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# OXYFUELS INFORMATION NEEDS

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# OXYFUELS INFORMATION NEEDS

The purpose of this document is to highlight the types of information needed to improve scientific understanding of the environmental risks and benefits of oxygenated gasoline and reformulated gasoline (collectively designated as "oxyfuels") in relation to conventional fuels. The intention is that this broad description of needs will provide a foundation for further efforts to establish priorities among different areas of work and to define specific studies in greater detail, rather than attempting here to rank issues or needs in terms of their relative importance.

This document is organized to provide first some background information on oxyfuels, along with a general framework for comparative risk assessments of fuels. Next comes a very brief summary of what has already been done in the way of scientific testing, research, and assessments on oxyfuels and conventional fuels, and what work is currently underway or planned to address such information needs. The final section of this document discusses further information needs.

## BACKGROUND

Throughout much of the twentieth century, the general population has been routinely exposed to conventional gasoline and its evaporative and combustion emissions. The environmental impacts of these emissions have been a principal focus of the Clean Air Act and various efforts to improve air quality. The 1990 amendments to the Clean Air Act required two separate programs to address air quality problems in areas that had failed to attain the national ambient air quality standards (NAAQSs) for carbon monoxide and for ozone. Starting in November 1992, oxygenated gasoline has been required during cold-weather months in several CO-nonattainment areas. Reformulated gasoline has been required year-round in the worst ozone-nonattainment areas since January 1995, with some additional areas voluntarily electing to adopt the reformulated gasoline program. Largely because of these programs, millions of people in the United States are now exposed to oxyfuel emissions. Although exposure to conventional gasoline has long been commonplace, the introduction of oxyfuels has raised new questions about the benefits and risks of chemicals that are used on such a widespread scale.

Oxygenated gasoline contains 2.7% oxygen (by weight), typically achieved by the addition of 15% methyl tertiary butyl ether (MTBE) or 7.5% ethanol (by volume). Reformulated gasoline (RFG) has lower concentrations of certain volatile organic compounds in a formulation intended to reduce ozone-forming hydrocarbons and air toxics (i.e., benzene, butadiene, formaldehyde, acetaldehyde, POM) by 15 to 17% in Phase 1 and even further in Phase 2, which begins January 2000. In addition, RFG has 2.0% oxygen (by weight), typically achieved by the addition of 11% MTBE or 5% ethanol (by volume). (MTBE has been used to enhance the octane rating of conventional gasolines in the United States since the 1970s, with the MTBE concentration usually between 2 and 9% by volume, but such fuels, to which MTBE is added for octane rather than oxygenate purposes, are not encompassed by the present usage of the term oxyfuels, which can also be defined as having $\geq$2.0% oxygen by weight.)

Although other oxygenates, including (but not limited to) ethanol and ethyl tertiary butyl ether (ETBE), may be used in gasoline, MTBE is the most widely used oxygenate at present. Very little or no information exists on the health effects of oxygenates other than MTBE and ethanol (and that for ethanol pertains to ingestion, not inhalation). Therefore, much of the

discussion here is dominated by the information that is available on MTBE. Notwithstanding this focus on MTBE, a meaningful assessment of the environmental risks and benefits of oxyfuels must be *comparative*; that is, it must consider any given oxyfuel in relation to the environmental risks and benefits of conventional fuels. Simply stated, the question is whether public health and the environment are or are not better off with the substitution of oxyfuels for conventional fuels.

A general framework for the comparative assessment of the environmental (health and ecosystem) risks and benefits of fuels may be found in Figure 1. The figure depicts the broad areas of research needed to support comparative risk assessments of fuels and fuel additives: emissions characterization, environmental fate, exposure, human health effects, ecosystem effects, global climate change, and risk reduction. The figure also serves to illustrate the major environmental pathways of impacts associated with motor fuel production, distribution,

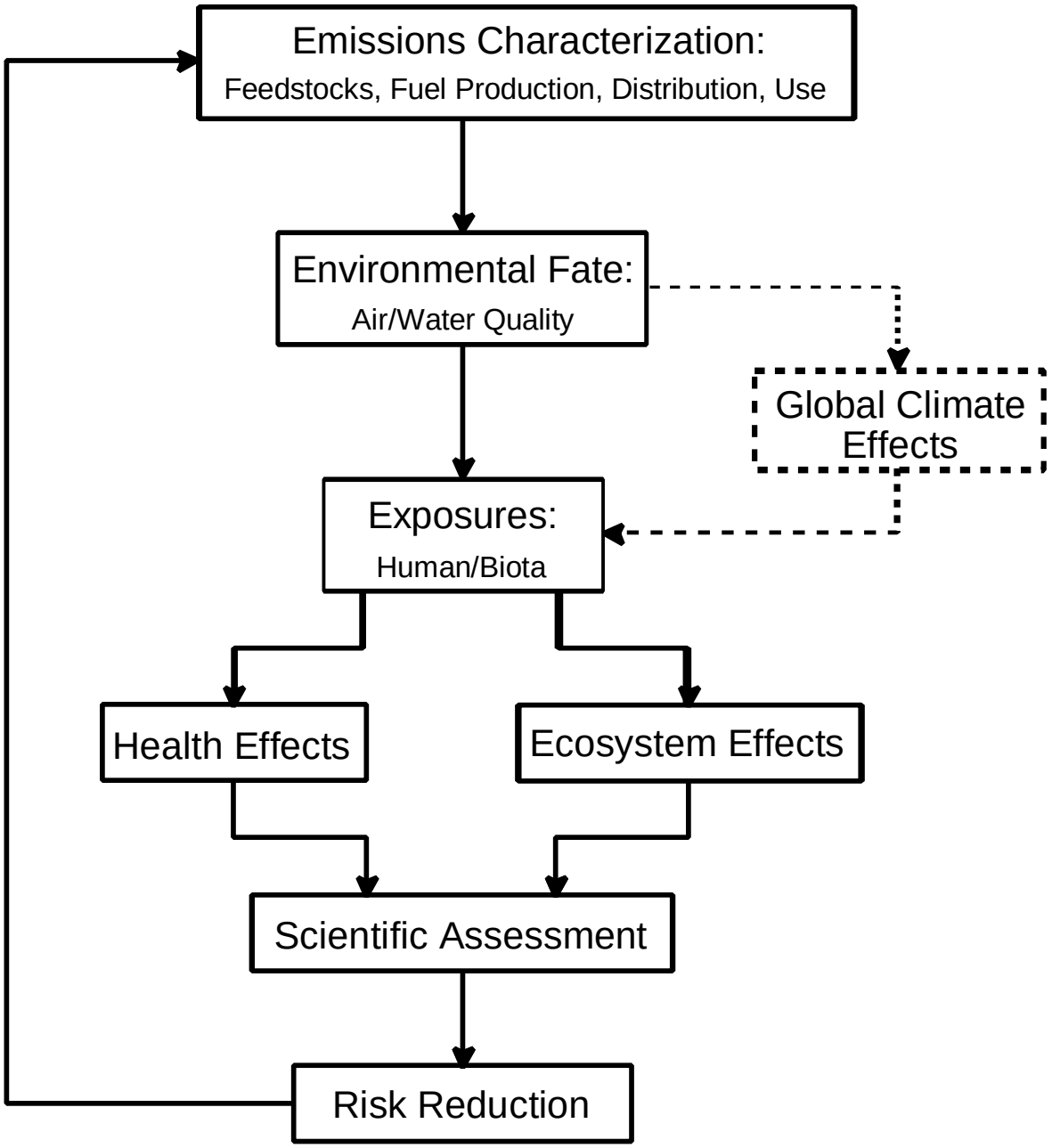


**Figure 1. Areas of research needed for comparative risk assessments of fuels and fuel additives.**

Source: U.S. Environmental Protection Agency (1992).

storage, and use. As reflected in the figure, research in any one area is related to one or more other areas of work. For example, health risk characterization requires not only information on health effects but also on human exposures, which in turn requires air and soil/water quality data. Each of the boxes in Figure 1 could be progressively expanded to indicate various subdisciplinary areas of research and individual projects within those respective areas. For example, an understanding of air quality impacts involves information on atmospheric emissions, transport, and transformation, with each of these areas potentially encompassing several projects. Given this general framework for comparing the relative benefits and risks of different fuels, this document highlights certain priority areas of needed work specific to oxyfuels.

## PAST WORK

As suggested by Table 1, a great deal of work has been devoted to the environmental effects of conventional (pre-1990) gasoline, including the characterization of mobile source emissions, albeit more so for selected constituents of the combustion emissions of conventional gasoline than for the whole combustion emissions or for evaporative emissions. Similarly, the health effects associated with conventional fuels have been extensively investigated and assessed [e.g., see recent symposia papers in Environmental Health Perspectives Supplements, 101 (suppl. 6), 1993, and 102 (suppl. 4), 1994]. To a lesser extent, concentration data collected in microenvironmental studies of conventional fuel emissions are available for estimating exposures. However, with the exception of carbon monoxide, population exposures to mobile source emissions have not been measured. In this and other respects, Table 1 provides only a rough indication of the information available under the various categories listed; however, it provides no guidance as to the extent or adequacy of the information.

Despite the many studies related to conventional fuels, much remains to be learned. For example, in contrast to the extensive databases on the health effects of some of the constituents of gasoline (e.g., benzene) and of wholly vaporized gasoline (which contains different proportions of constituent compounds than the evaporative emissions one normally encounters) and combustion emissions or by-products (e.g., carbon monoxide, nitrogen oxides, ozone),

## Table 1. Categories of Health Effects and Exposure Data Available for Motor Vehicle Fuel Additives and Fuel Products[1]

| | Animal | | | | | | | | Human | | | | Exposure | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pharmaco-kinetics | Muta-genicity | Sub-chronic Toxicity | Chronic Non-cancer | Reproduc-tive Toxicity | Develop-mental Toxicity | Neuro-toxicity | Onco-genicity | Acute Toxicity | Chronic Non-cancer | Cancer | Pharmaco-kinetics | Emissions | Transport and Fate | Moni-toring |
| **Neat Additive:** | | | | | | | | | | | | | | | |
| MTBE | | | | | | | | | | | | | | | |
| vapor | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 0 | 0 | ++ | +++ | ++ | + |
| liquid | + | 0 | + | + | + | + | + | + | + | 0 | 0 | + | ++ | ++ | + |
| EtOH | | | | | | | | | | | | | | | |
| vapor | + | 0 | + | 0 | 0 | 0 | + | 0 | + | 0 | 0 | 0 | +++ | ++ | 0 |
| liquid | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | ++ | 0 |
| ETBE | | | | | | | | | | | | | | | |
| vapor | 0 | ++ | + | 0 | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 | + | + | 0 |
| liquid | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | + | 0 |
| TAME | | | | | | | | | | | | | | | |
| vapor | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 |
| liquid | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 |
| TBA | | | | | | | | | | | | | | | |
| vapor | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 |
| liquid | 0 | + | + | + | 0 | 0 | 0 | ++ | 0 | 0 | 0 | 0 | + | 0 | 0 |
| TAEE, DIPE, etc.[2,3] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Fuel Product:** | | | | | | | | | | | | | | | |
| Pre-1990 gasoline: | | | | | | | | | | | | | | | |
| vapor[4] | ++ | ++ | ++ | ++ | + | + | ++ | ++ | ++ | ++ | ++ | + | +++ | ++ | ++ |
| combust. | ++ | +++ | ++ | ++ | + | + | + | ++ | +++ | ++ | ++ | + | +++ | ++ | ++ |
| Post-1990 gasoline: | | | | | | | | | | | | | | | |
| evap. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ++ | + | + |
| combust. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ++ | + | + |

**Table 1 (cont'd). Categories of Health Effects and Exposure Data Available for Motor Vehicle Fuel Additives and Fuel Products[1]**

| | Animal | | | | | | | | Human | | | | Exposure | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pharmaco-kinetics | Muta-genicity | Sub-chronic Toxicity | Chronic Non-cancer | Reproduc-tive Toxicity | Develop-mental Toxicity | Neuro-toxicity | Onco-genicity | Acute Toxicity | Chronic Non-cancer | Cancer | Pharmaco-kinetics | Emissions | Transport and Fate | Moni-toring |
| Post-1990 gasoline plus: | | | | | | | | | | | | | | | |
| MTBE | | | | | | | | | | | | | | | |
| evap. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ++ | 0 | 0 | 0 | ++ | + | + |
| combust. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 | 0 | ++ | + | + |
| EtOH[5] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ++ | + | + |
| ETBE[5] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ++ | 0 | 0 |
| TAME[5] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + |
| TBA[5] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| TAEE, DIPE, etc.[3,5] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

[1]+++ = extensive data; ++ = moderate; + = some; 0 = none.
[2]Includes both vapor and liquid.
[3]Several other fuels and fuel additives (e.g., various ethers and esters) could be added to this list of fuels and fuel additives; however, any attempt to list all such products would be almost certainly incomplete, and at this time there is little distinction among them in terms of the information available or needed.
[4]Experimental animal studies have generally used wholly vaporized gasoline, whereas typical vapors to which humans are exposed are likely to have fewer of the heavy molecular weight VOCs contained in liquid gasoline.
[5]Includes both evaporative and combustion emissions.

N.B.: These characterizations of the data available for the specified endpoints are not intended to denote the quality or adequacy of the database for risk assessment purposes. Moreover, the headings may be collapsed across quite disparate types or levels of information (e.g., "Transport and Fate" and "Monitoring" do not differentiate between air, water, and soil).

information on the effects of gasoline evaporative and whole combustion emissions (with or without atmospheric transformation) is limited. Moreover, most of the older data available on unleaded gasolines are based on formulations that are not necessarily representative of current (post-1990) formulations of gasolines.

With respect to oxyfuel emissions characterization, the Auto/Oil Air Quality Improvement Research Program (e.g., 1990, 1991a,b,c; Carter et al., 1991; Kiskis et al., 1989) has provided a considerable body of data on emissions from various formulations of gasoline, including MTBE-oxygenated gasoline. A limited amount of work on MTBE exposure levels in relation to oxyfuel use has been conducted thus far (Clayton Environmental Consultants, 1993; Hartle, 1993; Johnson, 1993; Lioy et al., 1994; Anderson et al., 1995). For example, using limited measurement data (rounding up to the nearest half order of magnitude) along with data on typical activity patterns, Huber (1993) estimated inhalation exposure levels for various scenarios such as refueling, commuting, and private or public garages and dwellings. Although the air concentrations experienced during refueling (as high as 36 $mg/m^3$ for a reasonable worst case) were estimated to be highest of all the scenarios considered, the cumulative exposure levels associated with refueling (94 $mg/m^3$ x h) did not rank as high as some other scenarios because less time is spent refueling than in other activities. Annual exposure estimates were 187 $mg/m^3$ x h for commuting (assuming 10 h/week commuting) and 75 to 150 $mg/m^3$ x h for personal residence with attached garage (assuming 98 h/week at home and different MTBE concentrations emitted from a vehicle in the garage). Assuming 20 h/week in outdoor activities and an ambient MTBE concentration ranging from 0.036 to 0.36 $mg/m^3$, cumulative annual exposure levels outdoors might range from 37 to 370 $mg/m^3$ x h. This example illustrates the importance of having microenvironmental concentration data in developing exposure estimates for health study "range finding" purposes.

Adjusting the above estimates for the differing concentrations of MTBE in oxygenated and reformulated gasolines for different periods of time during the year, EPA estimated high (reasonable worst case) annual inhalation exposures to be on the order of 0.11 $mg/m^3$ (U.S. Environmental Protection Agency, 1994). More recent exposure estimates (Health Effects Institute, 1996; Interagency Oxygenated Fuels Assessment Steering Committee, 1996) are not inconsistent with such an estimate. However, insufficient data exist to state definitively what a “true upper bound” exposure may be or even what an “average” exposure may be for the general

population. Also, these estimates do not address the possibility of exposure via other routes, e.g., through drinking water.

Studies on MTBE health effects date back to the early 1980's, including some animal toxicity studies (e.g., Greenough et al., 1980) and several reports of the clinical use of MTBE to dissolve gallstones in human patients (e.g., Allen et al., 1985). However, most of the information on MTBE health effects has come from a program of testing conducted under a 1987 negotiated enforceable consent agreement between EPA and the Oxygenated Fuels Association (OFA), which provided several studies on the inhalation toxicity of MTBE in laboratory animals (Table 1). In one of these studies, rats were exposed to approximately 1,450, 10,900, or 28,700 $mg/m^3$ (Chun et al., 1992). Based on findings of increased kidney and liver weights, increased severity of spontaneous renal lesions, prostration, and swollen periocular tissue at 10,900 $mg/m^3$, an inhalation reference concentration (RfC) of 3 $mg/m^3$ was derived for MTBE (IRIS, 1993). The reference concentration is defined as an estimate (with uncertainty spanning about an order of magnitude) of a continuous inhalation exposure level for the human population (including sensitive subpopulations) that is likely to be without appreciable risk of deleterious noncancer effects during a lifetime.

The database on MTBE toxicity also includes reproductive and developmental effects. A two-generation rat study (Neeper-Bradley, 1991) showed reduced offspring growth at 10,900 $mg/m^3$ but not at 1,450 $mg/m^3$ MTBE. Based on this finding, a conservative preliminary estimate of a level at which no adverse developmental toxicity is likely to occur in humans (including sensitive subpopulations) was judged to be 48 $mg/m^3$ (U.S. Environmental Protection Agency, 1994).

Two cancer studies of laboratory rodents exposed by inhalation to pure MTBE and eleven mutagenesis studies were also conducted pursuant to the 1987 consent agreement. Based on these studies, EPA's Office of Research and Development (ORD) considered the weight of evidence for MTBE carcinogenicity to fall in Group C (possible human carcinogen based on limited evidence from animal studies), but a more recent report of a study of cancer effects in rats exposed to MTBE by gavage (Belpoggi et al., 1995) would tend to support a B2 classification under the 1986 guidelines (Federal Register, 1986). However, no formal assessment of the carcinogenicity of MTBE has been performed by EPA at this time. Further discussion of this

issue may be found in the "Interagency Assessment of Potential Health Risks Associated with Oxygenated Gasoline" (Interagency Oxygenated Fuels Assessment Steering Committee, 1996).

Following the introduction of MTBE-oxygenated gasoline in Fairbanks and Anchorage, Alaska in November 1992, numerous reports of acute health symptoms in connection with the new fuel were registered by residents in those areas. In response to the concerns expressed by officials of the State of Alaska, a research program involving government, industry, and academia was initiated to investigate the acute human health effects of MTBE. This effort included two independently conducted inhalation chamber studies (Prah et al., 1994; Cain et al., 1994) on a total of 80 human volunteers who breathed neat MTBE concentrations of 5 to 6 $mg/m^3$ for 1 hour at a time. Subjects were evaluated for both subjective (self-reported) symptoms and objective (inflammation, neurobehavioral) effects. No effect of MTBE exposure could be detected in either study. More recently, a chamber study in Sweden (Johanson et al., 1995) using 2-hour exposures to MTBE concentrations up to 180 $mg/m^3$ also showed no effects in 10 subjects.

Field studies of human populations were also conducted in various locations. A study in New Jersey (Mohr et al., 1994) evaluated 237 garage workers from two groups: (1) northern New Jersey workers sampled during the wintertime oxyfuel program and (2) southern New Jersey workers sampled 10 weeks after the phase-out date for the program in that area. Essentially no differences in symptom reports were found between the northern (high-exposure) and southern (low-exposure) groups. (Subgroups of refuelers differed significantly in pre/postshift symptom reports between north and south, but not significantly when matched for age, gender, and education.) Another study in the New Jersey area (Fiedler et al., 1994) investigated MTBE-related symptom reports in 14 persons with known multiple chemical sensitivity (MCS), 5 persons with chronic fatigue syndrome (CFS), and 6 normal controls. Both MCS and CFS subjects reported more symptoms than controls, but the pattern of their reports "did not provide clear evidence to support that an unusually high rate of symptoms or an increase of symptoms was occurring uniquely where MTBE was most prevalent" (i.e., refueling or driving an automobile).

Another field study (White et al., 1993) attempted to compare the prevalence of symptom reports in 221 Stamford, CT, residents (with oxyfuels) and 265 Albany, NY, residents (without oxyfuels). The area without MTBE-oxyfuel had symptom prevalences as high as those in the area with MTBE-oxyfuel (possibly because of the prevalence of illnesses due to allergies and viruses at the time of the study). In Stamford, 8 workers with the highest blood MTBE levels were

significantly more likely to report symptoms (although the relationship between symptom reports and tertiary butyl alcohol [TBA], a major metabolite of MTBE and indicator of MTBE exposure, was not significant). A field study in Fairbanks, AK (Moolenaar et al., 1994), found evidence of a significant correlation between MTBE exposure and MTBE concentrations in the blood, but the positive relationship between health symptom reports and blood MTBE levels was not statistically significant.

Experimental studies of odor thresholds in human subjects indicate that MTBE has very low detection and recognition thresholds. Moreover, recent experimental work (Smith et al., 1994) on odor thresholds indicates interactive effects of MTBE and different types of gasoline. Alaskan gasoline with MTBE added was more readily detected than "lower 48" gasoline with MTBE.

In 1995, the State of Wisconsin conducted a random-digit-dial telephone survey of residents of Milwaukee and two control areas in response to the concerns of Milwaukee citizens regarding health effects of reformulated gasoline after the initiation of the RFG program in January 1995. In addition to about 500 residents of Milwaukee who were interviewed by telephone, approximately equal numbers of residents in Chicago and in non-RFG areas of Wisconsin were surveyed. Chicago was selected because essentially the same RFG fuels were used there, but very few health complaints had been registered by Chicagoans. The results of the study indicated that symptom prevalence was significantly higher in Milwaukee than in either Chicago or Wisconsin. In Milwaukee, persons were more likely to report symptoms if they had experienced a cold or flu, smoked cigarettes, or were aware that they had purchased RFG. The fact that symptom prevalence was essentially equivalent in Chicago and Wisconsin suggested "that factors, other than RFG use, significantly contributed to the differences in symptom prevalence between Milwaukee and the other two areas studied" (Anderson et al., 1995). However, because of its unavoidable design limitations, the study could not "rule out subtle effects of RFG exposure, or the possibility that a relatively small number of individuals may have a greater sensitivity to RFG mixtures."

In Milwaukee, MTBE was the oxygenate in 49% of the RFG samples, ethanol in 38%, and ETBE in 14%. It was not possible to identify with any confidence the specific type of these three oxyfuels to which individual Milwaukee residents were exposed. This raises the point that the use of multiple oxygenates in an area greatly complicates exposure analysis. It also

underscores the point that information on exposure and health effects for oxygenates other than MTBE is quite limited. However, a study in Alaska investigated personal exposures to gasoline during refueling with either regular unleaded gasoline or gasoline oxygenated with 10% ethanol (Backer et al., 1995). Blood samples provided before and after refueling, along with ambient air and personal breathing zone (PBZ) samples, were analyzed for selected volatile organic compounds (benzene, ethylbenzene, toluene, m-/p-xylene, and o-xylene). The presence or absence of ethanol in the gasoline made no difference to the concentrations of VOCs in blood or in PBZ air.

Although a very large body of literature on the health effects of ingested ethanol is available, virtually no work has been devoted to the effects of inhaled ethanol at environmentally relevant concentrations. Four-week inhalation toxicity studies of ETBE (Ryan et al., 1991; IIT Research Institute, 1991; Wells, 1993) and tertiary amyl methyl ether (TAME) (White, 1993;) have provided some evidence of hepatic, renal, and neurobehavioral toxicity, but these studies in themselves are not an adequate basis for inhalation health risk assessments of ETBE or TAME. No inhalation toxicity information is available for tertiary amyl ethyl ether (TAEE) or diisopropyl ether (DIPE).

The above discussion applies to inhalation health risks. The effects of exposure via other routes must also be considered. A recent report of a preliminary assessment by the U.S. Geological Survey (Squillace et al., 1995) indicates that MTBE was detected in approximately 80% of monitoring wells sampled in the Denver area. The report raises questions about the persistence of MTBE in groundwater and whether such apparently widespread contamination could be attributable solely to point source releases (e.g., leaking underground storage tanks). The potential for human exposure to MTBE in drinking water remains to be determined. However, even if no human exposure occurs, excessive levels of oxygenates in groundwater could possibly have adverse effects on ecosystems.

As indicated in Table 1, information on the health effects of oral exposure to MTBE is quite limited. To date, it has not been possible to establish an oral reference dose (RfD) for MTBE, because of the inadequate database. A study of carcinogenic effects in Sprague-Dawley rats exposed to MTBE in olive oil by gavage for 2 years showed dose-related increases in lymphomas and leukemias in females and in interstitial cell tumors of the testes in males (Belpoggi et al., 1995). No results of chronic cancer bioassays for any of the other oxygenates have been

published to date, except for TBA, which is also a metabolite of both MTBE and ETBE. Cirvello et al. (1995) administered TBA to rats and mice in their drinking water for two years and found an increased incidence of rare kidney tumors in male rats and thyroid tumors in female mice. The study did not determine whether alpha-2$\mu$-globulin was present in the male rat kidneys. Genotoxicity and subchronic toxicity studies in rodents dosed orally with TAME showed no evidence of mutagenicity or clastogenicity but did show dose-related increases in adrenal and kidney weights (Daughtrey and Bird, 1995).

In November 1993, ORD issued an "Assessment of the Potential Health Risks of Gasoline Oxygenated with MTBE" (U.S. Environmental Protection Agency, 1993). In assessing the evidence on acute inhalation health effects available at that time, the ORD assessment concluded:

> "There is unlikely to be a substantial risk of acute health symptoms among healthy members of the public receiving 'typical' environmental exposures under temperate conditions.... This leaves the question open about more subtle health risks, especially among susceptible subpopulations."

Also, in an effort to respond to evident public concerns about the MTBE cancer issue as well as acute inhalation health effects, ORD prepared "Health Risk Perspectives on Fuel Oxygenates" (U.S. Environmental Protection Agency, 1994), concluding:

> "With the currently available information, there is no basis to expect that the use of MTBE-oxygenated gasoline or MTBE-reformulated gasoline will pose a greater public health risk than traditional gasoline. [However], no conclusions are drawn about major fuel formulations using oxygenates other than MTBE because of the lack of health or exposure data on them."

The latter report also noted, "To improve understanding of the health trade-offs between different types of fuels, more research and evaluation is needed," particularly if one wants "to quantitatively estimate the relationship between use of these fuels and improvements in ozone and CO air quality" (U.S. Environmental Protection Agency, 1994).

More recently, a Federal Interagency Oxygenated Fuels Assessment Steering Committee, under the coordination of the National Science and Technology Council and the Office of Science and Technology Policy under the Executive Office of the President, concluded: "The available scientific evidence regarding human exposure to oxygenated gasoline and acute health symptoms was considered insufficient to develop estimates of exposure-related effects" (Interagency Oxygenated Fuels Assessment Steering Committee, 1996). As for cancer, "it is not known

whether the cancer risk of oxygenated gasoline containing MTBE is significantly different from the cancer risk of conventional gasoline," due in part to "a lack of health data on the nonoxygenated gasoline vapors to which humans are actually exposed." Moreover, "[t]he data were generally inadequate to evaluate the health risks of oxygenates other than MTBE, a factor which makes other oxygenates and gasoline mixtures to which they are added all the more important to investigate further" (Interagency Oxygenated Fuels Assessment Steering Committee, 1996).

Similar conclusions were reached by the Oxygenates Evaluation Committee convened by the Health Effects Institute. A special report of the Committee stated: "Adding oxygenates is unlikely to substantially increase the health risks associated with fuel used in motor vehicles: hence, the potential health risks of oxygenates are not sufficient to warrant an immediate reduction in oxygenate use at this time. However, a number of important questions need to be answered if these substances are to continue in widespread use over the long term" (Health Effects Institute, 1996).

The above reports are currently under review by a panel of scientists organized by the National Academy of Science of the National Research Council, with a report of the panel expected in mid-1996. It is already quite evident, however, that a consistent theme in all of the reports is the need for more information on the exposure and health aspects of conventional and oxygenated fuels.

## WORK CURRENTLY UNDERWAY OR PLANNED

As listed in Table 2, several initiatives are currently planned or underway to obtain information that may be of value to future health risk assessments of oxyfuels. It should be understood that the checked categories of work may reflect quite different levels of effort and that the presence of a check mark does not necessarily signify that the work to be conducted will provide adequate information for the endpoint in question.

Under a cooperative agreement between EPA and the State of Alaska, several projects are being conducted to investigate emissions related to ethanol-oxygenated gasoline, including studies of the evaporative and combustion emissions from Alaskan gasoline with and without 10%

ethanol. A study of the odor thresholds for these fuels is also included in this effort, which is expected to be largely completed by mid-1996.

Plans exist to conduct experimental chamber studies of persons with self-reported sensitivity to oxyfuels. These studies would attempt to produce symptoms and signs of oxyfuel exposure under controlled conditions and explore some of the variables contributing to any such effects. Various issues about the design of such a study were discussed at a workshop convened by EPA on April 5, 1995, and a report summarizing those discussions and an outline of a study protocol was prepared by Benignus (1995). At this writing, EPA is attempting to recruit subjects for the study. A similar study is planned by the Environmental and Occupational Health Sciences Institute (Lioy, personal communication).

The feasibility of designing an epidemiological study on acute health effects of MTBE was the subject of a workshop held by EPA on April 4, 1995. A panel of outside experts was charged with preparing a report for the Agency on issues to be considered in designing such an epidemiological study. That report (SRA Technologies, Inc., 1995) offered several recommendations, in particular suggesting that "[a] broad cross-section of epidemiologists should be provided an opportunity to develop study designs..., compete for funding, and investigate specific hypotheses on exposed populations before and after the introduction or use of MTBE/gasoline." However, the report cautioned that "[s]urveillance programs to monitor the public health impact of changes in gasoline formulation should not be considered in the absence of a clear and clinically-based case definition," although if suitable biomarkers of

Insert Table 2 here.

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Table 2 is available as a separate PDF file.

exposure can be identified, it may be useful to monitor such indicators. The report also suggested that aldehydes associated with oxyfuel combustion or photo-oxidation could be contributing to symptom reports and that this hypothesis needed further study.

Some work is currently being done on a voluntary basis by industry. The OFA is sponsoring work by the Chemical Industry Institute of Toxicology (CIIT) on the pharmacokinetics and cancer mechanisms of MTBE. A physiologically based pharmacokinetic (PBPK) model for MTBE and TBA has been developed in rats (Borghoff et al., 1996) to help interpret results of animal studies and to serve as a basis for developing a human PBPK model. The human PBPK model is then in turn to be used to integrate mechanistically the internal (effective) dose for various MTBE exposures with potential responses to MTBE. Mechanistic studies are also being conducted at CIIT to evaluate the relevance of male rat tumors to humans (Prescott-Mathews et al., 1996; Poet et al., 1996) and to determine if MTBE acts to initiate or to promote liver tumors in female mice (Moser et al., 1996). In addition, a molecular-dosimetry study is to evaluate whether the formaldehyde formed from the metabolism of MTBE results in the formation of DNA-protein cross-links in targeted tissues. Other tumor sites in rats and mice exposed over a lifetime to MTBE or TBA are also to be investigated for their relevance to humans.

Testing of TAME is being done under the terms of an enforceable consent agreement under the Toxic Substances Control Act (TSCA). A consortium of companies has agreed to conduct studies on pharmacokinetics, subchronic toxicity in two species, reproductive and developmental toxicity, mutagenicitiy, and neurotoxicity (Federal Register, 1995). ARCO Chemical has also indicated a commitment to conduct more in-depth studies of ETBE, including pharmacokinetics, a 90-day subchronic toxicity study in two species, cell proliferation studies, and a neurotoxicity screening battery (functional observation battery, motor activity, and neuropathology). The company also plans future studies of the developmental and reproductive effects of ETBE.

As provided for under Section 211 of the Clean Air Act, certain information on fuels and fuel additives must be supplied to EPA under terms specified in the Fuel/Fuel Additive (F/FA) rule (Code of Federal Regulations, 1994a; Federal Register, 1994). A consortium of oxygenate manufacturers coordinated through the American Petroleum Institute (API) has

formed to respond to testing requirements[1] for baseline gasoline and for gasoline with MTBE, ETBE, TAME, DIPE, ethanol (EtOH), and TBA). It remains to be seen whether sufficient interest exists within the industry to test other oxygenates, such as TAEE. An important feature of the F/FA rule is that it focuses on evaporative as well as combustion emissions from the fuels. The information obtained through the F/FA rule is expected to provide a basis for directly comparing effects of the baseline fuel emissions with oxygenated fuel emissions. The 90-day subchronic inhalation toxicity study and additional carcinogenicity/mutagenicity, reproductive/developmental, and neurotoxicity assays required under Tier 2 of the F/FA rule are summarized in Table 3.

## FURTHER INFORMATION NEEDS

Past work on conventional gasoline and certain gasoline constituents points to various types of effects that warrant particular attention in investigating the health effects of fuels, namely, carcinogenic effects, lung, kidney and liver toxicity, neurotoxicity, and reproductive/developmental toxicity. Despite a substantial database on such inhalation health effects for MTBE as well as for conventional gasoline (see Table 1), a comparative assessment of the two remains problematic for several reasons. Differences over time in fuel formulations and in testing methods may make it difficult to compare older data on conventional gasoline with more recent data on MTBE. In the case of MTBE-gasoline and conventional gasoline, even if the same testing methods were used in both cases, a comparison would not be very meaningful, because the most appropriate contrast would be between a baseline gasoline and gasoline with MTBE added, not MTBE alone.

[1]The F/FA rule specifies a tiered approach to providing information to EPA. Tier 1 may take up to three years and involves a literature search for specified health effects information, emissions speciation, and a qualitative exposure assessment. If adequate information cannot be obtained from the existing health effects literature, Tier 2 requires 90-day inhalation toxicity studies in rats exposed to evaporative as well as combustion mixtures of a base gasoline and the base gasoline with the additive. An additional three years may be used to satisfy Tier 2 requirements. Based on a review of information from Tiers 1 and 2, EPA may require additional testing under Tier 3. In addition, the F/FA rule also allows for Alternative Tier 2 testing, which can modify the standard Tier 2 testing requirements with substitute testing or research studies.

## Table 3. Fuel/Fuel Additive (F/FA) Rule Standard Tier 2 Tests

**90-Day Subchronic Inhalation General Toxicity** (Code of Federal Regulations, 1994b): Screening info on target organ toxicities and on concentrations useful for running chronic studies.

30 rodents per concentration per group (add specified numbers for different assessments combined with general toxicity); recovery group (N = 20) observed for reversible, persistent, or delayed effects
Observation (including body weight)
Clinical exams: hematology (e.g. Hct, Hb, RBC, DLC); clinical biochemistry (e.g., electrolyte balance, liver and kidney funct, Ca-P-Cl-Na-K, glucose, BUN)
Ophthalmological exam
Urinalysis
Gross pathology
Histopathology (especially respiratory tract)

**Fertility/Teratology** (Code of Federal Regulations, 1994b): Information on potential health hazards to fetus and on gonadal function, conception, and fertility.

25 males, 40 females per group; mating after 9 weeks of exposure, then exposure of females continues through GD 15
Limit test: if no effects at highest conc., then skip lower concs.
Observation for $\leq$13 weeks
Vaginal cytology
Mating and fertility
Gross necropsy (especially including reproductive organs)
Fetal anomalies, resorptions
Histopathology of reproductive organs

**In Vivo Micronucleus** (Code of Federal Regulations, 1994b): Detect damage to chromosomes or mitotic apparatus of cells (based on increase in frequency of micronucleated RBCs); provides information on potential carcinogenic and/or mutagenic effects.

5 females and 5 males per group
Positive control

**In Vivo Sister Chromatid Exchange** (Code of Federal Regulations, 1994b): Detect enhancement of exchange of DNA between two sister chromatids of a duplicating chromosome (using peripheral blood lymphocytes grown to confluence in cell culture); provides information on potential mutagenic and/or carcinogenic effects.

5 females and 5 males per group
Positive control

**Neuropathology** (Code of Federal Regulations, 1994b): Provides data on morphologic changes in central and peripheral nervous system.

N = 10 per group; N = 20 for reversible, persistent, or delayed effects
Positive control
Limit test (highest concentration first; skip other if no response)
Observations (including body weight, movement disorders, etc.)
Brain size and weight; light (and possible EM) microscopy of sections
Peripheral nerve teasing

**Glial Fibrillary Acidic Protein**: An indicator of neurotoxicity associated with astrocytic hypertrophy at site of damage.

10 animals per group

***Salmonella Typhimurium* Reverse Mutation** (Code of Federal Regulations, 1994b): Microbial assay that measures histadine (*his*) reversions (*his*$^-$ to *his*$^+$), which cause base changes or frameshift mutations in the genome; provides data on mutagenicity.

Positive controls
Data presented as number of revertant colonies per plate, per kilogram of fuel, and per kilometer for each replicate and dose.

Source: Federal Register (1994).

Although a fundamental need is to determine what, if any, difference in exposures or health effects is made by the addition of an oxygenate to a baseline fuel, other variables (e.g., differences in VOC proportions or in Reid vapor pressure) may also be changed in the actual fuels in the current marketplace. A thorough evaluation of the comparative risks and benefits of oxyfuels would therefore need to consider not just the impacts of adding oxygenate to a baseline fuel but the impacts of other changes in current fuels such as reformulated gasoline. At a minimum, the following description of needed information on oxyfuels assumes a baseline (1990) gasoline as a fundamental frame of reference throughout. Overarching all of these needs is the question of what is the net benefit or risk to the environment and public health resulting from a change from conventional gasoline to oxyfuels. Although the objectives of the oxygenated gasoline and reformulated gasoline programs are quite explicit in seeking to reduce CO, ozone, and air toxic pollutants, a thorough examination of the successes or failures of the oxyfuel programs is needed to answer the question just posed. To do so will require a quantitative and rigorous evaluation of changes in emissions, air and water quality, exposures, and health and ecosystem effects associated with a change from conventional gasoline to oxyfuels. Ultimately, health and ecosystem effects would have to be assigned some monetary or societal value as well. Such a complete analysis is clearly a very complex and difficult undertaking, but without this sort of attempt to conduct a thorough consideration of the full impacts (positive and negative) related to a change in fuel use, questions may continue to arise concerning the advisability of oxyfuel programs.

## Exposure Issues

Exposure assessment is an essential element of a comparative assessment of conventional and oxygenated fuels. As noted above, exposure assessment draws upon information on emissions characterization as well as environmental fate in different media.

Information on motor vehicle combustion and evaporative emissions exists for conventional gasolines and for MTBE- and ethanol-oxygenated gasolines but not for all conditions of potential importance (e.g., different meteorological, roadway, and other operating conditions). The Auto/Oil program has not tested a wide variety of operating conditions, nor has it evaluated vehicle emissions using the most recent (since January 1995) marketplace industry average reformulated gasoline. A more comprehensive characterization of vehicle emissions is

needed for actual marketplace reformulated/oxygenated gasolines to understand fully the complex emission mixtures potentially existing in important exposure microenvironments.

Ambient monitoring is needed to ascertain which toxic and criteria air pollutants are increased or decreased, and the extent of such changes, as a function of a change from conventional gasolines to oxyfuels. Empirical information of this type is essential to validating the effectiveness of the oxyfuel programs.

Very little is known about the atmospheric transport and transformation of the complex mixtures associated with use of oxyfuels and their potential exposure significance. For example, tertiary butyl formate is a photochemical transformation product of MTBE, as is formaldehyde (e.g., Tuazon et al., 1991). The potential for increased human exposures to such irritant substances as a result of oxyfuel use needs to be evaluated. Ambient and microenvironmental air monitoring needs to be conducted to determine the levels of these and other possibly significant by-products of oxyfuels. ARCO Chemical may attempt to conduct some work on TBF, including measurements of TBF in the atmosphere and comparative toxicity studies of its irritancy to the respiratory system (Andrews, personal communication).

Estimates of human exposure require concentration measurements at the points of human contact with the pollutant. Because humans typically spend more time indoors and in transit than they do outside, ambient concentration levels may misrepresent levels of actual human exposure. Thus, it becomes critically important for health risk assessors to have concentration data in locations where people spend large portions of their time and in locations where they might receive a relatively high exposure.

With some data indicating MTBE contamination of ground water, other pathways of exposure in addition to direct inhalation from the atmosphere may be of importance. It is first necessary to determine the extent to which point sources (e.g., leaking underground storage tanks) may be responsible for such contamination. If point sources are not found to account for all of the observed contamination, atmospheric transport and fate processes would be a critical focus for further investigation. At a minimum, such research would entail concurrent measurements of MTBE in ambient air, precipitation, run off, surface, and ground water. The U.S. Geological Survey has plans to conduct such a study (as part of a broader study of pesticides and VOCs) at Glassboro, NJ, beginning in mid-1996, and may extend the work later to other cities throughout the United States (Zogorski, personal communication).

Regardless of the source (i.e., whether from a point source or from atmospheric deposition), if the oxyfuel is present in ground water, studies of the subsurface transport and degradation of the fuel are needed to determine the environmental risks. Along with determining what environmental transport and transformation processes may be involved, it is important to investigate how biological processes may contribute to the net removal or accumulation of oxygenated organic compounds in ground water. Some efforts in this area have been or are now underway in both the private and public sectors, including the American Petroleum Institute, the U.S. Department of Energy, and the U.S. Geological Survey (Zogorski, personal communication). The impact on water quality and aquatic biota would also need to be assessed, and the potential for human exposures through the ingestion of oxyfuel-contaminated drinking water would need to be quantified.

Quantitative exposure assessments of different oxyfuels in relation to conventional fuels need to incorporate personal exposure scenarios involving various activities (e.g., refueling, driving) and routes of exposure (inhalation, dermal, ingestion). In past studies, limited measurements and models have been useful to provide ranges of potential exposures in several significant microenvironments. This limited scenario approach, while historically all that has been provided, has a large degree of uncertainty, and does not provide an accurate estimate of population exposures. To reduce these uncertainties, human exposure field studies and models based on the resulting data would be needed.

## Health Effects Issues

### Methyl Tertiary Butyl Ether

#### *Acute Effects*

Apart from the public attention that reports of symptom complaints have generated in certain areas of the United States, the widespread exposures and remaining scientific uncertainties associated with oxyfuels require that further consideration be given to potential acute inhalation health effects related to these fuels. At least three hypotheses warrant investigation and are discussed in more detail below. (1) Is it the mixture of MTBE and gasoline, rather than MTBE itself, that is proximally or ultimately responsible for effects (where "the mixture" presumably may include combustion as well as evaporative emissions and may well vary from place to place and at different times)? (2) Are some individuals especially sensitive to MTBE or one or more of the

chemicals in the MTBE-gasoline mixture (i.e., in evaporative and/or combustion emissions)? (3) Does some unidentified factor (e.g., cold temperature) modulate the effect of MTBE or the mixture? The question of nonbiological factors (e.g., economic concerns, social or psychological factors) underlying or contributing to the symptom reports must also be recognized.

***Mixtures***. All of the inhalation toxicity testing conducted with laboratory animals thus far has dealt with the effects of neat, laboratory-grade MTBE, not a mixture of gasoline and MTBE (much less an actual MTBE-oxyfuel that might contain various contaminants, including other ethers or alcohols). Similarly, the human clinical studies conducted at EPA (Prah et al., 1994), Yale (Cain et al., 1994), and the Swedish National Institute of Occupational Health (Johanson et al., 1995) used pure MTBE vapors. Thus, the effects of MTBE-gasoline mixtures have not been investigated under controlled inhalation conditions. Apart from ethical and other questions about the feasibility and practicality of inhalation chamber studies of humans or laboratory animals exposed to MTBE-gasoline mixtures, there are questions about how best to investigate mixture exposures that are more representative of real world conditions (i.e., mixtures of combustion as well as evaporative emissions). More emissions and human exposure data would help guide the design of such inhalation experiments.

***Sensitive Individuals***. The EPA (Prah et al., 1994) and Yale (Cain et al., 1994) clinical studies of MTBE used healthy young adults with no evident medical problems. An epidemiologic study (Fiedler et al., 1994) of persons with multiple chemical sensitivities (MCS) did not show a significant relationship between MTBE exposure and symptom reports, but only 14 persons with MCS were evaluated, and many individuals who describe themselves as sensitive to MTBE do not claim a general sensitivity to chemicals. Thus, the possibility that some portion of the general population may be particularly susceptible to MTBE or one or more chemicals associated with MTBE-gasoline is worthy of further investigation. A basic question in this case is how best to investigate this possibility (e.g., through a broad population study or by intensive evaluation of self-described "sensitives"). If true sensitives represent less than 5 to 10% of the general population, an epidemiologic study must be carefully designed with adequate power to detect such a proportion. A laboratory study of self-described sensitive individuals who would volunteer for exposure to MTBE-gasoline under controlled conditions is needed to determine whether

symptoms can be induced by such exposures. The anticipated chamber studies by EPA and EOHSI would help address this need, but demonstration of a phenomenon is only the first step. If symptoms can be induced until controlled conditions, further experimental investigation of the possible chemical, physiological, or other factors contributing to the occurrence of different symptoms would be warranted. For example, the possibility of metabolic polymorphisms that could underlie individual differences in susceptibility to MTBE is a topic of particular interest. The hypothetical possibility that some individuals might undergo sensitization through repeated exposure to MTBE or a chemical related to MTBE-oxyfuel might also be considered.

***Interactive Factors***. Cold temperature has been considered a possible factor for investigation in connection with the putative effects of MTBE since the first complaints arose in Alaska, and reports from Montana and Wisconsin apparently have not diminished the plausibility of very cold temperatures playing a role in symptoms that might be related to MTBE or MTBE-oxyfuels. The intentional correlation of the oxygenate program with cold weather and the coincidental start of the RFG program during the winter make it difficult to rule out the possible role of cold temperature as a contributing factor to the higher prevalence of symptom complaints in certain areas. Moreover, clinical studies conducted at 75° F have not addressed this issue. Other variables, such as odor or chemical differences in the fuels in different areas, might also be considered for further investigation, as suggested by studies of Alaskan fuels (Smith et al., 1994).

***Cancer***

The currently available data from MTBE cancer bioassays leave some uncertainty about the efficacy and potency of MTBE to induce cancer by inhalation at low concentrations. One or more replicative studies would help resolve uncertainties relating to early termination and high mortality in the earlier inhalation bioassay results. However, if mechanistic and pharmacokinetic data prove to be adequate to demonstrate the irrelevancy of the rodent findings to human cancer risk (e.g., due to the male rat-specific role of alpha-2$\mu$-globulin), the need for additional chronic bioassay data might be obviated. With respect to oral exposure and health risks associated with MTBE in drinking water, a chronic bioassay using drinking water is needed to complement the existing study (Belpoggi et al., 1995) that used olive oil as the vehicle for oral gavage administration.

The comparative carcinogenic potential of the combustion as well as evaporative emissions of baseline gasoline relative to oxyfuels is an outstanding fundamental issue. Although some studies have been conducted on the carcinogenicity of the combustion emissions of leaded and unleaded gasoline (Brightwell et al., 1986, 1989; Stara et al., 1980; Heinrich et al., 1985), it remains to be determined whether this evidence is adequate to conduct a quantitative cancer risk assessment of baseline gasoline in comparison to oxyfuels.

***Reproductive/Developmental Effects***

Although evidence of impaired growth in offspring of laboratory animals exposed to MTBE qualifies the chemical as a developmental toxicant, the effective duration and timing of MTBE exposure during gestation and/or postnatal development for the induction of such effects are not known. More precise data on the developmental window of toxicity would be needed to characterize better the developmental risk of MTBE in relation to potential human exposures. Pharmacokinetic and mechanistic studies would enhance this endeavor. Moreover, given the indication of neurotoxicity in adult rodents exposed to MTBE (including suggestions of decreased brain weight and/or length), a more intensive evaluation of developmental neurotoxicity may be warranted. The same needs pertain to baseline gasoline and MTBE-gasoline mixtures.

In addition, the reproductive effects of baseline gasoline and MTBE-gasoline mixtures need to be investigated, especially with respect to apparent differences between rats and mice in past work on gasoline. With respect to the effects of conventional gasoline, a particular need

exists for a multi-generation reproductive study of inhaled benzene, including endpoints for estrus cyclicity, oocyte toxicity, and sperm morphology and function. Indications of neuroendocrine effects (e.g., increased corticosterone levels) in MTBE-exposed animal studies lend further support to the need for closer examination of possible effects on reproductive function.

***Chronic Noncancer Effects***

Given the rather extensive database on chronic noncancer effects of neat MTBE, the primary need is evaluation of the effects of chronic inhalation exposure to MTBE-gasoline evaporative and combustion mixtures. Although standard Tier 2 testing, as prescribed under the F/FA rule, addresses the mixtures aspect of this need, it is not clear that the standard Tier 2 tests themselves will provide the type of information that is most critically needed to meet the objective of quantitative, comparative assessments. As the F/FA rule notes, the 90-day subchronic study is "...not capable of determining effects which have a long latency period...," and the tests themselves afford only a broad screening level evaluation (e.g., the neurotoxicity tests "... are not intended to provide a detailed evaluation of neurotoxicity [and] ... should be complemented by ... e.g., behavioral and neurophysiological studies..."). At this writing, alternatives to the standard Tier 2 testing requirements are being considered by EPA.

With respect to oral exposures, currently available data suggest that MTBE tends to lead the plume in oxyfuel releases to soil and groundwater, and thus an obvious need is to evaluate the effects of neat MTBE by ingestion. The substantial database on the effects of inhalation exposure to neat MTBE might suffice for this purpose if adequate pharmacokinetics data support such extrapolation. However, to the extent that MTBE may be present in a mixture with other compounds, the effects of such mixtures may have to be evaluated in their own right.

***Pharmacokinetics***

As suggested above, pharmacokinetics information could assist efforts to investigate various types of health effects and exposure by different routes. The role of metabolites of MTBE, such as formaldehyde and TBA, needs to be better understood. Pharmacokinetics data might also provide a basis for better predicting and assessing the effects of different ethers (see below). It may also be worthwhile to investigate the possibility of synergistic, competing, or antagonistic processes in the metabolism of MTBE.

### Other Oxygenates

By comparison to MTBE, much greater data gaps exist for the other oxygenates that are currently in use or under development. This statement might not apply to ethanol (EtOH) if pharmacokinetics work were to establish a basis for quantitatively relating EtOH inhalation exposure to a large body of existing research on EtOH exposure and health effects by ingestion. At present, it is not evident that any organization is planning to conduct such work. However, even the massive database on pure EtOH does not address the evaporative and combustion mixtures issues, as there may be differences in exposure or health effects that would not be predicted by the effects of EtOH itself.

The limited data on ETBE and TAME toxicity are inadequate to support quantitative risk assessments of the individual chemicals, much less a comparative assessment. Thus, ETBE, TAME, TAEE, and DIPE remain to be fully tested and evaluated for cancer and chronic noncancer health effects, both in pure form and as evaporative and combustion mixtures. The same is true for TBA except that a cancer bioassay study of ingested TBA in two rodent species has been completed. Other oral-route cancer studies are apparently underway on MTBE-gasoline, EtOH and EtOH-gasoline, ETBE and ETBE-gasoline, TAME, DIPE, and gasoline alone (Belpoggi et al., 1995), but these studies may not provide a sufficient basis for assessing cancer risks for inhalation exposures. As noted above, standard Tier 2 testing under the F/FA rule will provide only basic toxicity screening data, which are not expected to provide an adequate basis for quantitative, comparative risk assessments of the oxyfuels versus a baseline gasoline.

## SUMMARY

The available information on conventional gasolines and neat oxygenates (viz., MTBE) is not sufficient to support quantitative, comparative assessments of the health and environmental benefits and risks of oxyfuels in relation to conventional fuels. Such assessments must address the differences between conventional fuels and oxyfuels in their public health and environmental impacts. A complete assessment requires information on emissions, air and water quality impacts, population exposures, and effects on health and ecosystems. Within these broad areas, certain needs are particularly evident, including exposure evaluations and studies of chronic as well as acute health effects of evaporative and combustion emissions of base gasoline with and without

oxygenate added. Ultimately, the basic objective is to determine the net benefit or risk of oxyfuels compared to conventional gasoline.

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