm).
- Whether potential threats are balanced against other considerations, such as costs or non-economic factors, in deciding what precautionary measures to implement.
- Whether the principle imposes an obligation to act or whether it simply permits action.
- Whether liability for environmental harm is assigned and, if so, who bears the liability?

Based on these differences, different versions of the principle can be categorized as weak, moderate or strong (Cooney & Dickson, 2005; Peterson, 2006; Wiener & Rogers, 2002) and are outlined below (as summarized by Cameron, 2006):

Weak version:

The weak version is the least restrictive and allows preventative measures to be taken in the face of uncertainty, but does not require them (e.g. 1992 Rio Declaration; 1992 United Nations Framework Convention on Climate Change). To satisfy the threshold of harm, there must be some evidence relating to both the likelihood of occurrence and the severity of consequences. Some, but not all, require consideration of the costs of precautionary measures. Weak formulations do not preclude weighing benefits against the costs. Factors other than scientific uncertainty, including economic considerations, may provide legitimate grounds for postponing action. Under weak formulations, the requirement to justify the need for action (the burden of proof) generally falls on those advocating precautionary action. No mention is made of assignment of liability for environmental harm.

Moderate version:

In moderate versions of the principle, the presence of an uncertain threat is a positive basis for action, once it has been established that a sufficiently serious threat exists. For example, the United Kingdom Biodiversity Action Plan states:

> "In line with the precautionary principle, where interactions are complex and where the available evidence suggests that there is a significant chance of damage to our biodiversity heritage occurring, conservation measures are appropriate, even in the absence of conclusive scientific evidence that damage will occur" (Department of the Environment (UK), 1994).

Usually, there is no requirement for proposed precautionary measures to be assessed against other factors such as economic or social costs. The trigger for action may be less rigorously defined, for example, as "potential damage", rather than as "serious or irreversible" damage as in the weak version. Liability is not mentioned and the burden of proof generally remains with those advocating precautionary action.

Strong version:

Strong versions of the principle differ from the weak and moderate versions in reversing the burden of proof. Strong versions justify or require precautionary measures and some also establish liability for environmental harm, which is effectively a strong form of "polluter pays". For example, the Earth Charter (2000) states:

> "When knowledge is limited apply a precautionary approach. Place the burden of proof on those who argue that a proposed activity will not cause significant harm, and make the responsible parties liable for environmental harm."

Reversal of proof requires those proposing an activity to prove that the product, process, or technology is sufficiently "safe" before approval is granted. Requiring proof of "no environmental harm" before any action proceeds implies the public is not prepared to accept any environmental risk, no matter what the economic or social benefits (Peterson, 2006). At the extreme, such a requirement

could involve bans and prohibitions on entire classes or potentially threatening activities or substances (Cooney, 2005).

Although different versions of the precautionary principle exist, they all agree that when there is a reason to think – not absolute proof – that some human activity is or might be harming the environment, precautions should be taken. Proponents of the principle argue that its strength lies in its high degree of generality since it may be applied to all environmental protection and health safety issues (Ashford, 2005). Critics of the precautionary principle argue it is too general, lacks clarity, and offers little guidance for regulatory policies (Treich, 2001). Despite these differences, and as evidenced in Table 4 above, the precautionary principle has become more prominent in environmental laws and regulations, and its adoption and use is becoming more mainstream. A good example of this is the European Union's Registration, Evaluation, Authorisation, and Restriction of Chemical Substances (REACH) program.

CHAPTER 3 – GASOLINE AND FUEL OXYGENATES

GASOLINE PROPERTIES

Gasoline is a complex manufactured mixture that does not exist naturally in the environment. It is produced from petroleum in the refining process and typically contains more than 150 chemicals, to include small amounts of benzene, toluene, xylene, and sometimes lead. How the gasoline is produced determines which chemicals are present in the gasoline mixture and how much of each is present. The actual composition varies with the source of the crude petroleum, the manufacturer, and the time of year. Gasoline is highly flammable, evaporates quickly, and forms explosive mixtures with air. Most people can begin to smell gasoline at 0.25 parts of gasoline per million parts of air (ppm). Although gasoline does not dissolve readily in water, some of the chemicals that make up gasoline can dissolve easily in water (ATSDR, 1995).

GASOLINE ADDITIVES AND FUEL OXYGENATES

One of the first gasoline additives was tetraethyl lead, which was phased out when lead in automotive gasoline was banned in the United States in the early 1980s. Oxygenates are now the most common gasoline additives, used to increase octane levels once provided by lead, and to increase oxygen levels and reduce pollution emissions. Oxygenates are hydrocarbons that contain one or more oxygen atoms. Oxygenates are added to motor vehicle fuels to increase the

combustion efficiency of gasoline, thereby reducing toxic tailpipe emissions (particularly carbon monoxide) and allowing states to meet federal air quality guidelines. Introducing additives that are partially oxidized promotes the complete combustion of gasoline, so the engine emits CO_2 instead of CO. The primary oxygenates are alcohols and ethers and include ethanol, methyl tertiary butyl ether (MTBE), ethyl tertiary-butyl ether (ETBE), tertiary-amyl methyl ether (TAME), diisopropyl ether (DIPE), and tertiary-butyl alcohol (TBA). Oxygenates are also used as fuel additives to increase octane ratings. Most automobile engines require fuel with octane ratings of 87 to 93 to avoid "knocking," a regular rapping noise within a vehicle's engine compartment that is usually caused by faulty fuel combustion (Shakhashiri, 2009). Adding oxygenates to gasoline increase the octane rating of the fuel.

As shown in Table 5, oxygenates vary in their effectiveness in reducing toxic tailpipe emissions and several other parameters:

Table 5. Typical properties of fuel oxygenates

	MTBE	**ETBE**	**TAME**	**Ethanol**
Chemical formula	$CH_3OC(CH_3)_3$	$CH_3CH_2OC(CH_3)_3$	$(CH)_3CCH_2OCH_3$	CH_3CH_2OH
Oxygenate content, percent by weight	18.15	15.66	15.66	34.73
Octane	110	111	105	115
Reid vapor pressure (RVP)	8	4	1.5	18

Source: EIA, 2000

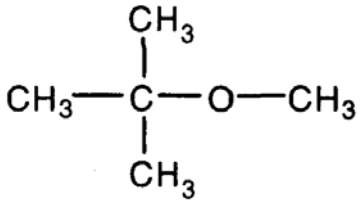
In addition to requiring that fuels burn cleaner, EPA requires areas with high levels of smog (including but not limited to RFG areas) to reduce the vapor pressure of gasoline in the summer months. When vapor pressure is reduced, it lessens the volatilization of petroleum products at storage facilities and during fuel transfer. Because MTBE-blended gasoline has a lower Reid Vapor Pressure, or RVP, than ethanol-blended gasoline, MTBE is the preferred oxygenate in warm weather (EPA, 1998b).

The petroleum refinery industry also favors the use of MTBE over ethanol for octane enhancement and RFG because it is less expensive and easier to use (EPA, 1998b). MTBE is more compatible with gasoline, and can be blended at the refinery and distributed with gasoline through pipelines. Ethanol, on the other hand, much be shipped seperately from gasoline and added at the distribution terminal soon before use. If ethanol-blended gasoline is exposed to water or even water vapor (as in pipelines), ethanol will bring the water into solution and make the gasoline unusable. Also, if ethanol-blended gasoline is stored for an extended period, the ethanol will begin to separate from the gasoline. As a result, ethanol is often manufactured close to the point of use or shipped by rail, increasing the cost of its use (EPA, 1998b).

MTBE PRODUCTION AND PROPERTIES

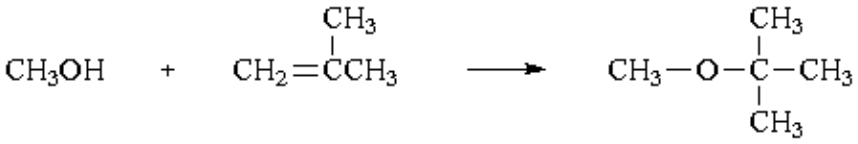
Methyl *tert*-butyl ether (MTBE) is a colorless, flammable liquid with a boiling point of 55°C and a density of 0.74 g/mL. MTBE's unique Chemical Abstract Service registry number, or CAS, is 1634-24-4 (CAS, 2009). The chemical formula for MTBE is $C_5H_{12}O$ and its molecular structure is shown below.

Figure 1. MTBE's chemical formula



In MTBE one carbon atom is that of a methyl group, $-CH_3$, and the other is the central atom in a tertiary butyl group, $-C(CH_3)_3$. MTBE is made by reacting methanol, made from natural gas, with isobutylene (2-methyl-1-propene) in the liquid state, using an acidic catalyst at 100°C.

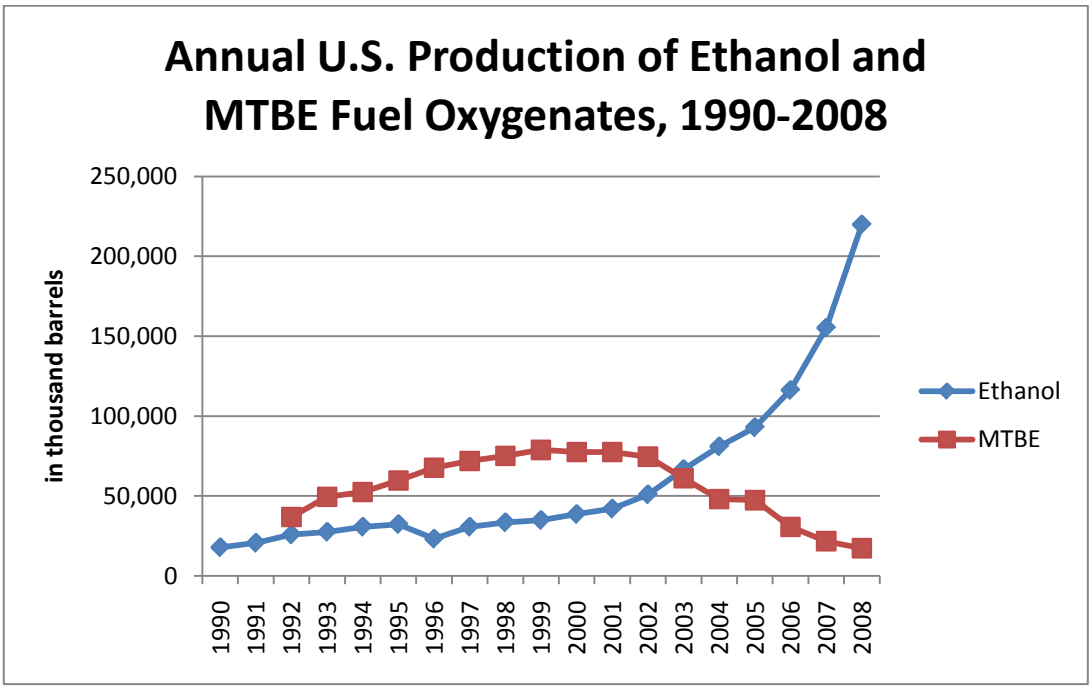
Figure 2. Formation of MTBE



MTBE's chemical structure determines its reactivity to other substances. MTBE does not have hydrogen attached to oxygen or nitrogen, so it cannot form a hydrogen bond to other molecules. It does, however, have an unbound electron pair on its oxygen atom. This means that substances that have hydrogen bonded to oxygen can bond to MTBE and is why MTBE, although soluble in petroleum at all combinations, also has solubility in water, H_2O. Therefore, any MTBE that gets to the ground will be dissolved in rain water or other aqueous systems.

The 1990 Clean Air Act created a guaranteed market for all types of fuel oxygenates. During the Winter Oxyfuel Program (WOP), MTBE demand increased from 36.8 million barrels per year in 1992 to 52.4 million barrels per year by 1994 (EIA, 2009). The reformulated gasoline (RFG) program provided a further boost to oxygenate blending and by 1997, MTBE production had increased to 71.9 million barrels annually (EIA, 2009). For comparison, in 1970 MTBE was the 39th highest produced organic chemical in the United States (Shakhashiri, 2009). By 1998, it had become the fourth highest. As concerns about MTBE contamination spread, production volumes decreased. In 2005 47.3 million barrels were produced annually, and by 2006 this number had dropped to 30.6 million (EIA, 2009). As shown in Table 6, as MTBE production decreased, there was a corresponding increase in ethanol production. Ethanol production was 92.9 million barrels annually 2005 and 116.2 million in 2006.

Table 6. Comparison of annual U.S. production of ethanol and MTBE as fuel oxygenates, 1990-2008



Source: EIA, 2009

Despite its relatively short production history, MTBE has frequently been detected in groundwater. MTBE's physical properties allow it to reach groundwater and to travel faster and farther than many other common gasoline components (Zogorski *et al.,* 2006). Many regulators of UST programs have observed that MTBE's relatively high solubility allows it to dissolve into groundwater in "pulses" that result in rapid orders of magnitude changes in groundwater concentrations (EPA, 1998c). Pulses, which may be caused by the infiltration of rain water or rising groundwater levels, may necessitate frequent groundwater sampling to determine actual MTBE concentrations. In addition, the biodegradation of MTBE in groundwater is relatively slow and MTBE can persist longer in aquifer systems

relative to many other gasoline compounds, such as benzene and toluene (Zogorski *et al.,* 2006). MTBE's high solubility in water, low rate of adsorption to soil, and low rate of biodegradation can make treating groundwater contaminated with MTBE more expensive than treating groundwater that does not contain MTBE (EPA, 1998c).

EFFECTS OF FUEL OXYGENATES ON VEHICLE EMISSIONS

The use of oxygenates has been reported to have favorable impacts on air quality (EPA, 1999). Analyses of ambient carbon monoxide measurements in some cities with winter oxyfuel programs find a reduction in ambient CO concentrations of about 10% (National Science and Technology Council, 1997). As illustrated in Table 7, fuel oxygenates decrease vehicle emissions of air toxics such as benzene and 1,3-butadiene, but increase the emissions of aldehydes (acetaldehyde from the use of ethanol or ETBE, and formaldehyde from MTBE) and of NOx gases (National Science and Technology Council, 1997). Acetaldehyde is a metabolite of ethanol, and a possible carcinogen that undergoes a photochemical reaction in the atmosphere to produce the respiratory irritant peroxylacetate nitrate (PAN) (Ahmed, 2001).

Table 7. Oxyfuel effects on twenty 1989 model year vehicles exhaust emissions

		% Changes with Oxyfuel per wt % Oxygen [c]		
Emission	**Mass Emission [b] (g/mi)**	**3.7% Oxygen EtOH**	**2.7% Oxygen MTBE**	**2.7% Oxygen ETBE**
Carbon monoxide (CO)	2.5	-3.6 ± 1.3	-3.4 ± 2.4	-5.4 ± 2.7
Hydrocarbons (HC)[a]	0.21	-1.3 ± 0.7	-2.4 ± 1.3	-1.9 ± 1.4
Nitrogen oxides (NOx)	0.6	+1.4 ± 1.1	+1.3 ± 2.0	+2.0 ± 2.3
Benzene	9 x 10-3	-3.1 ± 1.6	-4.1 ± 3.0	-3.5 ± 3.0
1,3-Butadiene	9 x 10-4	-1.6 ± 1.5	-0.6 ± 2.9	-1.0 ± 3.1
Formaldehyde	1.5 x 10-3	+5.2 ± 8.4	+5.9 ± 15.3	+6.3 ± 26.6
Acetaldehyde	1.4 x 10-3	+43 ± 12	-0.3 ± 13	+95 ± 25

[a] = Total hydrocarbons

[b] = average values for test fuels

[c] = Oxyfuel effects have been normalized to 1 wt % oxygen. Uncertainties represent 95% confidence limits.

Source: National Science and Technology Council, 1997

Although NOx emissions increased for all oxygenates, the result was statistically significant for only the ethanol fuels, the fuel set with the highest oxygen content. Acetaldehyde emissions increased greatly for ethanol and ETBE fuels. Except for the effects on acetaldehyde emissions, it is generally assumed the effects of oxygenates are indistinguishable (National Science and Technology Council, 1997). It is worth noting that acetaldehyde is not an insignigicant issue since it also believed to be a human carcinogen.

Table 8. Effects of 15% MTBE fuel (2.7% wt oxygen) on older 1983-1985 and newer 1989 model year vehicles

Emission	Mass Emission (g/mi)	% Changes with Oxyfuel per wt % Oxygen
CO		
Current Fleet	2.8	-4.1 ± 1.3
Older Fleet	6.2	-5.2 ± 1.4
HC [b]		
Current Fleet	0.22	-2.2 ± 0.9
Older Fleet	0.53	-3.4 ± 1.1
NOx		
Current Fleet	0.6	+0.5 ± 0.7
Older Fleet	1.2	+0.5 ± 0.7

Source: National Science and Technology Council, 1997

The favorable impacts on air quality from the use of oxygenates is also disputed. According to Interagency Assessment of Oxygenated Fuels (National Science & Technology Council, 1997), the general decline in urban concentrations of carbon monoxide over the past twenty years is largely attributed to stringent EPA-mandated vehicle emission standards and improved vehicle emission control technology. Newer model vehicles generally emit less pollution because of improved emission control devices and the use of fuel injection. Emissions may also vary from vehicle to vehicle depending upon how it is maintained and operated and the quality of the fuel used (National Science and Technology Council, 1997). As seen in Table 8, reductions in CO and hydrocarbon emissions from the use of fuel oxygenate are found to be smaller in newer technology vehicles compared to older technology and higher emitting vehicles. Older vehicles typically use carbureted and oxidation catalyst technology, compared with the fuel injected, adapted learning, and closed loop three-way catalyst systems commonly used in newer

vehicles (National Science and Technology Council, 1997). Although these older vehicles represent a smaller fraction of the on-road fleet, there is evidence to support they are responsible for a disproportionately large amount of urban CO (National Science and Technology Council, 1997). Over time, as older vehicles leave the on-road fleet, the need for fuel oxygenates will decrease.

In light of these factors, it may be hard to attribute improvement in air quality definitively to the use of fuel oxygenates or to MTBE in particular.

CHAPTER 4 – MTBE HEALTH EFFECTS STUDIES

INTRODUCTION

Shortly after MTBE's introduction as a fuel oxygenate, anecdotal reports of acute health symptoms such as eye and nose irritation, headaches, nausea, and dizziness surfaced, leading to concerns about the human health risks from exposure to MTBE. These health concerns were not anticipated. A review of available literature, to include toxicological studies and epidemiological investigations, show the body of evidence for possible health effects resulting from MTBE exposure in both humans and animals.

TOXICOLOGY AND EXPOSURE DURATIONS

One of the basic concepts of toxicology is that all chemicals are toxic under some conditions of exposure. The difficulty for toxicologists is to know under what condition or level of exposure chemicals are toxic, so that measures can be taken to limit human exposure so that toxicity can be avoided (Rodricks, 2007).

Toxicity is commonly categorized based on exposure duration – either acute, chronic, or subchronic exposures. Acute toxicity testing involves a single high dose. In animal testing, the acute lethal dose-50 (LD50) is the single dose of a chemical that will, on average, kill 50% of a group of experimental animals. The LD50 has become one standard measure of a chemical's acute toxicity and represents the

dose at which animals have a 50% probability, or risk, of dying. Acute toxicity tests in which non-lethal outcomes are sought include studies of the amounts of chemical needed to cause skin or eye irritation or more serious damage.

Chronic exposure generally refers to dosing over a whole lifetime, or something close to it. Subchronic exposures refer to repeated exposures for some fraction of a lifetime. In animal toxicity studies involving rodents, chronic exposure generally refer to daily doses over about a two-year period (rodent life-time), and subchronic generally refers to daily doses over 90 days. The purpose of subchronic and chronic testing is to identify the types of adverse health effects produced by a chemical administered repeatedly, for large fractions of a lifetime, the dose at which toxicity begins to appear, and the manner in which toxicity changes above the minimum toxic dose (Rodricks, 2007). The maximum dose at which the chemical produces no observable toxicity is referred to as NOEL, or "no-observed effect level." Risk assessors use NOEL to estimate the safe exposure level (the reference dose, or RfD) and evaluate the likelihood of health damage in groups of people exposed to various doses of a chemical.

HUMAN HEALTH EFFECTS AND KINETICS AFTER EXPOSURE TO MTBE

ACUTE

In an effort to understand the variations in reported acute health effects from MTBE exposure, Borak *et al.,* (1998) performed a critical literature review of 19 reports describing the results of twelve studies on the acute human health effects of inhalation exposure to MTBE and twelve reports describing the clinical use of parenteral MTBE (MTBE administered other than by mouth, usually injected or implanted into the body) to dissolve cholesterol gallstones. Each study was reviewed from three perspectives (epidemiology, industrial hygiene, and clinical diagnostics); judged either satisfactory, limited adequacy, or unsatisfactory; and grouped into one of three categories from most to least adequate in overall methodology. The results of this review found those studies judged most adequate on individual criteria and those with highest overall adequacy found no significant association between MTBE exposure and seven "key" symptoms – headache, eye irritation, burning of the nose and throat, cough, nausea and vomiting, dizziness, and spaciness. As a result, it has been suggested that the major source of public perception that MTBE poses hazards, and the principal basis for the ensuing political debate, were the initial findings of methodologically weak studies. Borak *et al.,* (1998) concluded that methodologically superior studies – those designed to rigorously test the MTBE hypothesis – found no association between exposure to oxygenated fuels and the seven "key" symptoms.

Nihlen *et al.,* (1998) attempted to assess the acute health effects of MTBE exposure by subjecting ten healthy male volunteers to MTBE vapor for two hours at three levels (5, 25, and 50 ppm). Each individual was exposed on three occasions with at least two weeks between successive exposures. All subjects were first exposed to the highest level, whereas the order of the 5- and 25-ppm exposure levels was randomly divided. There was no control group. A symptoms questionnaire was administered before, during, and after exposure inquiring whether participants had discomfort in the eyes, nose, throat or airways; whether they had difficulty breathing or experienced headache, nausea, fatigue, dizziness, or intoxication; and whether they could smell solvent. The subjects did not indicate any increased irritation effects or discomfort after MTBE exposure, with the exception of solvent smell. Measurements of ocular and nasal irritation were also performed before, during, and after exposure. No significant effects of MTBE were seen in any measurements, to include blinking frequency, eye redness, or corneal damage. Nasal blockage and nasal swelling are commonly reported symptoms during exposure to airborne substances. Although a nasal swelling effect was observed, the authors concluded there was no clear dose-effect relationship between this symptom and MTBE exposure. The results of this study indicate no or minimal acute effects of MTBE vapor upon short-term exposure at relatively high levels. However, this study did discuss potential limitations, to include possible hesitation of individuals with prior negative experiences with MTBE or of volatiles in general to participate in chamber studies (thus excluding sensitive individuals), and

that short exposure durations may reduce the ability of the study to reveal any acute effects of MTBE exposure.

The effects of MTBE on the immune system were measured by monitoring plasma interleukin-6 levels (an indicator of immune reaction) in 22 volunteers exposed to auto emissions derived from oxyfuels during a four-week period in late November and early December 1992 at several locations around Fairbanks, Alaska (Duffy *et al.,* 1994). Blood samples were collected at the beginning of work shifts and the end of the workday and analyzed for interleukin-6 by an immunochemical assay. No differences in interleukin-6 levels were found between the morning and evening blood samples.

To address some of the issues identified in the occupational and field studies, an experimental double-blind study was conducted in 22 healthy men and 21 healthy women, who were examined for both objective and subjective effects (Cain *et al.,* 1994). In this study, half of the subjects were exposed sequentially to 1.7 ppm MTBE for one hour on one day, to uncontaminated air for one hour two days later, and to 7.1 ppm of a 17-component mixture of volatile organic compounds (VOCs) for one hour two days later. The other group of subjects was similarly exposed in the reverse order. The subjects were able to detect the odor of MTBE, but expressed little objection to it. Analysis of nasal lavage material and tear fluid from the eyes revealed no statistically significant differences across the three exposure conditions. In addition, statistical analysis of the results of questionnaires administered every ten minutes during the various exposure conditions revealed no

differences for irritation of the nose or throat, dry skin or skin rash, dry or sore throat, stuffy or runny nose, sinus congestion, cough, wheezing, chest tightness, or shortness of breath when the subjects were exposed to MTBE or when they were exposed to air. Neurobehavioral tests were also administered at one hour before exposure and during the last 15 minutes of exposure. Results of statistical analysis in these tests (analysis of variance, or ANOVA) revealed no difference across the three conditions of exposure to MTBE, air, or VOCs. Subjects were also administered questionnaires regarding subjective symptoms of eye irritation (dry, itching, or irritated eyes; tired or strained eyes; burning eyes); headache; difficulty remembering things or concentrating; feelings of depression; unusual tiredness, fatigue or drowsiness; tension, irritability, or nervousness; dizziness or lightheadedness; mental fatigue or "fuzziness;" pain or numbness in the hands or wrists; and skin rash or dry skin. No differences in reporting of symptoms were noted for exposure to MTBE versus exposure to air.

In a similar study, 19 healthy men and 18 healthy women were exposed for one hour to clean air and 1.39 ppm MTBE in separate sessions separated by at least one week (Prah *et al.,* 1994). The order of exposure was randomly selected, but because of the odor of MTBE, it is likely that the subjects were aware of the exposure conditions. Questionnaires were administered prior to exposure, immediately upon entering the exposure chamber, after 30 minutes of exposure, and during the last five minutes of exposure. Responses to the questionnaires revealed no differences between pre- and post-exposure for several conditions:

headache, difficulty in memory or concentration, depressed feelings, unusual tiredness, fatigue, drowsiness, tension, irritability, nervousness, dizziness, lightheadedness, mental fatigue, "fuzziness," or pain, stiffness, or numbness of the back, shoulders, neck, hands, or wrists. Tests to evaluate neurobehavioral function were completed as baseline before entering the chamber and after 45 minutes of exposure. No measures approached statistical significance. There were also no differences between exposures for eye irritation, skin rash or dry skin, irritation of the nose, cough, wheezing, chest tightness, shortness of breath, stuffy or runny nose, or irritation of the throat. No differences were found for nasal inflammation upon examination of nasal lavage material. Female subjects reported that the air quality during MTBE exposure was worse than the air without MTBE. The odor threshold was determined to be approximately 0.18 ppm. Thus, other than detection of odor and the reported poor air quality in these experimental studies, no reactions to exposure to MTBE were observed or reported under the conditions of the studies. Although the exposure concentrations used in these experimental studies were chosen on the basis of airborne concentrations of MTBE to which commuters are exposed, the studies could not resolve whether multiple exposures, exposure to higher concentrations, and exposure for longer durations, which are more relevant for real-life exposure of motorists to MTBE, would have caused cumulative effects.

CHRONIC/SUBCHRONIC

In a study of physician visits before, during, and after the oxygenation of gasoline in the Philadelphia, Pennsylvania area, Joseph (2002) noted the proportion of visits related to asthma, wheezing, and headache increased dramatically and in association with increasing concentrations of MTBE in air during a time when criterion pollutants were stable. This suggests that MTBE might be associated with these symptoms, and not the air pollutants commonly measured. Joseph (2002) reported the symptoms attributed anecdotally to MTBE use in gasoline include skin rash, general allergy, anxiety, insomnia, cardiac symptoms, and malaise. As a control, statistics for six diseases and symptoms thought to be unrelated to air pollution (diabetes; essential hypertension; chronic liver disease, including alcoholic cirrhoses and hepatitis; back pain; diverticula of the intestine; and abdominal pain) were examined. With the exception of hypertension, none of the changes were statistically significant. However, the increase in hypertension was very small (4.1%), especially when compared to increases observed in symptoms attributed to pollution. By comparison, symptoms anecdotally related to MTBE increased between 59 and over 700 percent during the same time period. Confounding factors and sources of bias acknowledged in this study included the possible impact of MTBE publicity on patient and physician behavior with regard to symptom reporting. A review of MTBE publicity revealed that coverage in Pennsylvania tended to cover economic and regulatory aspects of gasoline, which was described

as reducing air pollution, so it is unlikely the increases in patient symptoms were due to negative patient reactions to the MTBE news coverage.

To determine the extent of exposure to gasoline vapors during vehicle refueling, Hakkola & Saarinen (2000) measured the differences in the exposure of 20 customers to gasoline and oxygenate vapors during refueling in service stations with and without vapor recovery systems. There are two types of recovery systems. The equipment and procedures at Stage I service stations reduce the vapor emissions during the delivery of gasoline from road tankers into underground storage tanks (closed conditions). Stage II vapor recovery systems reduce vapor emission during refueling by trapping the vapor with the fuel nozzle and containing it within the storage tank. The results of the study indicate that although the Stage II vapor recovery system did not remove all vapors, exposure to MTBE was reduced considerably by Stage II recovery systems (from a mean of 23.4 mg/m^3 to 5.6 mg/m^3 when compared to Stage I recovery systems). Although there are no studies of long-lasting negative health effects to customers from exposure to gasoline vapors during refueling and the time of exposure to gasoline vapors during refueling are brief (mean refueling times were 57 seconds (range 23-207sec) at the Stage I and 66 seconds (range 18-120) at Stage II stations), the use of fuel recovery systems further reduce the potential for human and environmental contamination from fuel oxygenates.

Fiedler *et al., (*1994) conducted a study to determine whether symptoms associated with MTBE were reported at an increased rate among subjects known to

be sensitive to chemicals and in situations where exposure to MTBE was likely to be greatest. In this study, 14 individuals with multiple chemical sensitivities, five individuals with chronic fatigue syndrome, and six control individuals were interviewed regarding symptoms in response to situations in which gasoline containing MTBE was used (driving a car, gasoline stations) and not used (shopping malls, grocery stores, office buildings, parks). The symptoms of interest included cough, burning sensation in the nose, and gastrointestinal upset. Although multiple chemical sensitivity subjects and chronic fatigue syndrome subjects reported more symptoms than normal controls in some situations, no significant differences were found among the groups for driving a car or visiting gas stations. The authors concluded that the study did not provide clear evidence to support that an unusually high rate of symptoms or an increase of symptoms occurred uniquely where MTBE exposure was likely.

In a later study, Fiedler *et al.,* (2000) again compared individuals with self-reported symptoms (SRSs) associated with MTBE (headache; nausea; and eye, nose, and throat irritation) to a control group. In a double-blind, repeated measures, controlled exposure, subjects were exposed for 15 min to clear air, gasoline, gasoline with 11% MTBE, and gasoline with 15% MTBE. Relative to controls, SRSs reported significantly more total symptoms when exposed to gasoline with 15% MTBE than when exposed to gasoline with 11% MTBE or to clean air. However, these differences in symptoms were not accompanied by significant differences in neurobehavioral performance or psychophysiologic responses, nor were significant

differences found when subjects exposed to gasoline with 11% MTBE were compared to clean air or to gasoline. The results of this study did not support a dose-response relationship for MTBE exposure nor the symptoms associated with MTBE in epidemiologic studies.

POSSIBLE HUMAN HEALTH BENEFITS ASSOCIATED WITH MTBE USE

In addition to potential risks associated with MTBE exposure, it has been suggested that use of MTBE as a fuel oxygenate may have anticipated health benefits. Modeled ambient air concentrations of VOCs were used to compare baseline gasoline (pre-1990 CAAA gasoline) to three fuel mixture scenarios: summer MTBE:RFG, winter MTBE:RFG, or MTBE oxyfuel (Spitzer, 1997). The model predicted that the addition of MTBE to RFG or oxyfuel would decrease acetaldehyde, benzene, 1,3-butadiene and particulate organic matter (POM), but increase formaldehyde tailpipe emissions (Table 10.) However, the increased formaldehyde emissions would be offset by the reduction of formaldehyde formation in the atmosphere from other VOCs.

Table 9. Impact of MTBE on vehicle emissions of volatile organic compounds (VOCs) in summer and winter

Component	Summer (mg/mile)		Winter (mg/mile)		
	Baseline gasoline	MTBE RFG	Baseline gasoline	MTBE RFG	MTBE oxyfuel
Acetaldehyde	8.1	7.5	14.4	13.4	13.4
Benzene	108.5	71.8	178.4	112.3	113.2
1,3-Butadiene	13.0	12.0	23.0	19.6	17.9
Formaldehyde	15.0	16.5	26.6	30.8	32.6
POM	5.9	5.4	10.5	10.0	10.1
Total	150.5	112.3	252.9	186.1	187.2

Source: Spitzer, 1997

Based on these model emissions, and assuming total US population exposure, the EPA predicted annual cancer risk estimates associated with tail pipe emissions of VOCs. As reported by Spitzer (1997), an incidence of 437 annual cancer-related deaths from use of 100% baseline gasoline year-round would decline 13% (to 379 annual cancer-related deaths) if baseline gasoline was used exclusively in the summer and MTBE:RFG in winter. If baseline gasoline replaced MTBE in summer and winter, the predicted cancer declined to 362 annual cancer-related deaths (17%). The maximum decline (359 annual cancer-related deaths or 18%) was achieved when MTBE:RFG was used exclusively in the summer and MTBE oxyfuel in winter. Based on these predictions, use of MTBE in RFG year-round coupled with winter use of the oxygenate in the Winter Oxyfuel Program would result in the greatest lives saved in terms of reduced cancer-related deaths attributable to air pollutants.

Similarly, Erdal *et al.,* (1997) reported that even small MTBE-associated reduction in peak ambient ozone levels (1-5 ppb, according to model estimates) should yield considerable public health benefits. Ozone is a highly reactive irritant gas that primarily affects the respiratory system. Acute responses to ozone include respiratory symptoms, decrements in lung function, decreased athletic performance, and biochemical and cellular changes indicating lung inflammation (Erdal *et al.,* 1997). MTBE use in fuel reduces ozone by reducing the emission of other VOCs.

EVALUATION OF MTBE KINETICS

In a short-term inhalation exposure study by Lee *et al.,* (2001) six subjects were exposed to MTBE in gasoline in order to assess the metabolic kinetics of MTBE and its metabolite, tertiary butyl alcohol (TBA) in the human body. Three male and three female participants were exposed to 1.7 ppm MTBE vapor for 15 minutes in a controlled setting. Urine void samples were collected first thing in the morning of exposure day (pre-exposure), then periodically until the following morning, including a sample 5-10 minutes prior to exposure. Breath and blood background samples were collected 5-10 minutes prior to the subjects entering the test facility. Once testing began, air and breath samples were taken concurrently during the exposure at four minute time intervals. Post-exposure biological samples were collected in a room with no known MTBE sources. MTBE air concentrations inside the testing room ranged from 5510μg/m^3 (1.5ppm) to 6480 μg/m^3 (1.6ppm) during

the exposures. The elimination patterns for the six test subjects were similar. Breath MTBE levels declined quickly following the 15-minute exposure. All post-exposure breath concentrations of MTBE dropped more than 50% in ten minutes and 69% of the absorbed doses were expired through respiration within eight hours following exposure. Breath levels of TBA never exceeded its detection limit of 1.5 $\mu g/m^3$. Blood MTBE concentrations reached its highest levels right after exposure with a range from 4 to 10 µg/ml, then declined to background levels in most cases. TBA reached its highest levels (5-10 µg/l) 2-4 hours after exposure and then declined slowly. TBA did not always reach background levels within 24 hours after exposure, the time when the last sample was collected. The half-lives of TBA in the blood for a single female and single male subject were 10.5 and 8.0 hours, respectively. MTBE urinary excretion rates increased immediately following exposure and declined to background 10 to 15 hours after exposure. TBA excretion rates reached its highest levels 6-8 hours later, returning to background levels around 20 hours after exposure. Approximately 0.7-1.5% of the amount of MTBE inhaled was excreted unchanged as urinary MTBE, and 1-3% was excreted as urinary TBA within 24 hours after exposure. The ranges of MTBE half-lives is believed to be 1-4 minutes for the lungs, 9-53 minutes for blood, 2-8 hours for vessel rich tissue, and 14-24 hours for vessel pore or adipose (fatty) tissue. Overall, exposure results from this study suggest MTBE and its metabolite, TBA, are processed and removed from the human body relatively quickly (within 24 hours) with expired air and urine comprising the main routes of excretion. Females tended

to process MTBE and TBA slower than males, suggesting a possible higher health risk for females in terms of exposure.

Prah *et al.,* (2004) measured blood, urine, and breath volumes after fourteen male volunteers were exposed to MTBE dermally, orally, or through inhalation. Specifically, volunteers were exposed to 51.3 µg/ml MTBE dermally in tap water for 1 hour, drank 2.8 mg MTBE in 250 ml Gatorade, and inhaled 3.1ppm MTBE for 1 hour. A baseline blood sample was obtained prior to exposure, and blood and breath samples were obtained throughout the exposure and post-exposure periods, to include 24-hours post-exposure samples. Participants were exposed in random order and each of the three exposures was separated by at least one week to minimize the physiological carryover of MTBE or TBA. Study results indicate blood MTBE peaked between 15 and 30 minutes following oral exposure, immediately at the end of inhalation exposure, and roughly five minutes after dermal exposure. TBA measured in blood slowly increased and reached a plateau, but did not return to pre-exposure baseline at the 24-hour follow-up. The dermal and inhalation exposure experiment shows MTBE was readily absorbed and metabolized into TBA. In contrast, the oral route of exposure demonstrated a significant first-pass metabolism effect that resulted in proportionally more TBA and therefore, less MTBE would be available for elimination via exhalation. This result means risk assessment calculations should take route or exposure into consideration. Oral exposure resulted in significantly greater MTBE metabolism into TBA than by other routes. Uptake was slowest for the dermal exposure route.

In a study performed by Johanson *et al.,* (1995), ten healthy male volunteers were exposed to MTBE vapor at 5, 25, and 50ppm for two hours during light physical exercise. Measurements were taken of MTBE and tertiary butyl alcohol in inhaled and exhaled air, blood and urine. The concentration of MTBE and TBA in blood was proportional to exposure level suggesting linear kinetics up to 50ppm. Subjective ratings (discomfort, irritative symptoms, CNS effects); eye (redness, tear film break-up time, conjunctival damage, blinking frequency); and nose measurements (peak expiratory flow, acoustic rhinometry, inflammatory markers in nasal lavage) indicated no or minimal effects of MTBE exposure.

ANIMAL HEALTH EFFECTS AFTER EXPOSURE TO MTBE

ACUTE

Acute inhalation 4-hour LC50 (lethal concentration, 50% kill) values in rats for two grades of MTBE was determined to be 33,370 ppm (120,132 mg/m^3) for commercial MTBE (99.1% MTBE) and 39,395 ppm (141,822 mg/m^3) for ARCO MTBE (96.2% MTBE) (ARCO, 1980). An acute LC50 in mice following inhalation of MTBE for ten minutes was determined to be 180,000 ppm (648,000 mg/m^3) (Snamprogetti, 1980). The LT50 (time at which death occurs in 50% of exposed animals) in mice following inhalation exposure to 209,300 ppm (753,480 mg/m^3) MTBE was 5.6 minutes. No deaths occurred in male or female Fischer rats exposed to < 8,000 ppm (28,800 mg/m^3) for six hours (Bioresearch Labs, 1990a; Gill, 1989).

A 4-hour inhalation exposure of rats to high concentrations of MTBE (>18,000 ppm, or 64,800 mg/m^3) caused rapid breathing, excessive tear secretion, nasal discharge, loss of coordination and loss of righting reflex, with respiration gradually slowing until the rats died (ARCO, 1980). MTBE exposure at concentrations of 8,321 ppm (29,956 mg/m^3) for one hour produced labored breathing in rats (Tepper *et al.,* 1994) and mice (Tyl & Neeper-Bradley, 1989). Exposure to MTBE at concentrations <3,000 ppm (10,800 mg/m^3) did not produce observable respiratory symptoms. No neurological effects were observed at 800 ppm (2,880 mg/m^3) for six hours. Based on this NOAEL, an acute-duration inhalation MRL of 2 ppm (7 mg/m^3) was calculated

Some rats and mice died after being given very large amounts of MTBE by mouth. The oral LD50 (lethal dose, 50% kill) for MTBE was found to be 3,866 mg/kg for rats (ARCO, 1980) and 4,000 mg/kg for mice (Little *et al.,* 1979).

No deaths occurred in rats (Bioresearch Labs, 1990b) or rabbits (ARCO, 1980) dermally exposed to MTBE.

The immediate acute effect of orally administered MTBE is on the central nervous system. Oral ingestion of MTBE at doses > 4,080 mg/kg MTBE caused lack of coordination, tremors, labored breathing, and loss of righting reflex in rats (ARCO, 1980). Onset of neurological signs was rapid, but they disappeared or were markedly reduced within 24 hours. Another study in rats reported drowsiness, which subsided within 24 hours after a single oral dose of 400 mg/kg (Bioresearch Labs, 1990b). A NOAEL (no observed adverse effect level) of 40 mg/kg for

neurological effects for acute oral exposure was identified for MTBE (Bioresearch Labs, 1990b). Based on this NOAEL value, MTBE's acute oral Minimal Risk Levels (MRL) was calculated to be 0.4 mg/kg/day.

The Agency for Toxic Substances and Disease Registry (ATSDR) derives MRLs when it determines that reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure to a substance (ATSDR, 2009). The MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancerous health effects over a specified duration of exposure (ATSDR, 2009). MRLs are derived for acute (1-14 days), intermediate (>14-364 days) and chronic (365 days and longer) exposure durations, and for the oral and inhalation routes of exposure. ATSDR has not yet identified a method suitable for determining MRLs for dermal exposure. Although human data is preferred, MRLs are often based on animal studies because relevant human studies are lacking (ATSDR, 2009). To be protective of human health, the MRL may be as much as a hundredfold below levels shown to be nontoxic in laboratory animals. Table 11 shows MRL values for MTBE.

Table 10. MTBE Minimal Risk Levels (MRLs) for humans based on animal studies

Route	Duration	MRL
Inhalation	Acute	2 ppm (7 mg/m^3)
	Intermediate	0.7 ppm (2.52 mg/m^3)
	Chronic	0.7 ppm (2.52 mg/m^3)
Oral	Acute	0.4 mg/kg/day
	Intermediate	0.3 mg/kg/day

Source: ATSDR, 2009

CHRONIC

The most common effect of MTBE in animals is on their nervous system. Breathing high concentrations (> 3,000 ppm, or 10,800 mg/m^3) of MTBE caused hypoactivity, lack of coordination, lack of startle reflex, and labored breathing (Vergnes & Morabit, 1989; Chun & Kintigh, 1993; Vergnes & Chun, 1994; Dodd & Kintigh, 1989; Tyl & Neeper-Bradley, 1989; Chun *et al.,* 1992; Burleigh-Flayer *et al.,* 1992). Inhalation of MTBE at lower concentrations (<2,000 ppm) also resulted in hypoactivity in rats and mice. Some animals that breathed high levels (8,000 ppm, or 28,800 mg/m^3) of MTBE for several hours a day for several weeks gained less weight than normal, probably because they ate less food while they were inactive. A concentration of 400 ppm (1,440 mg/m^3) did not produce any effects. Based on the NOAEL of 400 ppm, an intermediate-duration inhalation MRL of 0.7 ppm (2.52 mg/m^3) was calculated for MTBE.

When rats (Dodd & Kintigh, 1989), rabbits (Tyl & Neeper-Bradley, 1989), and mice (Burleigh-Flayer *et al.,* 1992; Chun & Kintigh, 1993) breathed high levels

(>3000 ppm) of MTBE intermittently for a period of time ranging from a few weeks to 18 months, some had larger livers than normal, increased kidney and adrenal weights, and decreased body weight gain. Some mice also developed tumors in the liver.

Fischer 344 rats (50 of each sex/dose level) were exposed to MTBE (99% pure) vapor in inhalation chambers at target concentrations of 0, 1440, 10880, and 28800 mg/m^3 (or 0, 400, 3000, and 8000 ppm, respectively) six hours/day, five days/week for up to two years (Chun *et al.,* 1992; Bird *et al.,* 1997; Mennear, 1997). Various clinical signs of toxicity (hypoactivity, ataxia, lack of startle reflex, swollen periocular tissue and salivation) were observed in both sexes at the two highest dose levels. An increased incidence of renal tubular cell adenomas and carcinomas, and of interstitial cell adenomas (Leydig cell tumors) of the testes in male rats was noted in the mid- and high-dose groups.

Sprague-Dawley rats were given MTBE (>99% pure) in olive oil by gavage four times per week for 104 weeks, at doses of 0, 250, or 1000 mg/kg body weight (Belpoggi *et al.,* 1995). There was a dose-related increase in cancers of the blood (leukemia) and cancer (lymphoma) of some of the tissues that produce blood cells 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.

In a 90 day study, groups of Sprague-Dawley rats (ten males and ten females in each test group) were gavaged 0 (corn oil), 100, 300, 900 or 1200 mg/kg of undiluted MTBE (>99.95% pure) daily for 90 days (Robinson *et al.,* 1990). The most

pronounced clinical effect was the profound anesthetic effect at the highest dose. In female rats, elevated cholesterol levels and increased kidney weights were observed at all levels of exposure. For male rats, kidney weights increased only at the two highest doses (>900 mg/kg). Liver weights increased with exposures >900 mg/kg for both male and female rats.

Application of 0.5 mL or 10,000 mg/kg ARCO MTBE (96.2% MTBE) or commercial MTBE (99.1% MTBE) to the skin of rabbits resulted in slight to severe skin irritation (ARCO, 1980). Injection of 0.5 mL of a 1% MTBE solution intradermally in guinea pigs also resulted in skin irritation (ARCO, 1980). Direct application of ARCO MTBE (96.2% MTBE) or commercial MTBE (99.1% MTBE) into the eyes of rabbits resulted in eye redness, discharge, clouding of the cornea, and thickening of the eyelids (ARCO, 1980; Snamprogetti, 1980).

TOXICITY EVALUATION OF MTBE METABOLITES

The potential carcinogenicity of two metabolites of MTBE, formaldehyde and tertiary-butyl alcohol (TBA) has also been examined in animals. Fischer-344 rats given 0, 1.25, 2.5, or 5 mg/mL (males) or 0, 2.5, 5, or 10 mg/mL (females) TBA in drinking water for two years, showed increased incidence of kidney tumors in males at the intermediate doses and increased incidence of focal renal tubule hyperplasia in males at the high dose (Cirvello *et al.,* 1995). In B6C3 F1 mice, 0, 5, 10, or 20 mg/mL TBA given in drinking water for two years significantly increased the incidence of thyroid tumors in all exposed male groups and in females at the two

higher doses. The incidence of follicular-cell adenoma or carcinoma was slightly higher in males at the intermediate dose and significantly higher in females at the high dose (Cirvello *et al.,* 1995).

Data for carcinogenic activity is ambiguous for drinking water exposure to formaldehyde. A study by Soffritti *et al.,* (1989) reported a dose-related increase in the incidence of leukemia and intestinal tumors in Sprague-Dawley rats, although the experimental data was limited. Another drinking water study on formaldehyde by Tyl *et al.,* (1989) using Wistar rats, found no evidence of carcinogenicity.

EVALUATION OF CANCER-CAUSING POTENTIAL BASED ON ANIMAL STUDIES

Experimental studies provide some evidence to suggest MTBE is carcinogenic in rats and mice at multiple organ sites after inhalation or oral-gavage exposure (National Science and Technology Council, 1997; Belpoggi *et al.,* 1995; Chun *et al.,* 1992; Bird *et al.,* 1997; Mennear, 1997) and to regard MTBE as having human cancer causing potential. Some studies suggested that carcinogenicity of MTBE might be due to its two main metabolites, formaldehyde or tertiary-butyl alcohol (TBA) (Ahmed, 2001). However, MTBE has not been classified as a carcinogen by either the Department of Health and Human Services (DHHS), the International Agency for Research on Cancer (IARC), or EPA.

APPLICABILITY OF ANIMAL TESTING DATA TO HUMANS

Animals have the same basic biological features of humans and much empirical evidence exists to show that laboratory animals and human beings respond similarly to chemical exposures (Rodricks, 2007). These similarities increase the probability that results observed in a laboratory setting will predict similar results in humans However, due to differences between species, it is not possible to conclude that humans will absorb the same amount of MTBE as rats or mice or that the effect will be the same. Problems of test interpretation and extrapolation of results to human beings is an area of some controversy. However, animals do generally serve as good models for humans and few other options for testing chemical toxicity exist (ethics prohibit human testing). Some of the differences can be interpreted by the identification of differences in the mechanism of action, or metabolism among species. More often than not the mechanisms are similar and therefore toxicity is similar.

Larger uncertainties exist in the estimates of cancer potency derived from animal studies. The mechanisms by which MTBE causes cancer in animals are not well understood. Animals are exposed to MTBE is much larger quantities and for much longer periods than humans are likely to be exposed to, lessening the likelihood that humans will have the same health outcome suggested by animal studies. Even with this uncertainty, animal study results contribute to the overall

weight of evidence for MTBE carcinogenicity and suggest MTBE may pose a potential for carcinogenicity to humans at high doses.

REGULATORY LIMITS

Based on available data, exposure limits protective of human health have been set for MTBE. EPA has developed a Reference Concentration (RfC) of 3 mg/m^3 (0.8 ppm) for inhaled MTBE (EPA 1994). The Reference Concentration (RfC) is the threshold value for inhalation that represents the doses to which it is believed that humans can be exposed continuously over a lifetime without experiencing adverse effects. The Agency for Toxic Substances and Disease Registry (ATSDR) also develops minimal risk levels (MRLs), which are defined as the "estimate of the daily human exposure to a hazardous substances that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure" (ATSDR, 2000). These MRLs are similar in nature to EPA's RfC values in that they specify health guidance or acceptable exposure levels, but they differ in that they are based on the most sensitive substance-induced endpoint considered to be of relevance to humans, which may be less severe than those considered under the EPA approach. ATSDR has established an MRL of 0.3 mg/kg/day (0.3 ppm) for intermediate-duration oral exposures to MTBE.

A reference dose (RfD) is similar to an RfC, except instead of continuous inhalation exposure, it refers to daily oral exposure. The EPA has not established an

RfD value for MTBE, but Moyer and Kostecki (2003) extrapolated an RfD value of one based on the chronic RfC value. The table below (Table 11) compares non-cancer threshold values established by EPA and ATSDR for MTBE and other selected gasoline constituents. As indicated in this table, the threshold values for MTBE are up to ten times greater than that for other gasoline constituents, suggesting that, in general, MTBE has much lower non-cancer toxicity than other common gasoline constituents.

Table 11. Summary of threshold doses for selected gasoline constituents

Constituent	Chronic Oral RfD (mg/kg-day)	Chronic Inhalation RfC (mg/m^3)	Acute Oral MRL (mg/kg-day)	Intermediate Oral MRL (mg/kg-day)	Chronic Oral MRL (mg/kg-day)
MTBE	1*	3	0.4	0.3	NA
Ethylbenzene	0.1	1	NA	NA	NA
Toluene	0.2	0.4	0.8	0.02	NA
Xylene	2	NA	1	0.2-0.6	NA

*Based on extrapolation from chronic RfC, NA=not available,
Source: Moyer & Kostecki, 2003

HUMAN PATHWAYS OF EXPOSURE TO MTBE

MTBE or any other chemical does not pose a risk to human health unless exposure occurs. The most likely pathway for human exposure is inhalation. For most people, this would likely occur while pumping gasoline and breathing the evaporative losses that occur during refueling; by breathing exhaust fumes while driving a car; or breathing air near highways or in cities where the concentration of MTBE in air would likely be higher. The next most likely exposure for the general public would occur from drinking, swimming, or showering in water that has been contaminated with MTBE. However, MTBE has a taste and smell that most people find unpleasant so prolonged exposure through ingestion or inhalation is less likely. On the other hand, people who consume smaller, less detectable quantities of MTBE in drinking water over long periods of time may not be aware of their exposure. Dermal contact may also occur through accidental spills of MTBE-blended gasoline or through the use of gasoline as a solvent (Ahmed, 2001).

For manufacturing and distribution workers, service station attendants, and auto mechanics, occupational exposure can occur at any point in the manufacture, transportation, distribution, or use of MTBE and gasoline containing MTBE. The duration of exposure is also likely to be higher for this group since contact with MTBE occurs over an eight-hour workday. For the general population, MTBE exposure would typically be brief and infrequent. For instance, refueling a vehicle

generally takes only a few minutes during which exposure to MTBE through evaporative losses might occur.

Intentional exposure to MTBE can also occur during medical treatment. MTBE can be used as an alternative to surgery to dissolve gallstones when injected intraductally (inside the bile duct) (ATSDR, 1996).

ESTIMATES OF HUMAN EXPOSURE TO MTBE

In an occupational exposure setting, employees could be exposed to peak levels of >50ppm during production and transportation processes, and median levels have been measured up to 2 ppm during six hours of exposure (Nihlen *et al.,* 1998). Service station attendants could be exposed in the range of 0.1-1 ppm (average 4 hours), and consumers could be exposed to 1-10 ppm (average 2 minutes) during refueling (Nihlen *et al.,* 1998). The presence of MTBE in ambient air, public buildings and residences can result in longer duration exposures, but at concentrations that are quite low, in the range of 0.001 to 0.01 ppm (Balter, 1997). In the United States, the American Conference of Governmental Industrial Hygienists (ACGIH) recommends that the amount of workroom air be limited to a time-weighted average of 50 ppm, but governmental agencies such as the National Institutes for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) have not established exposure criteria for MTBE (NIOSH, 2008).

Brown (1997) compiled data on concentrations of MTBE in air for 15 difference occupational, commuting, or residential exposure categories, and concentration in potable water were compiled from five states in MTBE-using areas of the United States. Based on these concentrations and characteristics of the exposed populations, average daily and lifetime average doses were estimated. Arithmetic mean occupational doses via air were in the range of 0.1 to 1.0 mg/kg-day (0.1 to 1.0 ppm), while doses from residential exposures, commuting, and refueling were in the range of 0.0004 to 0.006 mg/kg-day (0.0004 to 0.0006 ppm). Lifetime doses for workers were in the range 0.01 to 0.1 mg/kg-day (0.01 to 0.1 ppm). The cumulative dose distribution for the entire population of the MTBE-using regions of the United States was estimated by combining the distributions of doses and the numbers of people in each exposure category. In the MTBE-using areas, arithmetic mean doses via air were estimated to be 0.0053 and 0.00185 mg/kg-day (0.0053 and 0.00185 ppm) for the chronic and lifetime cases, respectively. Approximately 98.5% of the population living in MTBE-using regions uses water with concentrations affected only by atmospheric deposition, if at all, and too low to be detected with current methods (<2 μg/liter). The remaining population uses water with an estimated geometric mean concentration of 0.36 μg/liter, an arithmetic mean concentration of 49 μg/l, and a 95th percentile concentration of 64 μg/liter. Doses via ingestion, inhalation, and dermal absorption were included. The estimated arithmetic mean dose for the population exposed via water was 1.4×10^{-3}mg/kg-day.

COMPARISON OF HUMAN EXPOSURE ESTIMATES TO REGULATORY LIMITS

There are few regulatory limits for MTBE. However, there are protective standards in place to limit human exposure to MTBE. Table 12 compares Minimal Risk Levels, or MRLs, developed for MTBE with exposure values available in published literature showing the amounts of MTBE people are likely to encounter in occupational or ambient settings.

Table 12. Comparison of MTBE Minimal Risk Levels (MRLs) with exposure estimates for workers and consumers

Exposure Route	**Exposure Duration**	**MRL** (ATSDR, 2009)	**Exposure Estimate**	**Exposed Group**	**Exposure Estimate > MRL?**
Inhalation	Acute	2 ppm = 2 mg/kg	0.1 – 1.0 mg/kg/day (Brown, 1997)	Occupational	NO
			>50 ppm (Nihlen *et al.,* 1998)	**Occupational – peak levels during production & transportation**	**YES**
			2 ppm (Nihlen *et al.,* 1998)	Occupational – median during 6 hours of exposure	EQUAL
			0.1-1 ppm (Nihlen *et al.,* 1998)	Occupational – service station attendants average 4 hours	NO
			1-10 ppm (Nihlen *et al.,* 1998)	**Consumers during refueling average 2 minutes**	**MAYBE**
			0.001-0.01 ppm (Balter, 1997)	Residential – ambient air, public buildings, & residences	NO
			0.0004 – 0.006 mg/kg/day (Brown, 1997)	Residential	NO
	Intermediate	0.7 ppm = 7 mg/kg	NA	NA	
	Chronic	0.7 ppm = 0.7 mg/kg	0.01 – 0.1 mg/kg/day (Brown, 1997)	Occupational lifetime	NO
			.0053 mg/kg/day (Brown, 1997)	Residential	NO
			0.00185 mg/kg-day (Brown, 1997)	Residential lifetime	NO
Oral	Acute	0.4 mg/kg/day	1.4×10^{-3} mg/kg/day (Brown, 1997)	Residential	NO
	Intermediate	0.3 mg/kg/day	NA	NA	

For Duration, Acute = 1 to 14 days, Intermediate = 15 to 364 days, and Chronic = >1 year.

Based on these exposure scenarios and available data, the MRL for MTBE would be exceeded in certain occupational settings. According to published exposure estimates, the vast majority of the population is unlikely to encounter MTBE at levels considered harmful to human health. Exposure thresholds for consumers were only exceeded during vehicle refueling, and these exposures are typically very brief (average 2 minutes).

CHAPTER 5 SUMMARY AND RECOMMENDATIONS

SUMMARY

The Clean Air Act Amendments of 1990 mandated the use of fuel oxygenates in two programs. The Winter Oxyfuel Program began in the fall of 1992 and required the use of oxygenated fuel in cold winter months, and year-round use of reformulated gasoline was required beginning in 1995. MTBE production increased substantially after these programs were implemented, from 36.8 million barrels per year in 1992 to 71.9 million barrels annually by 1997 (EIA, 2009).

The presence of MTBE in groundwater has been observed at least since the mid-1980s. The first national survey on the occurrence of volatile organic compounds (VOCs) in untreated ambient groundwater analyzed samples collected between 1985 and 1995 (Squillace *et al.,* 1999). MTBE was one of the most frequently detected VOC in both urban and rural areas. Routine monitoring of ambient ground water between 1993 and 1998 noted the frequent occurrence of MTBE, typically at low levels, in shallow urban ground water in the northeastern United States (Grady, 2001). The occurrence of MTBE and other VOCs were also noted in surveys of community drinking water sources in the United States between 1999-2001 (Clawges *et al.,* 2001; Delzer & Ivahnenko, 2003).

Shortly after MTBE's introduction as a fuel oxygenate, anecdotal reports of acute health symptoms such as eye and nose irritation, headaches, nausea, and dizziness surfaced, leading to concerns about the human health risks from

exposure to MTBE. A review of available literature, to include toxicological studies and epidemiological investigations, show the body of evidence for possible health effects resulting from MTBE exposure in both humans and animals. The most likely pathway for human exposure to MTBE is through inhalation.

A review of nearly a dozen human health effects studies evaluating the association between MTBE exposure and symptoms found that although the reporting of symptoms anecdotally related to MTBE exposure did increase after the MTBE reformulated fuel (RFG) program began (Joseph, 2002), no clear evidence or significant association was found between exposure and adverse health effects (Borak *et al.,* 1998; Moolenaar *et al.,* 1996; Brown, 1997; Fiedler *et al.,* 1994; Cain *et al.,* 1994, Prah *et al.,* 1994; Duffy *et al.,* 1994; Nihlen *et al.,* 1998). The MTBE metabolite tertiary-butyl alcohol (TBA) is processed and removed from the human body within 24 hours (Lee *et al.,* 2001) and there was no suggestion of adverse health impacts from this mechanism.

There was some evidence to suggest MTBE is carcinogenic in rats and mice at multiple organ sites after inhalation or oral-gavage exposure (National Science and Technology Council, 1997; Belpoggi *et al.,* 1995; Chun *et al.,* 1992; Bird *et al.,* 1997; Mennear, 1997). For MTBE metabolites, there was a slight increase in leukemia and intestinal tumors in Sprague-Dawley rats (Soffritti *et al.,* 1989), but not in Wistar rats (Tyl *et al.,* (1989). Animal testing has suggested that MTBE may have the potential to cause cancer in humans at high doses, but MTBE has not been classified as a carcinogen by either the Department of Health and Human Services,

the International Agency for Research on Cancer, or EPA. Instead, it has been suggested that the use of MTBE as a fuel oxygenate may have anticipated health benefits by reducing the number of cancer-deaths attributable to air pollutants (Erdal *et al.,* 1997; Spitzer, 1997).

RECOMMENDATIONS

The precautionary principle states that with evidence of threats of significant harm, even in the face of scientific uncertainty, precautionary actions should be taken to protect public health and the environment. After reviewing the scientific literature available for MTBE, there is not compelling evidence to suggest that exposure to MTBE causes adverse health effects, especially under the conditions most people would likely be exposed (inhalation in small doses for brief periods of time). Since the threats of harm are relatively small, the use of MTBE as a fuel oxygenate provides, at best, an example of the weak version of the precautionary principle.

In the weak version of the precautionary principle, preventative measures can be taken in the face of uncertainty, but they are not required. With regard to harm, there must be some evidence that the threat is likely to occur and have some degree of severity in consequences. This version also includes consideration of the costs of the precautionary measure. And finally, the requirement to justify the need for action (the burden of proof) generally falls on those advocating

precautionary action. The case of MTBE fits all of these criteria. Actions to discontinue use of MTBE as a fuel oxygenate were taken after it was found in groundwater, even though there was uncertainty about MTBE's health impact to humans or the environment. MTBE's chemical structure and properties suggested that its release into the environment would result in widespread contamination in groundwater and that remediation might prove challenging. MTBE was chosen as the primary fuel additive largely based on cost and availability. And finally, once MTBE was brought into widespread use and complaints surfaced about potential health effects from exposure to MTBE, it was the public who signed petitions and lobbied for its removal as a fuel oxygenate (Erdal & Goldstein, 2000).

According to Cameron (2006), strong versions of the precautionary principle justify or require precautionary measures be taken, and when knowledge is limited, those who argue a proposed activity are responsible for demonstrating that the proposed activity is sufficiently "safe" before approval is granted. A stronger case could have been made for MTBE adhering to the precautionary principle had the following actions been taken. First of all, studies about the potential health impacts from exposure to MTBE should have been conducted and assessed fully prior to its use. As mentioned, the presence of MTBE in groundwater has been observed at least since the mid-1980s. However, its use as a fuel oxygenate came much later (1992) and the majority of health studies I located that addressed potential human health impacts from exposure to MTBE started after reports of health complaints emerged in Alaska and elsewhere in late 1992. If this had been done, the decision

to use MTBE would have been made with the full spectrum of information available and not driven primarily by economic factors. Analysis of MTBE health effects data showed little evidence of harm. Armed with this information, the introduction of MTBE as a fuel oxygenate could have been better supported and therefore would have garnered greater public awareness and support. Appropriate precautions could then be taken to mitigate some of these health risks. For example, exposure to MTBE-containing fuels is reduced through the use of vapor recovery systems at gas refueling stations.

The issue of leaking underground storage tanks needs to be addressed. Leaking tanks that continue to add MTBE-containing gasoline into groundwater should be removed or cleaned up so that their contents are no longer threats to the environment or human health. There are other components of gasoline (like benzene) that have known health risks that far exceed those of MTBE. The public debate about MTBE-contamination in groundwater has brought to light (or at least refocused attention) on a much larger issue about how these tanks are being managed. Great strides in environmental protection could be made if this issue alone was addressed.

Precautionary action also includes the consideration of alternatives. For example, emission control devices such as filters and catalytic converters capture and prevent carbon monoxide emissions without the use of fuel oxygenates. Changes to the way gasoline is formulated may have reduced the harmful properties of fuel emissions without the need for fuel oxygenates. Policy changes

to encourage drivers to decrease the number of vehicle miles driven may have also helped to decrease emissions, regardless of the gasoline formula or whether an oxygenate was added. And if a fuel oxygenate were used, it would at least have been evaluated against all available fuel oxygenates and selected based on its usefulness to lower harmful fuel emissions without associated health risks.

When concerns about MTBE surfaced, the reaction was to switch oxygenates, presumably to one with less risk. However, concerns with ethanol have surfaced. MTBE-contaminated groundwater is widespread and will presumably be compounded with the spread of contamination from ethanol-containing fuel because the problem of leaking underground storage tanks remains. Only when the validity of solving emissions problems through the use of fuel oxygenates is questioned will the underlying problem become clear. The problem is fuel driven. Despite improved technologies, emissions are still problematic due to increases in the number of cars and vehicle miles driven. The use of fuel oxygenates may have kept harmful emissions from worsening, but it is not a solution. A better method for reducing emissions would be to reduce fossil fuel use.

The possibility exists that in the end, MTBE may have achieved greater air quality benefits with fewer human health impacts than ethanol. If underground storage tanks had not spread MTBE contamination to the extent that it did and the public had not reacted so strongly, I believe MTBE would still be in use but still not quantified in terms of health risk.

At the time of this writing, chemical policy in the United States is changing and moving towards a more precautionary approach. With the European Union's adoption of the precautionary principle in its Registration, Evaluation, Authorisation and Restriction of Chemical substances (REACH) program, the world has had an opportunity to see the precautionary approach work in a large public forum. This program attempts to improve the knowledge gap that exists for the majority of chemicals in commerce and calls for toxicity testing of new chemicals prior to their introduction in the market. It also requires testing of existing chemicals starting with those of high production volume. Within the United States, there is already evidence that precautionary principles will be brought to the forefront of environmental planning and management. The work of several western states to create climate change policies more stringent and protective than those put forth by the federal government has drawn the attention of the new administration. In our own State of Washington, direct mention of the precautionary principle is now found on the websites of several state agencies: Department of Ecology, Department of Fish and Wildlife, Department of Health, Department of Natural Resources, Puget Sound Partnership, and Washington State Board of Health (State of Washington, 2009).

Evaluating MTBE's use as a fuel oxygenate against precautionary principles provides a lesson that can help guide future policy decisions, as it encourages actions that are more protective of human and environmental health.

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