Public Health Goal for Methyl Tertiary Butyl Ether (MTBE) in Drinking Water

Prepared by

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances that may cause chronic disease shall be based solely on health effects and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than the general population.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data for OEHHA to determine a level that creates no significant risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above in items six and seven.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed at least once every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations or technical feasibility, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each primary drinking water standard adopted by DHS shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By state and federal law, MCLs established by DHS must be at least as stringent as the federal MCL, if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA website at www.oehha.ca.gov.

LIST OF ABBREVIATIONS

AB	Assembly Bill
AL	Action Level
ACGIH	American Conference of Governmental Industrial Hygienists
API	American Petroleum Institute
ARB	California Air Resources Board
ATSDR	Agency for Toxic Substances and Disease Registry, USDHHS
AUC	area under the concentration-time curve
BAAQMD	Bay Area Air Quality Management District, San Francisco, California
BIBRA	British Industrial Biological Research Association
BTEX	benzene, toluene, ethylbenzene, and xylenes
BUN	blood urea nitrogen
BW	body weight
CAAA	1990 U.S. Clean Air Act Amendments
Cal/EPA	California Environmental Protection Agency
CAS	Chemical Abstracts Service
CCL	Drinking Water Contaminant Candidate List, U.S. EPA
CCR	California Code of Regulations
CDC	Centers for Disease Control and Prevention, USDHHS
CFS	chronic fatigue syndrome
CENR	Committee on Environment and Natural Resources, White House OSTP
CHRIS	Chemical Hazard Response Information System, U.S. Coast Guard
CNS	central nervous system
CO	carbon monoxide
CSF	cancer slope factor, a cancer potency value derived from the lower 95% confidence bound on the dose associated with a 10% (0.1) increased risk of cancer (LED_{10}) calculated by the LMS model. $CSF = 0.1/LED_{10}$.
CPF	cancer potency factor, cancer potency, carcinogenic potency, or carcinogenic potency factor
DHS	California Department of Health Services
DOE	U.S. Department of Energy
DOT	U.S. Department of Transportation

DOT/UN/NA/IMCO	U.S. Department of Transportation/United Nations/North America/ International Maritime Dangerous Goods Code
DLR	detection limit for purposes of reporting
DWC	daily water consumption
DWEL	Drinking Water Equivalent Level
EBMUD	East Bay Municipal Utility District, California
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
EHS	Extremely Hazardous Substances, SARA Title III
EOHSI	Environmental and Occupational Health Sciences Institute, New Jersey
ETBE	ethyl tertiary butyl ether
GAC	granulated activated charcoal
gd	gestation day
g/L	grams per liter
HA	Health Advisory
HAP	Hazardous Air Pollutant
HCHO	formaldehyde
HEI	Health Effects Institute, Boston, Massachusetts
HSDB	Hazardous Substances Data Bank, U.S. NLM
IARC	International Agency for Research on Cancer, WHO
i.p.	intraperitoneal
IPCS	International Programme on Chemical Safety, WHO
IRIS	Integrated Risk Information Systems, U.S. EPA
i.v.	intravenous
kg	kilograms
L	liter
LC_{50}	lethal concentrations with 50% kill
LD_{50}	lethal doses with 50% kill
LED_{10}	lower 95% confidence bound on the dose associated with a 10% increased risk of cancer
Leq/day	liter equivalent per day
LLNL	Lawrence Livermore National Laboratory, California
LMS	linearized multistage
LOAEL	lowest observed adverse effect level
LUFT	leaking underground fuel tank

MCCHD	Missoula City-County Health Department, Montana
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg/L	milligrams per liter
µg/L	micrograms per liter
MCS	multiple chemical sensitivities
mL	milliliter
MOE	margin of exposure
MORS	Office of Research and Standards, Department of Environmental Protection, the Commonwealth of Massachusetts
MRL	minimal risk levels
MTBE	methyl tertiary butyl ether
MTD	maximum tolerated dose
MWDSC	Metropolitan Water District of Southern California
NAERG	North American Emergency Response Guidebook Documents, U.S., Canada and Mexico
NAS	U.S. National Academy of Sciences
NAWQA	National Water-Quality Assessment, USGS
NCDEHNR	North Carolina Department of Environment, Health, and Natural Resources
NCEH	National Center for Environmental Health, U.S. EPA
NCI	U.S. National Cancer Institute
ng	nanograms
NIEHS	U.S. National Institute of Environmental Health Sciences
NIOSH	U.S. National Institute for Occupational Safety and Health
NJDEP	New Jersey Department of Environmental Protection
NJHSFS	New Jersey Hazardous Substance Fact Sheets
NJDWQI	New Jersey Drinking Water Quality Institute
NLM	National Library of Medicine
NOAEL	no observable adverse effect levels
NOEL	no observable effect levels
NRC	National Research Council, U.S. NAS
NSTC	U.S. National Science and Technology Council
NTP	U.S. National Toxicology Program
OEHHA	Office of Environmental Health Hazard Assessment, Cal/EPA
OEL	Occupational Exposure Limit

OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System, U.S. EPA
OSTP	White House Office of Science and Technology Policy
O_3	ozone
oxyfuel	oxygenated gasoline
PBPK	physiologically-based pharmacokinetic
PHG	Public Health Goal
PHS	Public Health Service, USDHHS
pnd	postnatal day
POTW	publicly owned treatment works
ppb	parts per billion
ppbv	ppb by volume
ppm	parts per million
ppt	parts per trillion
pptv	ppt by volume
Proposition 65	California Safe Drinking Water and Toxic Enforcement Act of 1986
q_1*	a cancer potency value that is the upper 95% confidence limit of the low dose extrapolation on cancer potency slope calculated by the LMS model
RfC	Reference Concentration
RfD	Reference Dose
RFG	reformulated gasoline
RSC	relative source contribution
RTECS	Registry of Toxic Effects of Chemical Substances, U.S. NIOSH
SARA	U.S. Superfund (CERCLA) Amendments and Reauthorization Act of 1986
SB	Senate Bill
SCVWD	Santa Clara Valley Water District, California
SFRWQCB	San Francisco Regional Water Quality Control Board
SGOT	serum glutamic-oxaloacetic transaminase
SS	statistically significant
STEL	Short-Term Occupational Exposure Limit
Superfund	U.S. Comprehensive Environmental Response, Compensation and Liability Act of 1980, a.k.a. CERCLA
SWRCB	California State Water Resources Control Board
TAC	toxic air contaminant
TAME	tertiary amyl methyl ether
TBA	tertiary butyl alcohol

TBF	tertiary butyl formate
TERIS	Teratogen Information System, University of Washington
TOMES	Toxicology and Occupational Medicine System, Micromedex, Inc.
TRI	Toxics Release Inventory, U.S. EPA
TSCA	U.S. Toxic Substances Control Act
TWA	Time-Weighted Average
t_e	experimental duration
t_l	lifetime of the animal used in the experiment
$t_{1/2}$	plasma elimination half-life
UC	University of California
UCLA	UC Los Angeles
UCSB	UC Santa Barbara
UF	uncertainty factors
U.S.	United States
USCG	U.S. Coast Guard
USDHHS	U.S. Department of Health and Human Services
U.S. EPA	U. S. Environmental Protection Agency
USGS	U. S. Geological Survey
UST	underground storage tanks
VOC	volatile organic compound
VRG	vessel rich group
WDOH	Wisconsin Division of Health, Department of Natural Resources
WHO	World Health Organization
WSPA	Western States Petroleum Association

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PUBLIC HEALTH GOAL FOR METHYL TERTIARY BUTYL ETHER (MTBE) IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 0.013 mg/L (13 μg/L or 13 ppb) is adopted for methyl tertiary butyl ether (MTBE) in drinking water. The PHG is based on carcinogenic effects observed in experimental animals. Carcinogenicity has been observed in both sexes of the rat in a lifetime gavage study (Belpoggi et al. 1995, 1997, 1998), in male rats of a different strain in a 24-month inhalation study (Chun et al. 1992, Bird et al. 1997), and in male and female mice in an 18-month inhalation study (Burleigh-Flayer et al. 1992, Bird et al. 1997). In Sprague-Dawley rats receiving MTBE by gavage, statistically significant increases in Leydig interstitial cell tumors of the testes were observed in males, and statistically significant increases in lymphomas and leukemias (combined) were observed in females. In Fischer 344 rats exposed to MTBE by inhalation, statistically significant increases in the incidences of Leydig interstitial cell tumors of the testes were also observed in males, as well as renal tubular tumors. In CD-1 mice exposed to MTBE by inhalation, statistically significant increases in the incidences of liver tumors were observed in females (hepatocellular adenomas, hepatocellular adenomas and carcinomas combined) and males (hepatocellular carcinomas). The two inhalation studies (Burleigh-Flayer et al. 1992, Chun et al. 1992, Bird et al. 1997) and one gavage study (Belpoggi et al. 1995, 1997, 1998) cited in this document for the development of the PHG provided evidence for the carcinogenicity of MTBE in multiple sites and in both sexes of the rat and mouse. While some reviews have given less weight to the findings of Belpoggi et al. (1995, 1997, 1998) due to the limitations of the studies, Office of Environmental Health Hazard Assessment (OEHHA) scientists found that they contribute to the overall weight of evidence. We reviewed these studies and the reported criticisms carefully, and found the studies are consistent with other MTBE findings, and are of similar quality to studies on many other carcinogens. This conclusion is consistent with the findings in the MTBE report (UC 1998) submitted by the University of California (UC). The results of all available studies indicate that MTBE is an animal carcinogen in two species, both sexes and at multiple sites, and five of the six studies were positive.

For the calculation of the PHG, cancer potency estimates were made, based on the recommended practices of the 1996 United States Environmental Protection Agency (U.S. EPA) proposed guidelines for carcinogenic risk assessment (U.S. EPA 1996f), in which a polynomial [similar to that used in the linearized multistage (LMS) model, but used empirically and without linearization] is fit to the experimental data in order to establish the lower 95% confidence bound on the dose associated with a 10% increased risk of cancer (LED_{10}). It is plausible that the true value of the human cancer potency has a lower bound of zero based on statistical and biological uncertainties. Part of this uncertainty is due to a lack of evidence to support either a genotoxic or nongenotoxic mechanism. However, due to the absence of specific scientific information explaining why the animal tumors are irrelevant to humans at environmental exposure levels, a standard health protective approach was taken to estimate cancer risk. The cancer potency estimate derived from the geometric mean of the cancer slope factors (CSFs) of the combined male rat kidney adenomas and carcinomas, the male rat Leydig cell tumors, and the leukemia and lymphomas in female rats was 1.8×10^{-3} $(mg/kg\text{-}day)^{-1}$.

The PHG was calculated assuming a de minimis theoretical excess individual cancer risk level of 10^{-6} (one in a million) from exposure to MTBE. Based on these considerations, OEHHA adopts a PHG of 0.013 mg/L (13 μg/L or 13 ppb) for MTBE in drinking water using a CSF of 1.8×10^{-3} $(mg/kg\text{-}day)^{-1}$. This value also incorporates a daily water consumption (DWC) rate of three liters equivalent per day (Leq/day). The range of possible values, based either on different individual tumor sites, or on different multi-route exposure estimates and the average cancer potency of the three sites (male rat kidney adenomas and carcinomas, male rat Leydig interstitial cell tumors, and leukemia and lymphomas in female rats) was 2.7 to 16 ppb. The adopted PHG is considered to contain an adequate margin of safety for the potential noncarcinogenic effects including adverse effects on the renal and neurological systems.

In addition to the 13 ppb value based on carcinogenicity, a value of 0.047 mg/L (47 ppb) was calculated based on noncancer effects of increased relative kidney weights in the Robinson et al. (1990) 90-day gavage study in rats. The kidney effect is the most sensitive noncarcinogenic effect by the oral route observed in experimental animals with a no observable adverse effect level (NOAEL) of 100 mg/kg/day. This value of 47 ppb incorporates four 10-fold uncertainty factors (UFs) for a less than lifetime study, interspecies and interindividual variation and possible carcinogenicity. This value also incorporates a DWC rate of three Leq/day and a relative source contribution (RSC) default value of 20%. The default value for water ingestion is the same as used by U.S. EPA, Office of Water and is also documented in OEHHA's draft technical support document "Exposure Assessment and Stochastic Analysis" (OEHHA 1996). The three Leq/day DWC value represents approximately the 90% upper confidence level on tap water consumption and the average total water consumption. The three Leq/day incorporates two liters of direct consumption and one liter for inhalation of MTBE volatilized from drinking water. The use of 20% RSC indicates that most of the exposure occurs from ambient air levels. It is used in the noncancer risk assessment, but, consistent with standard practice, is not incorporated into the cancer risk assessment. While the lower value of 13 ppb is adopted as the PHG the difference in the two approaches is less than four-fold.

INTRODUCTION

The purpose of this document is to establish a PHG for the gasoline additive MTBE in drinking water. MTBE is a synthetic solvent used primarily as an oxygenate in unleaded gasoline to boost octane and improve combustion efficacy by oxygenation. Reformulated fuel with MTBE has been used in 32 regions in 19 states in the United States (U.S.) to meet the 1990 federal Clean Air Act Amendments (CAAA) requirements for reducing carbon monoxide (CO) and ozone (O_3) levels (CAAA of 1990, Title II, Part A, Section 211) because the added oxygenate promotes more complete burning of gasoline. California's cleaner-burning reformulated gasoline (California RFG) has been implemented to meet statewide clean air goals [California Code of Regulations (CCR), Title 13, Sections 2250 to 2297]. While neither Federal nor State regulations require the use of a specific oxygenate, MTBE is most commonly utilized. MTBE is currently used (11% by volume) in California RFG to improve air quality (Denton and Masur 1996). California is the third largest consumer of gasoline in the world. Only the rest of the U.S. and the former Soviet Union surpasses it. Californians use more than 13.7 billion gallons of gasoline a year and another one billion gallons of diesel fuel.

MTBE and other oxygenates such as ethyl tertiary butyl ether (ETBE), tertiary butyl alcohol (TBA) and ethanol are currently being studied to determine the extent of their presence in drinking water and what, if any, potential health implications could result from exposure to them

(Freed 1997, Scheible 1997, U.S. EPA 1998a, 1998b). California Senate Office of Research last February released a position paper on MTBE (Wiley 1998). California Energy Commission last October released a mandated report entitled "Supply and Cost of Alternatives to MTBE in Gasoline" (Schremp et al. 1998) evaluating alternative oxygenates and a possible MTBE phase out. California Bureau of State Audits last December released a report entitled " California's Drinking Water: State and Local Agencies Need to Provide Leadership to Address Contamination of Groundwater by Gasoline Components and Additives" emphasizing the needs for improvements to better protect groundwater from contamination by MTBE (Sjoberg 1998). Maine, New Jersey and Texas are considering alternatives to MTBE in reducing air pollution in their state (Renner 1999).

MTBE was the second most-produced chemical in the U.S. in 1997, whereas previously it was ranked the twelfth in 1995 and eighteenth in 1994 (Cal/EPA 1998, Kirschner 1996, Reisch 1994). In 1994 and 1995, it was estimated that about 70 million Americans were exposed to oxygenated gasoline (oxyfuel) and approximately 57 million were exposed to reformulated gasoline (RFG) (ATSDR 1996, HEI 1996, NRC 1996, NSTC 1996, 1997). About 40% of the U.S. population live in areas where MTBE is used in oxyfuel or RFG (USGS 1996) and most people find its distinctive terpene-like odor disagreeable (CDC 1993a, 1993b, 1993c, Kneiss 1995, Medlin 1995, U.S. EPA 1997a). MTBE is now being found in the environment in many areas of the U.S. because of its increased use over the last several years.

Recently MTBE has become a drinking water contaminant due to its high water solubility and persistence. When gasoline with 10% MTBE by weight comes in contact with water, about five grams per liter (g/L) can dissolve (Squillace et al. 1996, 1997a). MTBE has been detected in groundwater as a result of leaking underground storage tanks (USTs) or pipelines and in surface water reservoirs via recreational boating activities. MTBE does not appear to adsorb to soil particles or readily degrade in the subsurface environment. It is more expensive to remove MTBE-added gasoline than gasoline without MTBE from contaminated water (Cal/EPA 1998, U.S. EPA 1987a, 1992c, 1996a, 1997a). The discussion of improvements in air quality versus the vulnerability of drinking water surrounding MTBE has raised concerns from the public as well as legislators (Hoffert 1998, McClurg 1998). The controversy and new mandated requirements have made MTBE an important chemical being evaluated by OEHHA.

Background – Prior and Current Evaluations

MTBE is not regulated currently under the federal drinking water regulations. The California Department of Health Services (DHS) recently established a secondary maximum contaminant level (MCL) for MTBE as 0.05 mg/L (five μg/L or five ppb) based on taste and odor effective January 7, 1999 (22 CCR Section 64449). An interim non-enforceable Action Level (AL) of 0.035 mg/L (35 μg/L or 35 ppb) in drinking water was established by DHS in 1991 to protect against adverse health effects. OEHHA (1991) at that time recommended this level based on noncarcinogenic effects of MTBE in laboratory animals (Greenough et al. 1980). OEHHA applied large uncertainty factors to provide a substantial margin of safety for drinking water. Since February 13, 1997, DHS (1997) regulations (22 CCR Section 64450) have included MTBE as an unregulated chemical for which monitoring is required. Pursuant to this requirement, data on the occurrence of MTBE in groundwater and surface water sources are being collected from drinking water systems in order to document the extent of MTBE contamination in drinking water supplies.

In California, the Local Drinking Water Protection Act of 1997 [Senate Bill (SB) 1189, Hayden, and Assembly Bill (AB) 592, Kuehl] requires DHS to develop a two-part drinking water standard for MTBE. The first part is a secondary MCL that addresses aesthetic qualities including taste and odor. The second part is a primary MCL that addresses health concerns, to be established by July 1, 1999. DHS is proceeding to establish drinking water standards for MTBE and requested OEHHA to conduct a risk assessment in order to meet the mandated schedule to set this regulation by July 1999. As mentioned above, DHS (1998) also adopts a secondary MCL of five ppb for MTBE to protect the public from exposure to MTBE in drinking water at levels that can be smelled or tasted, as an amendment to Table 64449-A, Section 64449, Article 16, Chapter 15, Division 4, Title 22 of the CCR.

The 1997 act (SB 1189) also requires the evaluation of MTBE for possible listing under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) as a chemical known to the state to cause cancer or reproductive and developmental toxicity on or before January 1, 1999. This involves consideration of the evidence that MTBE causes these effects by the State's qualified experts for Proposition 65 - the Carcinogen Identification Committee (CIC) and the Developmental and Reproductive Toxicant (DART) Identification Committee of OEHHA's Science Advisory Board (OEHHA 1998a, 1998b). These Committees evaluated MTBE in December 1998; MTBE was not recommended for listing under the Proposition 65 by either CIC or DART Committee.

The MTBE Public Health and Environmental Protection Act of 1997 (SB 521, Mountjoy) appropriates funds to the UC for specified studies of the human health and environmental risks and benefits of MTBE. The UC Toxic Substances Research and Teaching Program is managing the following six funded projects: 1) an evaluation of the peer-reviewed research literature on the effects of MTBE on human health, including asthma, and on the environment by UC Los Angeles (UCLA), 2) an integrated assessment of sources, fate and transport, ecological risk and control options for MTBE in surface and ground waters, with particular emphasis on drinking water supplies by UC Davis, 3) evaluation of costs and effectiveness of treatment technologies applicable to remove MTBE and other gasoline oxygenates from contaminated water by UC Santa Barbara (UCSB), 4) drinking water treatment for the removal of MTBE from groundwater and surface water reservoirs by UCLA, 5) evaluation of automotive MTBE combustion byproducts in California RFG by UC Berkeley, and 6) risk-based decision making analysis of the cost and benefits of MTBE and other gasoline oxygenates by UCSB.

Among the SB 521mandated projects, only the first project regarding human health effects (Froines 1998, Froines et al. 1998) and a part of the second project regarding human exposure to MTBE from drinking water (Johnson 1998) mentioned above are pertinent to the scope of this report. Their report has been submitted to the Governor and posted on their web site (www.tsrtp.ucdavis.edu/mtbept/) on November 12, 1998. In this report, Froines et al. (1998) concluded that MTBE is an animal carcinogen with the potential to cause cancers in humans. Also in this report, Johnson (1998) performed a risk analysis of MTBE in drinking water based on animal carcinogenicity data. The act requires the report be reviewed and two hearings be held (February 19 and 23, 1999) for the purpose of accepting public testimony on the assessment and report. The act also requires the Governor to issue a written certification as to the human health and environmental risks of using MTBE in gasoline in California.

The American Conference of Governmental Industrial Hygienists (ACGIH) lists MTBE as an A3 Animal Carcinogen (ACGIH 1996). That is, MTBE is carcinogenic in experimental animals at relatively high dose(s), by route(s) of administration, at site(s), of histologic type(s), or by mechanism(s) that are not considered relevant to workplace exposure. ACGIH considers that

available epidemiological studies do not confirm an increased risk of cancer in exposed humans. Available evidence suggests that the agent is not likely to cause cancer in humans except under uncommon or unlikely routes of exposure or levels of exposure.

In August 1996 the U.S. Agency for Toxic Substances and Disease Registry (ATSDR) released the final report "Toxicological Profile for MTBE" which evaluated the toxic effects of MTBE including carcinogenicity in detail. The cancer effect levels of MTBE through both inhalation and oral exposure routes have been developed based on data of carcinogenicity in animals (ATSDR 1996).

The U.S. National Toxicology Program (NTP) did not find MTBE to be "reasonably anticipated to be a human carcinogen" in December 1998 (NTP 1998a). The National Institute of Environmental Health Sciences (NIEHS) Review Committee for the Report on Carcinogens first recommended (four yes votes to three no votes) that the NTP list MTBE as "reasonably anticipated to be a human carcinogen" in the Ninth Report on Carcinogens in January 1998 (NTP 1998b). The NTP Executive Committee Interagency Working Group for the Report on Carcinogens then voted against a motion to list MTBE (three yes votes to four no votes). Later in December 1998, the NTP Board of Scientific Counselors Report on Carcinogens Subcommittee voted against a motion to list MTBE as "reasonably anticipated to be a human carcinogen…" (five yes votes to six no votes with one abstention). The conclusions of these meetings are summarized on the NTP website, however, the supporting documentation on how these conclusions were reached is still under preparation and not available to us for evaluation (NTP 1998a). NTP solicited for final public comments through February 15, 1999 on these actions.

MTBE has been reviewed by the Environmental Epidemiology Section of the North Carolina Department of Environment, Health, and Natural Resources (NCDEHNR) and it was determined that there was limited evidence for carcinogenicity in experimental animals and that the compound should be classified as a Group B2 probable human carcinogen (Rudo 1995). The North Carolina Scientific Advisory Board on Toxic Air Contaminants (TAC) considered MTBE to be eligible as a Group C possible human carcinogen (Lucier et al. 1995). New Jersey (NJDWQI 1994, Post 1994) also classified MTBE as a possible human carcinogen. The State of New York Department of Health is drafting a fact sheet to propose an ambient water quality value for MTBE based on animal carcinogenicity data.

The International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) found "limited", but not "sufficient" evidence of MTBE carcinogenicity in animals. IARC has recently classified MTBE as a Group 3 carcinogen (i.e., not classifiable as to carcinogenicity in humans), based on inadequate evidence in humans and limited evidence in experimental animals. The conclusions of this October 1998 IARC Monographs Working Group Meeting are summarized on the IARC website, however, the supporting documentation on how these conclusions were reached is still under preparation to be published as the IARC Monographs Volume 73 (IARC 1998a).

The International Programme on Chemical Safety (IPCS) of WHO has issued the second draft *Environmental Health Criteria* on MTBE (IPCS 1997) which was scheduled to be finalized in December 1998. IPCS stated that carcinogenic findings in animal bioassays seem to warrant some concern of potential carcinogenic risk to humans, but the document does not contain a risk characterization. However, the final document is not available as of February 1999.

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) prepared a technical report (ECETOC 1997) on MTBE health risk characterization mainly on occupational

inhalation exposure. ECETOC concluded that MTBE has some potential to increase the occurrence of certain tumors in female mice or male rats after chronic high-dose inhalation exposure.

In February 1996 the Office of Science and Technology Policy (OSTP) through the Committee on Environment and Natural Resources (CENR) of the White House National Science and Technology Council (NSTC) released a draft report titled "Interagency Assessment of Potential Health Risks Associated with Oxygenated Gasoline" (NSTC 1996). This report focused primarily on inhalation exposure to MTBE and its principal metabolite, TBA. In March 1996 NSTC released the draft document "Interagency Oxygenated Fuels Assessment" which addressed issues related to public health, air and water quality, fuel economy, and engine performance associated with MTBE in gasoline relative to conventional gasoline. This document was peer reviewed by the National Academy of Sciences (NAS) under guidance from the National Research Council (NRC) which then published its findings and recommendations in the document "Toxicological and Performance Aspects of Oxygenated Motor Vehicle Fuels" (NRC 1996). The limited review on the potential health effects of MTBE in the NRC report (1996) considered the animal carcinogenicity evidence to be positive. The NRC findings were used to revise the NSTC document and the final report was released in June of 1997. The NSTC (1997) concluded: “there is sufficient evidence that MTBE is an animal carcinogen”. NSTC (1997) also concluded: "... the weight of evidence supports regarding MTBE as having a carcinogenic hazard potential for humans."

In April 1996 the Health Effects Institute (HEI) released "The Potential Health Effects of Oxygenates Added to Gasoline, A Special Report of the Institute's Oxygenates Evaluation Committee" (HEI 1996). HEI (1996) concluded: “the possibility that ambient levels may pose some risk of carcinogenic effects in human populations cannot be excluded”. HEI in summary of studies of long-term health effects of MTBE concluded: “Evidence from animal bioassays demonstrates that long-term, high-level exposures to MTBE by either the oral or inhalation routes of exposure cause cancer in rodents.”

The U.S. EPA has not established primary or secondary MCLs or a Maximum Contaminant Level Goal (MCLG) for MTBE but included MTBE on the Drinking Water Contaminant Candidate List (CCL) published in the Federal Register on March 2, 1998 (U.S. EPA 1998c, 1997b, 1997d). An advisory released in December 1997 recommended that MTBE concentration in the range of 20 to 40 ppb or below would assure both consumer acceptance of the water and a large margin of safety from any toxic effects (U.S. EPA 1997a, Du et al. 1998).

On November 30, 1998, the U.S. EPA (1998a) announced the creation of a blue-ribbon panel to review the important issues posed by the use of MTBE and other oxygenates in gasoline so that public health concerns could be better understood. The Panel on Oxygenate Use in Gasoline under the Clean Air Act Advisory Committee (CAAC), including 12 members and eight federal representatives serving as consultants to the Panel, is to make recommendations to the U.S. EPA on how to ensure public health protection and continued improvement in both air and water quality after a six-month study.

In its 1997 advisory, U.S. EPA agreed with the 1997 NSTC conclusions and concluded: “Although MtBE is not mutagenic, a nonlinear mode of action has not been established for MtBE. In the absence of sufficient mode of action information at the present time, it is prudent for EPA to assume a linear dose-response for MtBE. Although there are no studies on the carcinogenicity of MtBE in humans, there are multiple animal studies (by inhalation and gavage routes in two rodent species) showing carcinogenic activity and there is supporting animal

carcinogenicity data for the metabolites. The weight of evidence indicates that MtBE is an animal carcinogen, and the chemical poses a carcinogenic potential to humans (NSTC, 1997, page 4-26)." The U.S. EPA (1994a, 1994c) proposed in 1994 to classify MTBE as a Group C possible human carcinogen based upon animal inhalation studies (published in 1992). At that time, U.S. EPA noted that a Group B2 probable human carcinogen designation may be appropriate if oral MTBE exposure studies in animals (published later in 1995) result in treatment-related tumors.

In 1987, MTBE was identified by the U.S. EPA (1987a) under Section Four of the Toxic Substances Control Act (TSCA) for priority testing because of its large production volume, potential widespread exposure, and limited data on long-term health effects (Duffy et al. 1992). The results of the testing have been published in a peer-reviewed journal (Bevan et al. 1997a, 1997b, Bird et al. 1997, Daughtrey et al. 1997, Lington et al. 1997, McKee et al. 1997, Miller et al. 1997, Stern and Kneiss 1997).

California Environmental Protection Agency (Cal/EPA) has reported some background information and ongoing activities on MTBE in California's "cleaner-burning fuel program" in a briefing paper (Cal/EPA 1998). U.S. EPA (1996d, 1996e) published fact sheets on MTBE in water in addition to several advisory documents. While concerns have been raised about its potential health impacts, based on hazard evaluation of the available data, MTBE is substantially less hazardous than benzene (a Group A human carcinogen) and 1,3-butadiene (a Group B2 probable human carcinogen), two carcinogenic chemicals it displaces in California's new gasoline formulations (Spitzer 1997). Potential health benefits from ambient O_3 reduction related to the use of MTBE in RFG were evaluated (Erdal et al. 1997). Whether the addition of MTBE in gasoline represents a net increase in cancer hazard is beyond the scope of this document.

In this document, the available data on the toxicity of MTBE primarily by the oral route based on the reports mentioned above are evaluated, and information available since the previous assessment by NSTC (1997) and U.S. EPA (1997a) is included. As indicated by the summaries provided above, there has been considerable scientific discussion regarding the carcinogenicity of MTBE and the relevance of the animal cancer study results to humans. Also indicated above, especially by some of the reported votes of convened committees, there is a considerable disagreement regarding the quality and relevance of the animal data among scientists. However, some of the disagreement stems from the differences in the level of evidence considered adequate for different degrees of confidence by the scientists considering the evidence. There is a greater level of evidence required to conclude that the data clearly show that humans are at cancer risk from exposure than to conclude that there may be some cancer risk or that it is prudent to assume there is a cancer risk to humans. In order to establish a PHG in drinking water, a nonregulatory guideline based solely on public health considerations, the prudent assumption of potential cancer risk was made. To determine a public health-protective level of MTBE in drinking water, relevant studies were identified, reviewed and evaluated, and sensitive groups and exposure scenarios are considered.

CHEMICAL PROFILE

Chemical Identity

MTBE [$(CH_3)_3C(OCH_3)$, CAS Registry Number 1634-04-4] is a synthetic chemical without known natural sources. The chemical structure, synonyms, and identification numbers are listed in Table 1 and are adapted from the Merck Index (1989), Hazardous Substances Data Bank (HSDB) of the National Library of Medicine (1997), Integrated Risk Information Systems (IRIS) of U.S. EPA (1997c), TOMES PLUS® (Hall and Rumack 1998) computerized database, and the ATSDR (1996), Cal/EPA (1998), ECETOC (1997), HEI (1996), NRC (1996), NSTC (1996, 1997), and U.S. EPA (1997a) documents.

TOMES (Toxicology and Occupational Medicine System) PLUS® is a computerized database which includes the data systems of Hazard Management®, Medical Management®, INFOTEXT®, HAZARDTEXT®, MEDITEXT®, REPROTEXT®, SERATEXT®, HSDB, IRIS, Registry of Toxic Effects of Chemical Substances (RTECS®) of National Institute for Occupational Safety and Health (NIOSH), Chemical Hazard Response Information System (CHRIS) of U.S. Coast Guard, Oil and Hazardous Materials/Technical Assistance Data System (OHM/TADS) of U.S. EPA, Department of Transportation (DOT) Emergency Response Guide, New Jersey Hazardous Substance Fact Sheets (NJHSFS), North American Emergency Response Guidebook Documents (NAERG) of U.S. DOT, Transport Canada and the Secretariat of Communications and Transportation of Mexico, REPROTOX® System of the Georgetown University, Shepard's Catalog of Teratogenic Agents of the Johns Hopkins University, Teratogen Information System (TERIS) of the University of Washington, and NIOSH Pocket Guide(TM). For MTBE, TOMES PLUS® (Hall and Rumack 1998) contains entries in HAZARDTEXT®, MEDITEXT®, REPROTEXT®, REPROTOX®, HSDB, IRIS, RTECS®, NAERG and NJHSFS.

Physical and Chemical Properties

Important physical and chemical properties of MTBE are given in Table 2 and are adapted from Merck Index (1989), HSDB (1997), TOMES PLUS® (Hall and Rumack 1998), and the ATSDR (1996), Cal/EPA (1998), HEI (1996), NRC (1996), NSTC (1996, 1997), and U.S. EPA (1997a) documents.

MTBE, an aliphatic ether, is a volatile organic compound (VOC) with a characteristic odor. It is a colorless liquid at room temperature. It is highly flammable and combustible when exposed to heat or flame or spark, and is a moderate fire risk. Vapors may form explosive mixtures with air. It is unstable in acid solutions. Fire may produce irritating, corrosive or toxic gases. Runoff from fire control may contain MTBE and its combustion products (HSDB 1997).

MTBE is miscible in gasoline and soluble in water, alcohol, and other ethers. It has a molecular weight of 88.15 daltons, a vapor pressure of about 245 mmHg at 25 °C, an octane number of 110, and solubility in water of about 50 g/L at 25 °C. It disperses evenly in gasoline and water and stays suspended without requiring physical mixing. It does not increase volatility of other gasoline components when it is mixed in the gasoline. MTBE released to the environment via surface spills or subsurface leaks was found to initially partition between water and air (Jeffrey 1997). The log of the octanol-water partition coefficient (log K_{ow}) is reported to range from 0.94 to 1.24 which indicates that there is 10 times more partitioning of MTBE in the lipophilic phase

than in the aqueous phase of solvents. The molecular size and log K_{ow} of MTBE are characteristic of molecules which are able to penetrate across biological membranes of the skin, lungs and gastrointestinal tracts (Mackay et al. 1993, Nihlen et al. 1995). The octanol-water partition coefficient is reported to be 16 by Nihlen et al. (1997). Fujiwara et al. (1984) reported laboratory-derived octanol-water partition coefficients ranging from 17.2 to 17.5 with a log K_{ow} of 1.2. The blood-air, urine-air, saline-air, fat-air and oil-air partition coefficients (lambda) are reported to be 20, 15.6, 15.3, 142 and 138, respectively (Imbriani et al. 1997). One part per million (ppm) of MTBE, volume to volume in air, is approximately 3.6 mg/m^3 of air at 20 °C (ATSDR 1996).

Organoleptic Properties

Taste or odor characteristics, often referred to as organoleptic properties, are not used by U.S. EPA or DHS for developing primary drinking water standards, but are used for developing secondary standards. The estimated thresholds for these properties of MTBE reported in the literature are given in Table 3 and are adapted from the ATSDR (1996), Cal/EPA (1998), HEI (1996), HSDB (1997), NSTC (1996, 1997), and U.S. EPA (1997a) documents. Taste and odor may alert consumers to the fact that the water is contaminated with MTBE (Angle 1991) and many people object to the taste and odor of MTBE in drinking water (Killian 1998, Reynolds 1998). However, not all individuals respond equally to taste and odor because of differences in individual sensitivity. It is not possible to identify point threshold values for the taste and odor of MTBE in drinking water, as the concentration will vary for different individuals, for the same individuals at different times, for different populations, and for different water matrices, temperatures, and many other variables.

The odor threshold ranges from about 0.32 to 0.47 mg/m^3 (about 90 to 130 ppb) in air and can be as low as five ppb (about 0.02 mg/m^3) for some sensitive people. In gasoline containing 97% pure MTBE at mixture concentrations of three percent, 11% and 15% MTBE, the threshold for detecting MTBE odor in air was estimated to be 50 ppb (about 0.18 mg/m^3), 280 ppb (about one mg/m^3), and 260 ppb (about 0.9 mg/m^3), respectively (ACGIH 1996). A range of five ppb to 53 ppb (about 0.19 mg/m^3) odor threshold in the air was reported in an American Petroleum Institute (API) document (API 1994).

The individual taste and odor responses reported for MTBE in water are on average in the 15 to 180 ppb (µg/L) range for odor and the 24 to 135 ppb range for taste (API 1994, Prah et al. 1994, Young et al. 1996, Dale et al. 1997b, Shen et al. 1997, NSTC 1997). The ranges are indicative of the average variability in individual response. U.S. EPA (1997a) has analyzed these studies in detail and recommended a range of 20 to 40 ppb as an approximate threshold for organoleptic responses. The study (Dale et al. 1997b) by the Metropolitan Water District of Southern California (MWDSC) found people more sensitive to the taste than odor. This result is consistent with API's (1994) findings for MTBE taste and odor thresholds. But in the study by Young et al. (1996), test subjects were more sensitive to odor than taste. The subjects described the taste of MTBE in water as "nasty", "bitter", "nauseating", and "similar to rubbing alcohol" (API 1994).

It is noted that chlorination and temperature of the water would likely affect the taste and odor of MTBE in water. Thresholds for the taste and odor of MTBE in chlorinated water would be higher than thresholds of MTBE in nonchlorinated water. Thresholds for the taste and odor of MTBE in water at higher temperatures (e.g., for showering) would likely be lower than those of MTBE in water at lower temperatures.

There were undoubtedly individuals who could only detect the odor of MTBE at even higher concentrations than 180 ppb (Prah et al. 1994). Odor thresholds as high as 680 ppb have been reported (Gilbert and Calabrese 1992). On the other hand, some subjects in these studies were able to detect the odor of MTBE in water at much lower concentrations, i.e. 2.5 ppb (Shen et al. 1997), five ppb (McKinnon and Dyksen 1984), or 15 ppb (Young et al. 1996). Some sensitive subjects in the taste studies were able to detect MTBE in water at concentrations as low as two ppb (Dale et al. 1997b), 10 ppb (Barker et al. 1990), 21 ppb (Dale et al. 1997b), or 39 ppb (Young et al. 1996). Thus, in a general population, some unknown percentage of people will be likely to detect the taste and odor of MTBE in drinking water at concentrations below the U.S. EPA (1997a) 20 to 40 ppb advisory level. DHS (1997) has recently proposed five ppb as the secondary MCL for MTBE. The lowest olfaction threshold in water is likely to be at or about 2.5 ppb (Shen et al. 1997). The lowest taste threshold in water is likely to be at or about two ppb (Dale et al. 1997b).

Table 1. Chemical Identity of Methyl Tertiary Butyl Ether (MTBE)

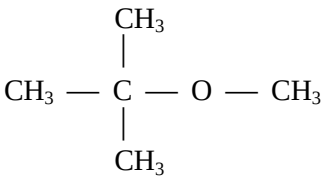
Characteristic	Information	Reference
Chemical Name	Methyl tertiary butyl ether	Merck 1989
Synonyms	Methyl tertiary-butyl ether; methyl tert-butyl ether; tert-butyl methyl ether; tertiary-butyl methyl ether; methyl-1,1-dimethylethyl ether; 2-methoxy-2-methylpropane; 2-methyl-2-methoxypropane; methyl t-butyl ether; MtBE; MTBE	Merck 1989
Registered trade names	No data	
Chemical formula	$C_5H_{12}O$ or $(CH_3)_3C(OCH_3)$	Merck 1989
Chemical structure		
Identification numbers:		
Chemical Abstracts Service (CAS) Registry number	1634-04-4	Merck 1989
National Institute for Occupational Safety and Health (NIOSH) Registry of Toxic Effects of Chemical Substances (RTECS) number	KN5250000	HSDB 1997
Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code (DOT/UN/NA/IMCO) Shipping number	UN 2398, IMO 3.2	HSDB 1997
Hazardous Substances Data Bank (HSDB) number	5847	HSDB 1997
North American Emergency Response Guidebook Documents (NAERG) number	127	HSDB 1997
National Cancer Institute (NCI) number	No data	
U.S. Environmental Protection Agency (U.S. EPA) Hazardous Waste number	No data	
U.S. EPA Oil and Hazardous Materials/ Technical Assistance Data System (OHM/TADS) number	No data	
European EINECS number	216.653.1	ECETOC 1997

Table 2. Chemical and Physical Properties of MTBE

Property	Value or information	Reference
Molecular weight	88.15 g/mole	Merck 1989
Color	colorless	Merck 1989
Physical state	liquid	Merck 1989
Melting point	-109 °C	HSDB 1997
Boiling point	53.6 - 55.2 °C	Mackay et al. 1993
Density at 20 °C	0.7404 - 0.7578 g/mL	Squillace et al. 1997a
Solubility		
in water	4.8 g/100 g water	Merck 1989
in water	23.2 - 54.4 g/L water	Garrett et al. 1986, Mackay et al. 1993
in water	43 - 54.3 g/L water	Squillace et al. 1997a
in water, 20 °C	4 - 5%	Gilbert and Calabrese 1992
in water, 25 °C	51 g/L water	HSDB 1997
Partition coefficients		
octanol-water	16	Nihlen et al. 1997
	17.2 - 17.5	Fujiwara et al. 1984
Log K_{ow}	0.94 - 1.16	Mackay et al. 1993
	1.2	Fujiwara et al. 1984
	1.24	U.S. EPA 1997a
Log K_{oc}	1.05 (estimated)	Squillace et al. 1997a
	2.89 (calculated)	U.S. EPA 1995b
Vapor pressure		
at 25 °C	245 - 251 mm Hg	Mackay et al. 1993
at 100 °F	7.8 psi (Reid Vapor Pressure)	ARCO 1995a
Henry's law constant	0.00058 - 0.003 atm-m^3/mole	Mackay et al. 1993
at 25 °C	5.87×10^{-4} atm-m^3/mole	ATSDR 1996
at 15 °C	0.011 (dimensionless)	Robbins et al. 1993
Ignition temperature	224 °C	Merck 1989
Flash point	-28 °C	Merck 1989
	28 °C (closed cup)	Gilbert and Calabrese 1992
Explosion limits	1.65 to 8.4% in air	Gilbert and Calabrese 1992
Heat of combustion	101,000 Btu/gal at 25 °C	HSDB 1997
Heat of vaporization	145 Btu/lb at 55 °C	HSDB 1997
Stability	MTBE is unstable in acidic solution	Merck 1989
Conversion factors		
ppm (v/v) to mg/m^3 in air at 25 °C	1 ppm = 3.61 mg/m^3	ACGIH 1996
mg/m^3 to ppm (v/v) in air at 25 °C	1 mg/m^3 = 0.28 ppm	ACGIH 1996

Table 3. Organoleptic Properties of MTBE

Property	Value or information	Reference
Odor	terpene-like at 25 °C	Gilbert and Calabrese 1992
Threshold in air	300 ppb	Smith and Duffy 1995
	0.32 - 0.47 mg/m^3 (~90 - 130 ppb)	ACGIH 1996
	5 - 53 ppb (detection)	API 1994
99% pure MTBE	8 ppb (recognition)	API 1994
97% pure MTBE	125 ppb (recognition)	API 1994
97% pure MTBE in gasoline		
15% MTBE	260 ppb	ACGIH 1996
11% MTBE	280 ppb	ACGIH 1996
3% MTBE	50 ppb	ACGIH 1996
Threshold in water	680 ppb	Gilbert and Calabrese 1992
	180 ppb	Prah et al. 1994
	95 ppb	ARCO 1995a
	55 ppb (recognition)	API 1994
	45 ppb (detection)	API 1994
	15 - 95 ppb (mean 34 ppb)	Young et al. 1996
	15 - 180 ppb	U.S. EPA 1997a
	13.5 - 45.4 ppb	Shen et al. 1997
	5 - 15 ppb	McKinnon and Dyksen 1984
	2.5 ppb	Shen et al. 1997
Taste	solvent-like at 25 °C	U.S. EPA 1997a
Threshold in water	21 - 190 ppb	Dale et al. 1997b
	24 - 135 ppb	U.S. EPA 1997a
	39 - 134 ppb (mean 48 ppb)	Young et al. 1996
	39 - 134 ppb	API 1994
	10 - 100 ppb	Barker et al. 1990
	2 ppb (one subject)	Dale et al. 1997b

Production and Uses

MTBE is manufactured from isobutene; also known as isobutylene or 2-methylpropene (Merck 1989), which is a product of petroleum refining. It is made mainly by combining methanol with isobutene, or derived from combining methanol and TBA. It is used primarily as an oxygenate in unleaded gasoline, in the manufacture of isobutene, and as a chromatographic eluent especially in high pressure liquid chromatography (ATSDR 1996, HSDB 1997). MTBE also has had a limited use as a therapeutic drug for dissolving cholesterol gallbladder stones (Leuschner et al. 1994).

MTBE is the primary oxygenate used in gasoline because it is the least expensive and in greatest supply. It is promoted as a gasoline blending component due to its high octane rating, low cost of production, ability to readily mix with other gasoline components, ease in distribution through existing pipelines, distillation temperature depression, and beneficial dilution effect on undesirable components of aromatics, sulfur, olefin and benzene. In addition, the relatively low co-solvent volatility of MTBE does not result in a more volatile gasoline that could be hazardous in terms of flammability and explosivity. The use of MTBE has helped offset the octane specification loss due to the discontinued use of higher toxicity high octane aromatics and has reduced emissions of benzene, a known human carcinogen, and 1,3-butadiene, an animal carcinogen (Cal/EPA 1998, Spitzer 1997).

MTBE has been commercially used in Europe since 1973 as an octane enhancer to replace lead in gasoline and was approved as a blending component in 1979 by U.S. EPA. Since the early 1990s, it has been used in reformulated fuel in 18 states in the U.S. Under Section 211 of the 1990 CAAA, the federal oxyfuel program began requiring gasoline to contain 2.7% oxygen by weight which is equivalent to roughly 15% by volume of MTBE be used during the four winter months in regions not meeting CO reduction standards in November 1992. In January 1995, the federal RFG containing two percent oxygen by weight or roughly 11% of MTBE by volume was required year-round to reduce O_3 levels. Oxygenates are added to more than 30% of the gasoline used in the U.S. and this proportion is expected to rise (Squillace et al. 1997a).

In California, federal law required the use of Phase I RFG in the worst polluted areas including Los Angeles and San Diego as of January 1, 1995, and in the entire state as of January 1, 1996. By June 1, 1996, state law required that all gasoline sold be California Phase 2 RFG and federal Phase II RFG will be required by the year 2000 (Cornitius 1996). MTBE promotes more complete burning of gasoline, thereby reducing CO and O_3 levels in localities which do not meet the National Ambient Air Quality Standards (ATSDR 1996, USGS 1996). Almost all of the MTBE produced is used as a gasoline additive; small amounts are used by laboratory scientists (ATSDR 1996). When used as a gasoline additive, MTBE may constitute up to 15% volume to volume of the gasoline mixture. Currently, MTBE is added to virtually all of the gasoline consumed in California (Cal/EPA 1998).

The amount of MTBE used in the U.S. has increased from about 0.5 million gallons per day in 1980 to over 10 million gallons per day in early 1997. Of the total amount of MTBE used in the U.S., approximately 70% are produced domestically, about 29% are imported from other countries, and about one percent is existing stocks. Over 4.1 billion gallons of MTBE are consumed in the U.S. annually, including 1.49 billion gallons -- more than 36% of the national figure -- in California (Wiley 1998). California uses about 4.2 million gallons per day of MTBE, about 85% of which is imported into the state, primarily by ocean tankers from the Middle East

(Cal/EPA 1998). California also imports MTBE from Texas and other major MTBE-producing states in the U.S.

MTBE production in the U.S. began in 1979 and increased rapidly after 1983. It was the second most-produced chemical, in terms of amount, in the U.S. in 1997, whereas previously it was ranked the twelfth in 1995 and eighteenth in 1994 (Cal/EPA 1998, Kirschner 1996, Reisch 1994). The production was 13.61 million pounds in 1994 and 17.62 million pounds in 1995 (Kirschner 1996). MTBE production was estimated at about 2.9 billion gallons in the U.S. and about 181 million gallons in California in 1997 (Wiley 1998). MTBE is manufactured at more than 40 facilities by about 27 producers primarily concentrated along the Houston Ship Channel in Texas and the Louisiana Gulf Coast. Texas supplies about 80% of the MTBE produced in the U.S. with about 10% produced in Louisiana and about five percent in California (Cal/EPA 1998). The major portion of MTBE produced utilizes, as a co-reactant, isobutylene that is a waste product of the refining process (Wiley 1998).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

The NSTC (1997) report provides extensive occurrence data for MTBE and other fuel oxygenates, as well as information on applicable treatment technologies. Similar information, specifically based on data in California, can be found in the recent UC (1998) report mandated under SB 521. For additional information concerning MTBE in the environment, the NSTC report can be accessed through the NSTC Home Page via a link from the OSTP. The U.S. Geological Survey (USGS) has been compiling data sets for national assessment of MTBE and other VOCs in ground and surface water as part of the National Water-Quality Assessment (NAWQA) Program (Buxton et al. 1997, Lapham et al. 1997, Squillace et al. 1997a, 1997b, Zogorski et al. 1996, 1997). Information on analytical methods for determining MTBE in environmental media is compiled in the ATSDR (1996) Toxicological Profile document.

The U.S. EPA (1993, 1995a) estimated that about 1.7 million kilograms (kgs) MTBE were released from 141 facilities reporting in the Toxics Release Inventory (TRI) per year, 97.3% to air, 2.44% to surface water, 0.25% to underground injection, and 0.01% to land. Cohen (1998) reported that an estimated 27,000 kgs or 30 tons per day were emitted from 9,000 tons of MTBE consumed in California per day. The California Air Resources Board (ARB) estimated that the exhaust and evaporative emission was about 39,000 kgs or 43 tons per day in California in 1996 (Cal/EPA 1998).

A multimedia assessment of refinery emissions in the Yorktown region (Cohen et al. 1991) indicated that the MTBE mass distribution was over 73% in water, about 25% in air, less than two percent in soil, about 0.02% in sediment, about 10^{-6}% in suspended solids, and 10^{-7}% in biota. A recent laboratory study on liquid-gas partitioning (Rousch and Sommerfeld 1998) suggests that dissolved MTBE concentrations can vary substantially from nominal. The main route of exposure for occupational and non-occupational groups is via inhalation, ingestion is considered as secondary, and dermal contact is also possible.

The persistence half-life of MTBE (Jeffrey 1997) is about four weeks to six months in soil, about four weeks to six months in surface water, and about eight weeks to 12 months in groundwater based on estimated anaerobic biodegradation, and about 20.7 hours to 11 days in air based on measured photooxidation rate constants (Howard et al. 1991, Howard 1993). Church et al. (1997) described an analytical method for detecting MTBE and other major oxygenates and their degradation products in water at sub-ppb concentrations. MTBE appears to be biodegraded

under anaerobic conditions (Borden et al. 1997, Daniel 1995, Jensen and Arvin 1990, Mormile et al. 1994, Steffan et al. 1997). Brown et al. (1997) and Davidson and Parsons (1996) reviewed state-of-the-art remediation technologies for treatment of MTBE in water. McKinnon and Dyksen (1984) described the removal of MTBE from groundwater through aeration plus granulated activated charcoal (GAC). Koenigsberg (1997) described a newly developed bioremediation technology for MTBE cleanup in groundwater. Cullen (1998) reported a one-year field test of a polymer-enhanced carbon technology for MTBE removal at the drinking water supply source.

Air, Soil, Food, and Other Sources

The presence of MTBE in ambient air is documented and likely to be the principal source of human exposure. MTBE is released into the atmosphere during the manufacture and distribution of oxyfuel and RFG, in the vehicle refueling process, and from evaporative and tailpipe emissions from motor vehicles. The general public can be exposed to MTBE through inhalation while fueling motor vehicles or igniting fuel under cold start-up conditions (Lindstrom and Pleil 1996). The level of inhaled MTBE at the range relevant to human exposures appears to be directly proportional to the MTBE concentrations in air (Bio/dynamics, Inc. 1981, 1984c, Nihlen et al. 1994). In air, MTBE may represent five to 10% of the VOCs that are emitted from gasoline-burning vehicles, particularly in areas where MTBE is added to fuels as part of an oxygenated fuel program (ARCO 1995a). MTBE has an atmospheric lifetime of approximately four days and its primary byproducts are tert-butyl formate (TBF), formaldehyde (HCHO), acetic acid, acetone, and TBA.

MTBE was found in urban air in the U.S. (Zogorski et al. 1996, 1997) and the median concentrations ranged from 0.13 to 4.6 parts per billion by volume (ppbv). Fairbanks, Alaska reported concentrations ranging from two to six ppbv when the gasoline contained 15% MTBE (CDC 1993a). Grosjean et al. (1998) reported ambient concentrations of ethanol and MTBE at a downtown location in Porto Alegre, Brazil where about 74% of about 600,000 vehicles use gasoline with 15% MTBE, from March 20, 1996 to April 16, 1997. Ambient concentrations of MTBE ranged from 0.2 to 17.1 ppbv with an average of 6.6 ± 4.3 ppbv. This article also cited unpublished data including Cape Cod (four samples, July to August 1995): 39 to 201 parts per trillion by volume (pptv or 1/1,000 ppbv), Shenandoah National Park (14 samples, July to August 1995): less or equal to (≤) seven pptv, Brookhaven (16 samples, July to August 1995): 33 to 416 pptv, Wisconsin (62 samples, August 1994 to December 1996, with all but five samples yielding no detectable MTBE with a detection limit of 12 pptv): ≤ 177 pptv, and downtown Los Angeles, California (one sample, collected in 1993 prior to the introduction of California RFG with MTBE): 0.8 ppbv.

Ambient levels of MTBE in California are similar or slightly higher than the limited data suggest for other states. The results of two recent (from 1995 to 1996) monitoring surveys (Poore et al. 1997, Zielinska et al. 1997) indicate that ambient levels of MTBE averaged 0.6 to 7.2 ppbv with sampling for three hours at four southern California locations, and 1.3 to 4.8 ppbv with sampling for 24 hours at seven California locations. The Bay Area Air Quality Management District (BAAQMD) has an 18-station network and has been monitoring for MTBE since 1995. The average concentration of MTBE in the San Francisco Bay area is approximately one ppbv (Cal/EPA 1998).

The ARB established a 20-station TAC air-monitoring network in 1985, and began analyzing ambient air for MTBE in 1996 (ARB 1996). Preliminary data suggest a statewide average of

approximately two ppbv with higher concentrations in the South Coast of about four ppbv. The limit of detection is 0.2 ppbv. The Desert Research Institute, under contract to ARB as a part of the 1997 Southern California Ozone Study (Fujita et al. 1997), monitored for MTBE in July through September of 1995 and 1996 in Southern California, at the Asuza, Burbank, and North Main monitoring sites. The monitoring was designed to determine peak morning rush hour concentrations (six to nine a.m.) and was part of a comprehensive study to analyze reactive organics in the South Coast Air Basin. The results showed a mean of approximately four ppbv with a range of one to 11 ppbv. These concentrations are similar to the ARB findings. Although ARB sampled for 24 hours, the highest concentrations are seen in the morning rush hour traffic because MTBE is a tailpipe pollutant.

Industrial hygiene monitoring data for a MTBE operating unit shows an average eight-hour exposure of 1.42 ppm. Average exposure for dockworkers was determined to be 1.23 ppm. Occupational exposure to gasoline containing two to eight percent MTBE is estimated at one to 1.4 ppm per day (ARCO 1995a, 1995b). In a New Jersey study, MTBE concentrations as high as 2.6 ppm were reported in the breathing zone of individuals using self-service gasoline stations without vapor recovery equipment, and the average MTBE exposure among service station attendants was estimated to be below one ppm when at least 12% MTBE was used in fuels (Hartle 1993). The highest Canadian predicted airborne concentration of 75 ng/m^3 is 3.9×10^7 times lower than the lowest reported effect level of 2,915 mg/m^3 in a subchronic inhalation study in rats (Environmental Canada 1992, 1993, Long et al. 1994).

In a Finnish study based on inhalation exposure (Hakkola and Saarinen 1996), oil company road tanker drivers were exposed to MTBE during loading and delivery at concentrations between 13 and 91 mg/m^3 (about 3.6 to 25 ppm) and the authors suggested some improvement techniques to reduce the occupational exposure. A recent Finnish study, Saarinen et al. (1998) investigated the exposure and uptake of 11 drivers to gasoline vapors during road-tanker loading and unloading. On average the drivers were exposed to vapors for 21 ± 14 minutes, three times during a work shift. The mean concentration of MTBE was 8.1 ± 8.4 mg/m^3 (about 2.3 ppm). Vainiotalo et al. (1999) studied customer breathing zone exposure during refueling for four days in summer 1996 at two Finnish self-service gasoline station with "stage 1" vapor recovery systems. The MTBE concentration ranged from less than 0.02 to 51 mg/m^3. The geometric mean concentration of MTBE in individual samples was 3.9 mg/m^3 at station A and 2.2 mg/m^3 at station B. The average refueling (sampling) time was 63 seconds at station A and 74 seconds at station B. Mean MTBE concentration in ambient air (a stationary point in the middle of the pump island) was 0.16 mg/m^3 for station A and 0.07 mg/m^3 for station B.

Exposure to CO, MTBE, and benzene levels inside vehicles traveling in an urban area in Korea was reported (Jo and Park 1998). The in-vehicle concentrations of MTBE were significantly higher ($p < 0.0001$), on the average 3.5 times higher, in the car with a carbureted engine than in the other three electronic fuel-injected cars. The author considered the in-auto MTBE levels, 48.5 μg/m^3 (about 13 ppb) as a median, as two to three times higher than the measurements in New Jersey and Connecticut. Goldsmith (1998) reported that vapor recovery systems could reduce risks from MTBE.

Unlike most gasoline components that are lipophilic, the small, water-soluble MTBE molecule has low affinity for soil particles and moves quickly to reach groundwater. In estuaries, MTBE is not expected to stay in sediment soil but can accumulate at least on a seasonal basis in sediment interstitial water (ATSDR 1996). There are no reliable data on MTBE levels in food, but food is not suspected as a significant source of exposure to MTBE. There is little information on the presence of MTBE in plants or food chains. The bioconcentration potential

for MTBE in fish is rated as insignificant based on the studies with Japanese carp by Fujiwara et al. (1984) generating bioconcentration factors for MTBE ranging from 0.8 to 1.5. Limited data suggest that MTBE will not bioaccumulate in fish or food chains (ATSDR 1996). Based on fugacity modeling and limited information on concentrations in shellfish, it is estimated that the average daily intake of MTBE for the age group of the Canadian population most exposed on a body weight basis, i.e., five to 11-year-olds, is 0.67 ng/kg/day (Environmental Canada 1992, 1993, Long et al. 1994).

Water

MTBE, being a water-soluble molecule, binds poorly to soils and readily enters surface and underground water. MTBE appears to be resistant to chemical and microbial degradation in water (ATSDR 1996). When it does degrade, the primary product is TBA. Two processes, degradation and volatilization, appear to reduce the concentrations of MTBE in water (Baehr et al. 1997, Borden et al. 1997, Schirmer and Baker 1998). The level of ingested MTBE from drinking water at the range relevant to human exposures appears to be directly proportional to the MTBE concentrations in water (Bio/dynamics, Inc. 1981, 1984c, Nihlen et al. 1994). The concentrations of MTBE in Canadian surface water predicted under a worst-case scenario is six ppt (or six ng/L), which is 1.12×10^8 times lower than the 96-hour LC_{50} for fathead minnow of 672 ppm (or 672 mg/L) (Environmental Canada 1992, 1993). The transport, behavior and fate of MTBE in streams have been summarized by the USGS NAWQA Program (Rathbun 1998).

MTBE can be a water contaminant around major production sites, pipelines, large tank batteries, transfer terminals, and active or abandoned waste disposal sites. It tends to be the most frequently detected VOC in shallow groundwater (Bruce and McMahon 1996). The primary release of MTBE into groundwater is from leaking USTs. Gasoline leaks, spills or exhaust, and recharge from stormwater runoff contribute to MTBE in groundwater. In small quantities, MTBE in air dissolves in water such as deposition in rain (Pankow et al. 1997). Recreational gasoline-powered boating and personal watercraft is thought to be the primary source of MTBE in surface water. MTBE has been detected in public drinking water systems based on limited monitoring data (Zogorski et al. 1997). Surveillance of public drinking water systems in Maine, begun in February 1997, has detected MTBE at levels ranging from one to 16 ppb in seven percent of 570 tested systems with a median concentration of three ppb (IPCS 1997, Smith and Kemp 1998). Sampling program conducted during summer of 1998 found trace levels of MTBE in 15% of Maine's drinking water supplies. Concentrations above 38 ppb were found in one percent of the wells (Renner 1999).

MTBE is detected in groundwater following a reformulated fuel spill (Garrett et al. 1986, Shaffer and Uchrin 1997). MTBE in water can be volatilized to air, especially at higher temperature or if the water is subjected to turbulence. However, it is less easily removed from groundwater than other VOCs such as benzene, toluene, ethylbenzene, and xylenes (BTEX) that are commonly associated with gasoline spills. MTBE and BTEX are the most water-soluble fractions in gasoline and therefore the most mobile in an aquifer system. Based on equilibrium fugacity models and especially during warm seasons, the high vapor pressure of MTBE leads to partitioning to air and half-lives in moving water are estimated around 4.1 hours (Davidson 1995, Hubbard et al. 1994). In shallow urban groundwater, MTBE was not found with BTEX. Landmeyer et al. (1998) presented the areal and vertical distribution of MTBE relative to the most soluble gasoline hydrocarbon, benzene, in a shallow gasoline-contaminated aquifer and biodegradation was not a major attenuation process at this site. MTBE may be fairly persistent

since it is refractory to most types of biodegradation (Borden et al. 1997, Daniel 1995, Jensen and Arvin 1990). Adsorption is expected to have little effect and dissolved MTBE will move at the same rate as the groundwater. MTBE may be volatilized into air or into soil gas from groundwater and these mechanisms may account for the removal of MTBE from groundwater.

MTBE has been detected in water, mainly by the USGS, in Colorado (Livo 1995, Bruce and McMahon 1996), California (Boughton and Lico 1998), Connecticut (Grady 1997), Georgia, Indiana (Fenelon and Moore 1996), Maine (Smith and Kemp 1998), Maryland (Daly and Lindsey 1996), Massachusetts (Grady 1997), Minnesota, Nevada (Boughton and Lico 1998), New Hampshire (Grady 1997), New Jersey (Terracciano and O'Brien 1997, O'Brien et al. 1998), New Mexico, New York (Stackelberg et al. 1997, Lince et al. 1998, O'Brien et al. 1998), North Carolina (Rudo 1995), Pennsylvania (Daly and Lindsey 1996), South Carolina (Baehr et al. 1997), Texas, Vermont (Grady 1997), Wisconsin and other states. A recent USGS NAWQA survey (Boughton and Lico 1998) reported the detection of MTBE in Lake Tahoe, Nevada and California, from July to September 1997, in concentrations ranging from 0.18 to 4.2 ppb and to depths of 30 meters. Zogorski et al. (1998) summarized the findings and research by the USGS in ground and surface water that MTBE has been detected in 14% of urban wells and two percent of rural wells sampled from aquifers used for drinking water.

USGS has published the results of the NAWQA Program (Squillace et al. 1995, 1996, 1997a, 1997b, 1998) of monitoring wells, which are not drinking water wells. This program analyzed concentrations of 60 VOCs from 198 shallow wells and 12 springs in eight urban areas (none in California) and 549 shallow wells in 21 agricultural areas (including the San Joaquin Valley). MTBE was detected in 27% of the urban wells and springs and 1.3% of the agricultural wells. The average MTBE concentration found in shallow groundwater was 0.6 ppb. MTBE was the second most frequently detected VOC (behind chloroform) in shallow groundwater in urban wells with a detection frequency of 27% of the 210 wells and springs sampled (Anonymous 1995, Squillace et al. 1996, Zogorski et al. 1998). No MTBE was detected in 100 agricultural wells in the San Joaquin Valley.

A recent evaluation of MTBE impacts to California groundwater resources (Happel et al. 1998), jointly sponsored by the Underground Storage Tank (UST) Program of the California State Water Resources Control Board (SWRCB), the Office of Fossil Fuels of U.S. Department of Energy (DOE), and the Western States Petroleum Association (WSPA), found evidence of MTBE in nearly 80% of the 1,858 monitoring wells from 236 leaking underground fuel tank (LUFT) sites in 24 counties examined by the Lawrence Livermore National Laboratory (LLNL). LLNL originally estimated that more than 10,000 LUFT sites out of the recognized 32,409 sites in California are contaminated with MTBE. Recent ongoing monitoring report (UC 1998) confirms that at least 3,000 to 4,500 LUFT sites are contaminated with MTBE. Maximum concentrations found at these sites ranged from several ppb to approximately 100,000 ppb or 100 ppm, indicating a wide range in the magnitude of potential MTBE impacts at gasoline release sites. MTBE plumes are more mobile than BTEX plumes, and the plumes are usually large migrates. Primary attenuation mechanism for MTBE is dispersion. LLNL concluded that MTBE might present a cumulative contamination hazard.

In response to the growing concern over the detection of MTBE in California's groundwater and surface water bodies, the SWRCB was requested to convene an advisory panel to review the refueling facilities and practices at marinas located on surface water bodies serving as drinking water sources to determine if any upgrades should be made to eliminate releases to the water body (Patton et al. 1999a). In addition, SWRCB's advisory panel was asked to review existing database of UST contamination sites to determine if there is a leak history and identify

appropriate measures to assure the prevention and detection of oxygenate releases from retail marketing facilities (Patton et al. 1999b).

MTBE was detected in municipal stormwater in seven percent of the 592 samples from 16 U.S. cities during 1991 to 1995 with a range of 0.2 to 8.7 ppb and a median of 1.5 ppb (Delzer et al. 1997). MTBE was found to be the seventh most frequently detected VOCs in municipal stormwater. Among the stormwater samples that had detectable concentrations of MTBE, 87% were collected between October 1 and March 31 which is the period of time when oxygenated gasoline is used in CO nonattainment areas (Squillace et al. 1998). Surveys by the U.S. EPA found that 51 public water suppliers in seven responding states had detected MTBE. There are ongoing regional studies of MTBE occurrence in California, New England, Long Island, New Jersey and Pennsylvania (Wiley 1998). MTBE was detected in aquifers (Landmeyer et al. 1997, 1998, Lindsey 1997).

Cal/EPA and other state agencies have taken a proactive approach toward investigating MTBE in water in California. MTBE has recently been detected in shallow groundwater at over 75% of about 300 leaking UST sites in the Santa Clara Valley Water District (SCVWD), at 90 out of 131 fuel leak sites under jurisdiction of the San Francisco Regional Water Quality Control Board (SFRWQCB) and at over 200 leaking sites in the Orange County Water District. According to the Santa Ana Regional Water Quality Control Board, MTBE has been found at concentrations higher than 200 ppb at 68% of the leaking UST sites in its jurisdiction and at concentrations above 10,000 ppb at 24% of the leaking sites. In Solano County, concentrations of MTBE as high as 550,000 ppb have been reported in groundwater at sites with leaking USTs. However, these wells are not sources for drinking water (SCDEM 1997). At sites of gasoline leakage, MTBE concentrations as high as 200,000 ppb have been measured in groundwater (Davidson 1995, Garrett et al. 1986).

In July 1998, the SFRWQCB (1998) has compiled a list of 948 LUFT sites in the nine Bay Area counties in which groundwater has been contaminated with MTBE to a concentration of more than five ppb, which is the detection limit. The MTBE concentrations from the monitoring wells ranged from six ppb to as high as 19,000,000 ppb or 19,000 ppm. The monitoring well with 19,000,000 ppb of MTBE also was reported with benzene contamination in groundwater at 1,900 ppb and a maximum concentration of 6,100 ppb during the past two years. The range of MTBE concentrations was from seven to 390,000 ppb in Alameda County, six to 240,000 ppb in Contra Costa County, six to 210,000 ppb in Marin County, 12 to 60,000 ppb in Napa County, six to 710,000 ppb in San Francisco County, seven to 2,400,000 ppb in San Mateo County, six to 140,000 ppb in Santa Clara County, nine to 19,000,000 ppb in Solano County, and seven to 390,000 ppb in Sonoma County.

In 1994, SB 1764 (Thompson, California Health and Safety Code, Section 25299.38) established an independent advisory committee to the SWRCB to review the cleanup of USTs including requesting companies to monitor MTBE (Farr et al. 1996). State and federal statues require that all USTs including LUFTs be removed, replaced or upgraded to meet current standards by December 22, 1998. In June 1996, the SWRCB asked local regulatory agencies to require analysis at all leaking UST sites with affected groundwater. MTBE has been detected at a majority of the sites. Concentrations of MTBE in shallow groundwater near the source of the fuel release can exceed 10,000 ppb or 10 ppm (Cal/EPA 1998).

In 1995, ARB requested DHS' Division of Drinking Water and Environmental Management to test for MTBE in the state's drinking water. In February 1996, DHS sent an advisory letter to water suppliers it regulates, requesting voluntary testing for MTBE while a monitoring

regulation was being developed. The regulation was adopted on February 13, 1997, and requires monitoring of MTBE as an unregulated chemical by the water suppliers from a drinking water well or a surface water intake at least once every three years. DHS routinely updates the reported detection of MTBE in groundwater and surface water sources on its website. DHS uses a detection limit for purposes of reporting (DLR) for MTBE of five ppb based on consideration of the State's commercial laboratories' use of MTBE in other common analyses and the potential for sample contamination and the reporting of false positives. Laboratories are only required to report MTBE analytical results at or above the five ppb DLR, but some laboratories are reporting lower concentrations.

According to the DHS report, from February 13 to June 13, 1997, MTBE had been detected in 14 of the 388 drinking water systems that had been monitored. As of December 22, 1997, 18 of the 516 systems monitored had reported MTBE detection. These are drinking water wells tapping deep aquifers and some aquifers at depths of 200 feet or greater. In addition, approximately 2,500 public drinking water sources had been sampled and reported. Only 33 sources including 19 groundwater sources and 14 surface water sources, nine of which are reservoirs, had reported detectable concentrations of MTBE. Three groundwater sources including City of Santa Monica (up to 300 ppb in February 1996), City of Marysville (up to 115 ppb in January 1997), and Presidio of San Francisco (up to 500 ppb in July 1990 from a currently abandoned well) had reported concentrations above the U.S. EPA (1997a) advisory level of 20 to 40 ppb. Otherwise, the range of reported values was less than (<) one to 34.1 ppb in groundwater sources and < one to 15 ppb in surface water sources (DHS 1997).

The City of Santa Monica has shut down two well fields, Charnock and Arcadia, due to MTBE contamination. These well fields used to supply 80% of the drinking water to the city residents. Concentrations as high as 610 ppb were observed in the Charnock aquifer and the seven wells in the field have been closed. In the Arcadia well field, two wells have been closed due to MTBE contamination from an UST at a nearby gasoline station (Cal/EPA 1998, Cooney 1997). DHS (1997) reported MTBE concentrations up to 130 ppb in a Charnock well and 300 ppb in another Charnock well in February 1996, and up to 72.4 ppb in an Arcadia well in August 1996. In Santa Clara County, the Great Oaks Water Company has closed a drinking water well in South San Jose due to trace MTBE contamination. The Lake Tahoe Public Utilities District has shut down six of their 36 drinking water wells because of MTBE contamination.

MTBE has also been found in many surface water lakes and reservoirs (DHS 1997). The reservoirs allowing gasoline powerboat activities have been detected with MTBE at higher concentrations than those reservoirs prohibiting boating activities. DHS reported MTBE in Lake Tahoe, Lake Shasta, Whiskeytown Lake in the City of Redding, San Pablo Reservoir in East Bay Municipal Utility District (EBMUD) in the San Francisco Bay area, Lobos Creek in Presidio of San Francisco, Del Valle and Patterson Pass of Zone Seven Water Agency serving east Alameda County, Clear Lake in Konocti County Water District, Canyon Lake in the Elsinore Valley Municipal Water District, Lake Perris in the MWDSC in the Los Angeles area, and Alvarado, Miramar, and Otay Plant influent in City of San Diego. MTBE concentrations ranged from < one to 15 ppb. Donner Lake, Lake Merced, Cherry and New Don Pedro Reservoirs in EBMUD, Anderson and Coyote Reservoirs in the SCVWD, Modesto Reservoir in the Stanislaus Water District, and Castaic Reservoir in MWDSC also had detectable levels of MTBE.

The City of Shasta Lake domestic water supply intake raw water was reported with 0.57 ppb MTBE in September 1996 although Lake Shasta had 88 ppb in a surface water sample next to a houseboat at a marina dock. BTEX were found in lower concentrations than MTBE. Water was analyzed for hydrocarbons before and after organized jet ski events held in the summer and fall

of 1996 in Orange County and Lake Havasu (Dale et al. 1997a). MTBE was measured in the water at the small holding basin in Orange County at concentrations of up to 40 ppb a few days after the event while there was only negligible BTEX. At the larger Lake Havasu, the MTBE concentrations increased from below the level of detection to 13 ppb. A recent report to the SCVWD described the detection of an average concentration of three ppb MTBE in Anderson, Calero, and Coyote Reservoirs which are drinking water sources where powerboating is allowed. Calero Reservoir banned jetskis in July 1998. The National Park Service is proposing a systemwide ban on similar types of personal watercraft, which are presently allowed in 34 of America's 375 national park units.

The Carson publicly owned treatment works (POTW) in Carson, California has also reported MTBE in its wastewater. The Carson POTW processes the largest volume of refinery wastewater in the nation (13 refineries sporadically discharge wastewater to the POTW). Refineries in California perform their own pretreatment prior to discharging to sewers. The refineries' discharges contain average levels from one to 7,000 ppb (seven ppm) with concentrations occasionally as high as 40,000 ppb. California refineries are situated mainly along the coast and discharge directly or indirectly to marine waters. No California refineries discharge their wastewater to sources of drinking water.

METABOLISM AND PHARMACOKINETICS

The available information on the metabolism and pharmacokinetics of MTBE is limited to humans and rats with little information from mice. MTBE can be absorbed into the body after inhalation in humans (Johanson et al. 1995, Nihlen et al. 1998a, 1998b, Vainiotalo et al. 1998) and rats (Buckley et al. 1997, Miller et al. 1997, Prah et al. 1994, Savolainen et al. 1985), ingestion or skin contact in rats (Miller et al. 1997). It is metabolized and eliminated from the body within hours. MTBE caused lipid peroxidation in the liver and induction of hepatic microsomal cytochrome P_{450} content in mice (Katoh et al. 1993). The major metabolic pathway of MTBE in both animals and humans is oxidative demethylation leading to the production of TBA (Poet et al. 1997c). In animals, HCHO is also a metabolite (Hutcheon et al. 1996). This reaction is catalyzed by cytochrome P_{450} enzymes (Brady et al. 1990, Hong et al. 1997b).

MTBE and TBA have been detected in blood, urine, and breath of humans exposed to MTBE via inhalation for 12 hours. Nihlen et al. (1998b) in a chamber study exposing human subjects for two hours suggests that TBA in blood or urine is a more appropriate biological exposure marker for MTBE than the parent ether itself. Bonin et al. (1995) and Lee and Weisel (1998) described analytical methods for detecting MTBE and TBA in human blood and urine at concentrations below one ppb. A recent Finnish study, Saarinen et al. (1998) investigated the uptake of 11 drivers to gasoline vapors during road-tanker loading and unloading. The total MTBE uptake during the shift was calculated to be an average of 106 ± 65 μmole. The mean concentrations of MTBE and TBA detected in the first urine after the work shift were 113 ± 76 and 461 ± 337 nanomole/L, and those found 16 hours later in the next morning were 18 ± 12 and 322 ± 213 nanomole/L, respectively.

Absorption

There is limited information on the rate and extent that MTBE enters the systemic circulation. MTBE is lipophilic which will facilitate its absorption across the lipid matrix of cell membranes (Nihlen et al. 1997). In its liquid or gaseous state, MTBE is expected to be absorbed into the

blood stream (Nihlen et al. 1995). MTBE is absorbed into the circulation of rats following oral, intraperitoneal (i.p.), intravenous (i.v.), or inhalation exposures (Bioresearch Laboratories 1990a, 1990b, 1990c, 1990d, Miller et al. 1997, NSTC 1997). Dermal absorption of MTBE is limited, as compared with other routes.

The concentration-time course of MTBE in blood plasma of male rats administered 40 mg/kg/day by oral, dermal, or i.v. routes was followed (Miller et al. 1997). Peak blood concentrations of MTBE (Cmax) were obtained within five to 10 minutes. Higher levels of MTBE were seen after oral versus i.v. exposure indicating elimination of the latter via the lungs. Miller et al. (1997) compared the areas under the concentration-time curves (AUC) for MTBE following i.v. and oral administrations and concluded that MTBE was completely absorbed from the gastrointestinal tract. Plasma levels of MTBE following dermal exposure were limited; peak concentrations were achieved two to four hours after dosing. Absorption ranged from 16 to 34% of applied doses of 40 mg/kg/day and 400 mg/kg/day respectively. After inhalation exposure, plasma concentrations of MTBE reached apparent steady state within two hours at both low (400 ppm) and high (8,000 ppm) doses. Peak MTBE concentrations were reached at four to six hours and were 14 and 493 ppb, respectively.

Distribution

Once in the blood, MTBE is distributed to all major tissues in the rat. Due to its hydrophilic properties, neither MTBE nor its metabolites would be expected to accumulate in body tissues. TBA appears to remain longer, and chronic exposure could result in accumulation to some steady-state level, but this needs further study. Once absorbed, MTBE is either exhaled as the parent compound or metabolized. Oxidative demethylation by cytochrome P_{450}-dependent enzymes is the first step in the metabolism that yields HCHO and TBA. TBA is detected in blood and urine and appears to have a longer half-life in blood than MTBE (Poet et al 1996, Prah et al. 1994, Prescott-Mathews et al. 1996, Savolainen et al. 1985).

Metabolism

The metabolism of absorbed MTBE proceeds in a similar fashion regardless of route of exposure. MTBE is metabolized via microsomal enzymes in the cells of organs (Turini et al. 1998). MTBE undergoes oxidative demethylation in the liver via the cytochrome P_{450}-dependent enzymes (P_{450} IIE1, P_{450}IIB1, and P_{450} IIA6 are thought to be involved) to give TBA and HCHO (Brady et al. 1990, Hong et al. 1997b). Rat olfactory mucosa displays a high activity in metabolizing MTBE via the cytochrome P_{450}-dependent enzymes (Hong et al. 1997a). In vitro studies of MTBE in human (Poet and Borghoff 1998) and rat (Poet and Borghoff 1997b) liver microsomes confirm that MTBE is metabolized by P_{450}-dependent enzymes and suggest that the metabolism of MTBE will be highly variable in humans. TBA may be eliminated unchanged in expired air or may undergo secondary metabolism forming 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid. Both of these latter metabolites are excreted in the urine and account for about 14% and 70% respectively of urine radioactivity for ^{14}C-MTBE dosed rats (Miller et al. 1997). Two unidentified minor metabolites are also excreted in urine.

Bernauer et al. (1998) studied biotransformation of ^{12}C- and 2-^{13}C-labeled MTBE and TBA in rats after inhalation or gavage exposure to identify 2-methyl-1,2-propanediol and 2-hydroxyisobutyrate as major metabolites in urine by ^{13}C nuclear magnetic resonance and gas chromatography/mass spectrometry. In one human individual given five mg ^{13}C-TBA/kg orally,

2-methyl-1,2-propanediol and 2-hydroxyisobutyrate were major metabolites in urine. The results suggest that TBA formed from MTBE be extensively metabolized by further oxidation reactions. In vitro evidence suggests that TBA may also undergo oxidative demethylation to produce HCHO and acetone (Cederbaum and Cohen 1980). Identification of $^{14}CO_2$ in expired air of ^{14}C-MTBE treated rats suggests some complete oxidation of MTBE or metabolites occurs, probably via HCHO. Studies in humans are more limited but TBA has been observed as a blood metabolite of MTBE. The participation of hepatic cytochrome P_{450}-dependent enzymes also indicates a potential role of co-exposure to other environmental chemicals in affecting MTBE metabolism and toxicity (Hong et al. 1997b, NSTC 1997).

Excretion

Elimination of MTBE and its metabolites by Fischer 344 rats is primarily via the lungs (expired air) and the kidneys (urine). In expired air, MTBE and TBA are the predominant forms. After i.v. administration of ^{14}C-MTBE to male rats most of the radioactivity was excreted in the exhaled air (60%) and urine (34.9%) with only two percent in the feces and 0.4% remaining in the tissues/carcass. Most of the administered dose was eliminated as MTBE during the first three hours following administration. About 70% of the dose recovered in the urine were eliminated in the first 24 hours and 90% in 48 hours. After dermal exposure to MTBE for six hours, 70 to 77% of the applied radioactivity was unabsorbed while 7.6 to 18.9% was excreted in expired air, 6.3 to 16.2% in urine, and 0.25 to 0.39% in feces at 40 and 400 mg/kg/day respectively. A negligible amount (< 0.2%) was found in tissues/carcass. The composition of ^{14}C-radiolabel in expired air was 96.7% MTBE and 3.3% TBA at the high dose. After inhalation exposures most of the ^{14}C was eliminated in the urine with 64.7% after single and 71.6% after repeated low doses. At the high dose, a larger fraction was eliminated in exhaled air: 53.6% compared to 17% for single or 21% for repeated low doses. Less than 1% of the dose was recovered in the feces and < 3.5% in the tissues/carcass. The composition of ^{14}C-radiolabel in exhaled breath in the first six hours following administration of MTBE was 66 to 69% MTBE and 21 to 34% TBA. By 24 hours post-dose 85 to 88% of the urine radioactivity was eliminated in rats from all exposure groups (Miller et al. 1997).

Pulmonary elimination of MTBE after intraperitoneal injection in mice (Yoshikawa et al. 1994) at three treated doses (50, 100 and 500 mg/kg) indicated an initial rapid decrease of the elimination ratio followed by a slow decrease at the doses of 100 and 500 mg/kg. The calculated half-lives of the two elimination curves obtained by the least squares method were approximately 45 minutes and 80 minutes. The pulmonary elimination ratios at the three different doses were from 23.2% to 69%. Most of the excreted MTBE was eliminated within three hours.

In a human chamber study (Buckley et al. 1997), two subjects were exposed to 1.39 ppm MTBE, that is comparable to low levels which might be found in the environment for one hour, followed by clean air for seven hours. The results showed that urine accounted for less than one percent of the total MTBE elimination. The concentrations of MTBE and TBA in urine were similar to that of the blood ranging from 0.37 to 15 µg/L and two to 15 µg/L, respectively. Human breath samples of end-expiration volume were collected from two individuals during motor vehicle refueling, one person pumping the fuel and a nearby observer, immediately before and for 64 minutes after the vehicle was refueled with premium grade gasoline (Lindstrom and Pleil 1996). Low levels of MTBE were detected in both subjects' breaths before refueling and levels were increased by a factor of 35 to 100 after the exposure. Breath elimination indicated that the half-life of MTBE in the first physiological compartment was between 1.3 and 2.9 minutes. The

breath elimination of MTBE during the 64-minute monitoring period was about four-fold for the refueling subject comparing to the observer subject.

Johanson et al. (1995) and Nihlen et al. (1998a, 1998b) reported toxicokinetics and acute effects of inhalation exposure of 10 male subjects to MTBE vapor at five, 25, and 50 ppm for two hours during light physical exercise. MTBE and TBA were monitored in exhaled air, blood, and urine. The elimination of MTBE from blood was multi-phasic with no significant differences between exposure levels. The elimination phases had half-lives of one minute, 10 minutes, 1.5 hours, and 19 hours respectively. Elimination of MTBE in urine occurred in two phases with average half-lives of 20 minutes and three hours. Excretion of MTBE appeared to be nearly complete within 10 hours. For TBA excretion the average post-exposure half-lives in blood and urine were 10 and 8.2 hours respectively. Some exposure dependence was noted for the urinary half-life with shorter values seen at the highest exposure level (50 ppm $\times$ 2 hour). A low renal clearance for TBA (0.6 to 0.7 mL/hour/kg) may indicate extensive blood protein binding or renal tubular reabsorption of TBA.

Pharmacokinetics

The plasma elimination half-life ($t_{1/2}$) of MTBE in male rats was about 0.45 to 0.57 hour after i.v., oral (low dose), and inhalation exposures. A significantly longer $t_{1/2}$ of 0.79 hour was observed with the high oral dose of 400 mg/kg/day. For dermal exposure the initial MTBE elimination $t_{1/2}$ was 1.8 to 2.3 hours. TBA elimination $t_{1/2}$ values were 0.92 hour for i.v., 0.95 to 1.6 hours for oral, 1.9 to 2.1 hours for dermal, and 1.8 to 3.4 hours for inhalation exposures. The apparent volume of distribution for MTBE ranged from 0.25 to 0.41 L after i.v., oral, and inhalation dosing and from 1.4 to 3.9 liters (L) after dermal exposures. The total plasma clearance of MTBE, corrected for relative bioavailability, ranged from 358 to 413 mL/hour in i.v., oral, and dermal administrations. Inhalation values ranged from 531 mL/hour for low single dose to 298 mL/hour for high single dose. For oral administration of 40 or 400 mg/kg/day MTBE the AUC values were 17 and 230 (µg/mL)hour for MTBE and 39 and 304 (µg/mL)hour for TBA (Miller et al. 1997).

The disposition and pharmacokinetics observed in these studies are similar to those observed in human volunteers following inhalation and dermal exposures (U.S. EPA 1993). For inhalation exposure to five mg/m^3 for one hour the $t_{1/2}$ value for MTBE was 36 minutes. Blood TBA levels rose during exposure and remained steady for up to seven hours post-exposure suggesting a longer $t_{1/2}$ for TBA in humans compared to rats. Other more recent data (cited in NSTC 1997) indicate a multi-exponential character to MTBE elimination from human blood with $t_{1/2}$ values of two to five minutes, 15 to 60 minutes and greater than 190 minutes. These results possibly indicate a more complex distribution or binding of MTBE in humans than observed in rats. Such differences probably are related to larger fat compartments in humans compared to rats.

Overall, these studies show that following i.v., oral, or inhalation exposures MTBE is absorbed, distributed, and eliminated from the body with a half-life of about 0.5 hour. Dermal absorption is limited. The extent of metabolism to TBA (and HCHO) the major metabolite is somewhat dependent on route and dose. TBA is eliminated from the body with a half-life of one to three hours or longer in humans. Virtually all MTBE is cleared from the body 48 hours post-exposure.

Physiologically-Based Pharmacokinetic (PBPK) Models

Computer-based PBPK models have been developed for rats (Borghoff et al. 1996a, Rao and Ginsberg 1997). These models vary in complexity, metabolic parameters, and one chemical specific parameter. The Borghoff et al. (1996a) model uses five compartments for MTBE and either five or two for TBA. While model predictions of MTBE blood concentrations and clearance following inhalation or oral exposures were generally good, the model underpredicted MTBE blood levels at 8,000 ppm by a factor of two. Accurate model predictions of TBA blood levels and clearance were more elusive with the two compartment model giving more accurate predictions at lower oral and inhalation doses than at higher doses or than the five compartment model. The Rao and Ginsberg (1997) model is more complex using eight compartments for MTBE and eight for TBA. While both models assume two Michaelis-Menten processes (Vmaxc/Km) from MTBE to TBA namely high capacity to low affinity ($Vmaxc_2/Km_2$), and low capacity to high affinity ($Vmaxc_1/Km_1$), the Rao and Ginsberg (1997) model uses different parameters than Borghoff et al. (1996a) with a lower $Vmaxc_1/Km_1$. Rao and Ginsberg (1997) use a lower tissue/blood partition coefficient for TBA in the slowly perfused compartment (e.g., muscle) of 0.4 versus 1. Predictions of blood levels and clearance rates for MTBE and TBA with MTBE inhalation exposures appear to be more accurate with this model. Similar validation is claimed for the oral and i.v. routes for MTBE exposure and for i.p. exposure to TBA although these data have not been seen in detail. Rao and Ginsberg (1997) used their model to evaluate some key uncertainties of acute inhalation exposures to MTBE during bathing and showering and concluded that the acute central nervous system (CNS) toxicity is likely due to MTBE rather than to its TBA metabolite. The simulated brain TBA concentration for CNS effects was in the 500 to 600 mg/L range. In contrast, the simulated brain concentration for MTBE's CNS effects was considerably lower (89 to 146 mg/L). By comparing TBA only versus MTBE exposure studies the authors concluded that under conditions where MTBE dosing produced acute CNS toxicity, the simulated TBA brain concentrations were too low to be effective.

Despite the lack of human data on tissue/blood partition coefficients and other key parameters, both models have been adjusted to human anatomical and physiological values and estimated metabolic and chemical parameters and compared with limited human blood data. Although the Borghoff et al. (1996a) model was able to predict MTBE levels seen in Cain et al. (1996) during inhalation exposure, it underpredicted MTBE blood concentrations after exposure, resulting in a faster clearance than seen experimentally. The Rao and Ginsberg (1997) model more closely simulated the data (1.7 ppm MTBE for one hour) of Cain et al. (1996) but underpredicted the peak and postexposure concentrations at higher inhalation exposures of five and 50 ppm MTBE for two hours (Johanson et al. 1995). It is clear that while human MTBE PBPK models may be improved considerably, they may prove useful in their present state to assess risks associated with some environmental exposures to MTBE (e.g., exposures when taking a shower).

TOXICOLOGY

The toxicology profile of MTBE has been summarized in the U.S. (Von Burg 1992, ATSDR 1996) and in Great Britain (BIBRA 1990). Zhang et al. (1997) used computer modeling to predict metabolism and toxicological profile of gasoline oxygenates including MTBE based on structure activity relationships. Health risk assessment of MTBE has been performed (Gilbert and Calabrese 1992, Hartly and Englande 1992, Hiremath and Parker 1994, Stern and Tardiff 1997, Tardiff and Stern 1997). The general toxicity of MTBE is not considered as "highly

hazardous" in a hazard ranking system for organic contaminants in refinery effluents (Siljeholm 1997) and is considered as less hazardous than most chemicals in 10 ranking systems in the Chemical Scorecard of the Environmental Defense Fund (EDF 1998). A substantial amount of health-related research has been conducted or initiated on MTBE in recent years (ATSDR 1996, U.S. EPA 1997a). A recent literature review (Borak et al. 1998) summarizes the exposure to MTBE and acute human health effects including nine epidemiological studies, ten industrial hygiene studies, and 12 clinical studies. However, most of the studies and reviews focus on the inhalation route of exposure in human health effects and laboratory animal toxicities. No studies were located regarding toxic effects in humans after oral exposure to MTBE alone. Because this document is mainly concerned with the effects of MTBE in drinking water, it focuses on oral toxicity studies in animals. There is limited information on dermal exposure effects in humans and animals. Very little is known about the toxic effects of MTBE in plants and ecosystems.

Toxicological Effects in Animals

Table 4 summarizes the lowest concentrations resulting in toxicity in laboratory animals via inhalation or oral exposure as reported in the ATSDR (1996) document and the latest U.S. EPA (1997c) advisory. Clary (1997) reviewed the systemic toxicity of MTBE including 12 inhalation and four oral studies. Stelljes (1997) summarized similar information based on only the ATSDR (1996) document. The various noncancer health effects via oral route of exposure in all tested species and the duration of exposure are summarized in Table 5. The highest NOAELs and all the lowest observed adverse effect level (LOAELs) are also included in Table 5. Details of each of the studies listed in Table 5 are described in the following sections on acute, subacute, subchronic and chronic toxicity. The cancer effects observed in animals are discussed in a separate section on carcinogenicity in this chapter. There were no studies located regarding cancer in humans after oral, or any other exposure to MTBE.

In animal studies, oral exposure to MTBE for acute, subacute, subchronic, or chronic duration appears to be without effects on the cardiovascular, musculoskeletal, dermal, ocular, or reproductive systems. In acute and subacute oral exposure studies, limited effects on the respiratory, gastrointestinal, hematological, hepatic, renal, or neurological systems and some minor systemic toxicities have been observed. In subchronic oral exposure, limited effects on gastrointestinal, hematological, hepatic, or renal systems and some minor systemic toxicities have been observed. In chronic oral exposure, the main observation is cancer and preneoplastic effects (ATSDR 1996). In this document, all the potential toxic effects of MTBE have been reviewed with an emphasis on the oral exposure; particularly the potential reproductive, developmental and carcinogenic effects have been extensively reviewed by OEHHA staff.

Some acute, intermediate or chronic duration minimal risk levels (MRLs) have been derived by the ATSDR for inhalation or oral exposure to MTBE (ATSDR 1996). U.S. EPA (1997c) lists in IRIS a Reference Concentration (RfC) for inhalation that is similar to the ATSDR's inhalation MRL. However, the current IRIS (U.S. EPA 1997c) does not list a Reference Dose (RfD) for ingestion (U.S. EPA 1987b) that is similar to the ATSDR's ingestion MRL. In addition to the key documents from governmental agencies and literature search articles mentioned above, toxicology information in the TOMES PLUS® database (Hall and Rumack 1998) also has been used in the following summary of toxic effects of MTBE.

Table 4. Summary of Selected Data on MTBE: Noncancer Toxic Effects in Animals*

Dose level	Inhalation (mg/m^3)			Oral (mg/kg/day)	
	ACUTE	SUBACUTE/ SUBCHRONIC	CHRONIC	ACUTE	SUBACUTE/ SUBCHRONIC
NOAEL	1,440	1,440	1,440	40	100
LOAEL	3,600	2,880	10,800	90	300
Lethal Dose	649,000	NA	NA	3,866	NA

*Values represent the lowest reported in ATSDR (1996) and U.S. EPA (1997a)

Table 5. Significant Noncancer Health Effects and Levels of Oral Exposure to MTBE in Animals*

Species/ (Strain)	Exposure/ Duration/ Frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
ACUTE EXPOSURE					
Death					
Rat	once (gavage)			3,866 (LD_{50})	ARCO 1980
Mouse	once (gavage)			4,000 (LD_{50})	Little et al. 1979
Systemic Toxicity					
Rat	once (gavage)	Respiratory Neurological		4,080 (labored respiration) 1,900 (slight to marked CNS depression) 2,450 (ataxia)	ARCO 1980
Rat (Sprague-Dawley)	once (gavage in oil)	Gastrointestinal Neurological	900	100 (diarrhea) 1,200 (profound but transient anesthesia)	Robinson et al. 1990
Rat (Fischer 344)	once (gavage in water)	Neurological	40	400(drowsiness)	Bioresearch Labs. 1990b
Rat (Sprague-Dawley)	once (gavage)	Neurological		90 (salivation) 440 (Male) (hypoactivity, ataxia) 1,750 (Female)	Johnson et al. 1992, Klan et al. 1992

Species/ (Strain)	Exposure/ Duration/ Frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
SUBACUTE EXPOSURE					
Systemic Toxicity					
Rat (Sprague-Dawley	14 days 7 days/week once/day (gavage in oil)	Respiratory	1,428		Robinson et al. 1990
		Cardiovascular	1,428		
		Gastrointestinal		357 (diarrhea)	
		Hematological	1,428 (Female)	357 (Male) (decreased monocytes)	
		Hepatic	714 (Male)	1,071 (Male) [increased serum glutamic-oxaloacetic transaminase (SGOT) and lactic dehydrogenase]	
			1,428 (Female)	[decreased blood urea nitrogen (BUN) values]	
		Renal	1,071 (Male) 1,428 (Female)	1,428 (Male) (increased hyaline droplets)	
		Endocrine	1,428		
		Body weight	714 (Female) 357 (Male)	1,071 (Female) (unspecified reduced weight gain)	
		Immunological/ Lymphoreticular		1,428	
		Neurological	1,071	1,428 (profound but transient anesthesia, hypoactivity, ataxia)	
		Reproductive	1,428		
		Other	1,071 (Male) 357 (Female)	1,428 (Male) 714 (Female) (elevated cholesterol)	
Mouse (CD-1)	3 weeks, 5 days/week (gavage in oil)	Body weight	1,000		Ward et al. 1994, 1995
		Reproductive	1,000		

Species/ (Strain)	Exposure/ Duration/ Frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
SUBCHRONIC EXPOSURE					
Death					
Rat (Sprague-Dawley)	16 weeks 4 days/week once/day (gavage in oil)			250 (Female) (increased mortality)	Belpoggi et al. 1995
Systemic Toxicity					
Rat (Sprague-Dawley)	4 weeks 5 days/week once/day (gavage)	Respiratory	1,750		Johnson et al. 1992, Klan et al. 1992
		Cardiovascular	1,750		
		Gastrointestinal	440	1,750 (inflammation, submucosal edema, epithelial hyperplasia, stomach ulcers)	
		Hematological	1,750		
		Muscle/skeleton	1,750		
		Hepatic	440	1,750 (increased relative liver weights)	
		Renal	1,750 (Female)	440 (Male) (increased hyaline droplets in proximal convoluted tubules and increased relative kidney weights)	
		Endocrine	1,750		
		Dermal	1,750		
		Ocular	1,750		
		Body weight	1,750		
		Immunological/ Lymphoreticular	1,750		
		Neurological		440 (hypoactivity, ataxia)	
		Reproductive	1,750		
		Other	440	1,750 (increased serum cholesterol)	

Species/ (Strain)	Exposure/ Duration/ Frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
SUBCHRONIC EXPOSURE (Continued)					
Systemic Toxicity					
Rat (Sprague-Dawley)	90 days 7 days/week once/day (gavage in oil)	Respiratory	1,200		Robinson et al. 1990
		Cardiovascular	1,200		
		Gastrointestinal		all treated doses (diarrhea)	
		Hematological	900	1,200 (increased monocytes, decreased mean corpuscular volume in males, increased red blood cell, hemoglobin, hematocrit and decreased white blood cells in females)	
		Hepatic		all treated doses (decreased BUN values)	
		Renal	900 (Male) 1,200 (Female)	1,200 (Male) (hyaline droplets, granular casts)	
			100	300 (alterations in kidney weights)	
		Endocrine	1,200		
		Body weight	1,200		
		Immunological/ Lymphoreticular		1,200	
		Reproductive	1,200		
		Other	300 (Male)	900 (Male) 100 (Female) (elevated cholesterol)	

Species/ (Strain)	Exposure/ Duration/ Frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
CHRONIC EXPOSURE					
Systemic Toxicity					
Rat (Sprague-Dawley)	104 weeks 4 days/week once/day (gavage in oil)	Respiratory Cardiovascular Gastrointestinal Muscle/skeleton Hepatic Renal Endocrine Dermal Body weight Immunological/ Lymphoreticular	1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 (Male)	250 (Female) (dysplastic proliferation of lympho-reticular tissues, possibly preneoplastic)	Belpoggi et al. 1995
		Reproductive	1,000		

*adapted from ATSDR (1996) and U.S. EPA (1997c)

Acute Toxicity

Studies of the systemic effects of MTBE have been conducted in animals, but the majority involves inhalation exposure (Clary 1997). Inhalation or contact with MTBE may irritate or burn skin and eyes. Vapors may cause dizziness or suffocation. Acute toxicity studies in animals demonstrate the extremely low toxicity of MTBE (ARCO 1980, Little et al. 1979, Reese and Kimbrough 1993).

The oral LD_{50}s (lethal doses with 50% kill) are approximately 3,866 mg/kg or four mL/kg in rats, and approximately 4,000 mg/kg or 5.96 mL/kg in mice. The inhalation four-hour LC_{50}s (lethal concentrations with 50% kill) in rats have been calculated to be approximately 39,395 ppm for 96.2% MTBE, 33,370 ppm for 99.1% MTBE and 23,576 ppm for MTBE. The inhalation 10-minute LC_{50} in mice is approximately 180,000 ppm and the inhalation 15-minute LC_{50} in mice is approximately 141 g/m^3. The inhalation LT_{50} (time at which death occurs in 50% of the exposed animals) in mice exposed to 209,300 ppm MTBE is 5.6 minutes (ATSDR 1996). The dermal LD_{50} is estimated to be greater than 10 mL/kg in New Zealand rabbits (HSDB 1997). The i.p. LD_{50} is 1.7 mL/kg or approximately 1,100 mg/kg in mice and greater than 148 mg/kg in rats (Arashidani et al. 1993, RTECS 1997).

Zakko et al. (1997) reported cytotoxicity of MTBE to intestinal mucosa of rats via i.p. injection similar to the effects of MTBE treatment for gallstone dissolution in humans. MTBE infused intraduodenally for three hours in male New Zealand rabbits caused local intestinal cytotoxic and systemic hepatoxic effects (Clerici et al. 1997).

At lethal doses, ocular and mucous membrane irritation, ataxia, labored breathing, CNS depression, and general anesthetic effects precede death. An inhalation study also demonstrated inflammation in the nasal mucosa of rats at a dose of 3,000 ppm for six hours per day for nine days (HSDB 1997). Mice that inhaled up to approximately 8,400 ppm MTBE for one hour had approximately a 52% decrease in breathing frequency (Tepper et al. 1994). The decrease occurred immediately, reached a maximum by 10 minutes and returned to baseline 15 minutes after exposure. High oral doses of greater than 4,080 mg of MTBE/kg caused labored respiration in rats (ARCO 1980). A four-hour direct exposure to MTBE vapor at concentrations greater than 18,829 ppm in an inhalation study resulted in ocular discharges in rats (ARCO 1980). A six-hour inhalation study produced signs of reversible CNS depression following exposure to 8,000 ppm and, to a lesser extent, to 4,000 ppm vapor with a NOAEL of 800 ppm (Dodd and Kintigh 1989, Daughtrey et al. 1997). As indicated in Tables 4 and 5, a NOAEL of 40 mg/kg/day and a LOAEL of 90 mg/kg/day are established by these acute oral exposure experiments based on the neurological effects (Bioresearch Laboratories 1990b, Johnson et al. 1992, Klan et al. 1992).

Subacute Toxicity

In a consecutive 14-day study, Sprague-Dawley rats (10/sex/dose) were administered MTBE in corn oil by gavage at zero, 357, 714, 1,071 or 1,428 mg/kg/day. MTBE appears to be irritating to the gastrointestinal tract of rats as evidenced by diarrhea and histological lesions at all levels of MTBE by the third day of dosing throughout the 14-day study. Decreased lung weight was observed in female rats at all MTBE doses and at 714 mg/kg/day in male rats. Decreased levels of monocytes in blood were observed in male rats at all MTBE doses. Increased liver enzymes in males at 1,071 mg/kg/day and decreased blood urea nitrogen (BUN) values in females at 1,428 mg/kg/day were observed. At the highest dose, anesthesia was immediate, but recovery was complete within two hours. Ataxia and hyperactivity, an increase in the weight of kidneys, adrenal glands, and livers in both genders at 1,428 mg/kg/day, and an increase in hyaline droplet formation in kidneys of male rats at 1,428 mg/kg/day were observed. Increases in relative kidney weights were noted in the males at 1,071 and at 1,428 mg/kg/day and in females at the 1,428 mg/kg/day dose. Although there was a dose-related decrease in body weight gain, it was significant only in females at the highest treatment regimen. At 1,428 mg/kg/day in males and at 714 mg/kg/day in females, elevated cholesterol was observed. There were no gross lesions seen at any treatment level. Based on the increases in relative kidney weight, a NOAEL of 714 mg/kg/day and a LOAEL of 1,071 mg/kg/day are established by these experiments (Robinson et al. 1990). These studies indicate that the male kidney is the primary target of short-term toxicity at relatively high doses. Subchronic toxicity studies of TBA indicated that, in rodents, the urinary tract is a target system and males are more sensitive to TBA toxicity than females (NTP 1995).

Subchronic Toxicity

In a 104-week gavage cancer study, increased mortality was observed in female Sprague-Dawley rats at 250 mg/kg/day beginning at 16 weeks from the start of the study (Belpoggi et al. 1995). Daily oral administration in rats for four weeks resulted in increased hyaline droplets and kidney weight in males at 440 mg/kg/day and higher doses, and stomach ulcers, increased liver weights and serum cholesterol at 1,750 mg/kg/day (Johnson et al. 1992, Klan et al. 1992).

Sprague-Dawley rats (10/sex/dose) were treated orally with MTBE in corn oil for 90 days at zero, 100, 300, 900, or 1,200 mg/kg/day. Anesthesia was evident at the highest dose, but as in the 14-day study, full recovery occurred in two hours. There was a significant decrease in final body weight of females only at the highest level of treatment. The diarrhea seen in the treated animals was considered to be the consequence of the bolus dosing regime. In female rats, there were significantly increased heart weights at 900 mg/kg/day and increases in relative kidney weights at 300, 900, and 1,200 mg/kg/day. In male rats, increases were noted only at the two highest treatment levels. BUN levels were significantly reduced in both males and females at all MTBE doses. Reductions in serum calcium and creatinine were observed in males and a reduction in cholesterol in females was reported, but there were no clear dose-dependent results. Based on the alterations in kidney weights, a NOAEL and LOAEL of 100 and 300 mg/kg/day, respectively, are identified from this study (Robinson et al. 1990).

The subchronic data from the study by Robinson et al. (1990) were proposed by U.S. EPA (1996a) to develop a draft RfD and a draft Drinking Water Equivalent Level (DWEL) for kidney effects from MTBE. The increase in kidney weights at doses of 300 mg/kg/day and higher was considered to be an adverse effect, since increases in organ weights are a marker for adverse organ effects (Weil 1970). The diarrhea observed was considered to be a gastrointestinal complication of the gavage dosing. Based on the NOAEL of 100 mg/kg/day, a DWEL for kidney effects of 3,500 ppb can be derived for a 70 kg male adult with two liters (L) of daily water consumption (DWC), using an uncertainty factor of 1,000. The uncertainty factor reflects a 10 for the less-than-lifetime duration of the study, a 10 for interspecies variability, and a 10 for intraspecies variability. Using an additional uncertainty factor of 10 for potential carcinogenicity and a 20% default relative source contribution (RSC), U.S.EPA (1996a) drafted a lifetime Health Advisory (HA) of 70 ppb or 70 μg/L. Details of the equation and calculation of the HA are described later in the chapter on the calculation of the PHG.

Genetic Toxicity

The results of genetic toxicity studies for MTBE were generally negative; however, positive results have been reported in one in vitro test system in studies that included information on mechanisms of action, and in one in vivo test system . As detailed later in this section, MTBE was not mutagenic in bacteria and tissue culture gene mutation assays, a sister chromatid exchange assay, a Drosophila sex-linked recessive lethal test, in vitro and in vivo chromosomal aberration assays, in vivo and in vitro unscheduled DNA synthesis assays, an in vivo DNA repair assay, an in vivo cytotoxicity assay, and in vitro and in vivo micronucleus assays. The only positive in vitro genotoxicity test was for forward mutations in the mouse lymphoma assay with exogenous activation (ARCO 1980, Mackerer et al. 1996) and Mackerer et al. (1996) suggested that HCHO was the metabolite responsible for mutagenic activity in the assay (Garnier et al. 1993). The only positive in vivo genotoxicity test was for DNA strand breaks in the rat lymphocyte comet assay (Lee et al. 1998). ATSDR (1996) indicated that MTBE has little or no genotoxic activity. However, the positive results in the mouse lymphoma and rat lymphocyte assays indicate that the genetic toxicity of MTBE needs to be investigated further.

MTBE was negative in the Ames in vitro assay for reverse mutation in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100 in the absence or presence of metabolic activation (ARCO 1980, Cinelli et al. 1992, Life Science Research Roma Toxicology Centre S.P.A. 1989a). Since MTBE is volatile, a closed system was used in a recent microsuspension assay (Kado et al. 1998), and negative results were observed even though some elevated revertant values were seen with TA100 and TA104. MTBE produced no evidence of a dose-related increase for sister chromatid exchange (ARCO 1980), for gene mutation in Chinese

hamster V79 cells (Life Science Research Roma Toxicology Centre S.P.A. 1989b) and for in vitro unscheduled DNA synthesis in primary rat hepatocytes (Life Science Research Roma Toxicology Centre S.P.A. 1989c, Vergnes and Chun 1994). It was negative for micronuclei formation in erythrocytes (Vergnes and Kintigh 1993).

The only in vitro test system in which MTBE has tested positive is the activated mouse lymphoma forward mutation assay (ARCO 1980, Mackerer et al. 1996). TBA, one of MTBE's major metabolites, was negative in this assay (McGregor et al. 1988). MTBE was positive for forward mutations in mouse lymphoma L5178Y tk^+/tk^- cells in the presence, but not the absence, of metabolic activation (ARCO 1980, Stoneybrook Labs. Inc. 1993). HCHO, another one of MTBE's metabolites, is genotoxic, causing both gene mutations and chromosomal damage in the presence of exogenous metabolic activation systems. HCHO is also a known carcinogen causing nasal tumors in rodents when inhaled at high concentrations, and may also cause nasopharyngeal tumors in humans via inhalation. Work by Mackerer et al. (1996) suggested that HCHO was the MTBE metabolite responsible for mutagenic activity in the activated mouse lymphoma forward mutation assay. Additional studies from this laboratory demonstrated that the HCHO was produced from in vitro metabolism of MTBE in this assay system (Garnier et al. 1993).

MTBE was assessed for its in vivo mutagenic potential (McKee et al. 1997). It was negative in the sex-linked recessive lethal assay in Drosophila melanogaster (Sernau 1989). It was negative for chromosomal aberrations in Fischer 344 rats exposed via inhalation (Vergnes and Morabit 1989), in Sprague-Dawley rats (ARCO 1980) and CD-1 mice (Ward et al. 1994) exposed orally. It was negative for hypoxanthine-guanine phosphoribosyl transferase (hprt) mutant frequency increase in spleen lymphocytes of CD-1 mice exposed orally for six weeks (Ward et al. 1994, 1995), for micronuclei formation in bone marrow in mice exposed via inhalation (Vergnes and Kintigh 1993) or via i.p. injection (Kado et al. 1998), for in vivo DNA repair increase in cultured primary hepatocytes of CD-1 mice exposed via inhalation (Vergnes and Chun 1994) and for an in vivo cytotoxicity assay in rats exposed via inhalation (Vergnes and Morabit 1989).

The only in vivo test system in which MTBE has tested positive is the rat lymphocyte comet assay, as reported in a recent meeting abstract (Lee et al. 1998). Rats were treated with MTBE by gavage, and lymphocytes assessed for alkaline-labile strand breaks. A significant increase in DNA strand breaks was reported for the highest dose group. An increase in apoptotic comets was also observed in lymphocytes from exposed rats, but this result was not statistically significant for any one dose group.

MTBE is volatile and water-soluble. Given the technical difficulties associated with testing volatile chemicals in bacterial and cultured cell systems, it is possible that careful delivery to genetic materials may have yielded data on reasons for the relative lack of genotoxic activity of MTBE in vitro (Mackerer et al. 1996, Kado et al. 1998). Additionally, the in vivo test systems used to test MTBE were primarily chromosomal damage assays, with two exceptions being the spleen lymphocyte hprt mutation assay (Ward et al. 1994) and the in vivo-in vitro mouse hepatocyte unscheduled DNA synthesis assay (Vergnes and Chun 1994). Only one in vivo assay system, the hprt mutation assay, had the potential to detect gene mutations, and it is relatively insensitive in detecting genotoxic chemicals with known false negatives. In vivo genotoxicity and metabolism data is not available for a number of the organ systems such as rat kidney, testis, and spleen and bone marrow, which developed tumors in carcinogenicity bioassays.

Developmental and Reproductive Toxicity

No human studies relevant to MTBE reproductive and developmental toxicity were located. There are a limited number of animal developmental and reproductive toxicity studies, all using the inhalation route of exposure, as listed below:

- one developmental toxicity study in rats exposed to 250 to 2,500 ppm for six hours per day on gestation days (gd) six to 15 (Conaway et al. 1985, Bio/dynamics, Inc. 1984a),
- two developmental toxicity studies in mice exposed to 250 to 2,500 ppm for six hours per day on gestation days six to 15 (Conaway et al. 1985, Bio/dynamics, Inc. 1984b), or to 1,000 to 8,000 ppm for six hours per day on gestation days six to 15 (Bevan et al. 1997b, Tyl and Neeper-Bradley 1989),
- one developmental toxicity study in rabbits exposed to 1,000 to 8,000 ppm for six hours per day on gestation days six to 18 (Bevan et al. 1997b, Tyl 1989),
- one single generation reproductive toxicity study in rats exposed to 300 to 3,400 ppm (Biles et al. 1987),
- one two-generation reproductive toxicity study in rats exposed to 400 to 8,000 ppm (Bevan et al. 1997a, Neeper-Bradley 1991).

Study designs and results are outlined in Table 6. Some information on reproductive organs can also be obtained from subchronic and chronic toxicity studies (also outlined in Table 6), and there are a few recent studies of possible endocrine effects.

While no effects on fertility endpoints were reported, these studies provide evidence for adverse effects of MTBE on development. Reduced fetal weight and increased frequency of fetal skeletal variations were reported in mice after MTBE exposure during organogenesis, with a NOAEL of 1,000 ppm (Bevan et al. 1997b, Tyl and Neeper-Bradley 1989). Also, in the rat two-generation study, increased postnatal death and decreased postnatal weights were found; the NOAEL was 400 ppm MTBE (Bevan et al. 1997a). A provisional RfC of 173 ppm (48 mg/m^3) has been derived using U.S. EPA risk assessment methodology (Sonawane 1994) on the basis of developmental toxicity that occurred in the two-generation rat study (Bevan et al. 1997a, Neeper-Bradley 1991). Additionally, a projected no-effect-concentration in drinking water for humans of 2.3 to 9.2 mg/L has been derived by U.S. EPA (1997a) based on a range of NOAELs (250 to 1,000 ppm) in the two developmental toxicity studies in mice. The NSTC (1997) report stated that "MTBE is not expected to pose a reproductive or developmental hazard under the intermittent, low-level exposure experienced by humans".

The developmental and reproductive toxicity studies were of good quality, and generally conformed to U.S. EPA testing guidelines. The highest inhalation concentration used (8,000 ppm) produced hypoactivity, ataxia, and reduced auditory responsiveness in adult males and females during exposure, reflecting the anesthetic properties of MTBE. Prostration, labored respiration, lacrimation, and periocular encrustation were among the clinical signs reported. There was no increase in adult male and female mortality or organ pathology at any inhalation concentration, but lower food intake and weight gain was sometimes seen at the 8,000 ppm concentration. The developmental toxicity study (Conaway et al. 1985) and single generation study (Biles et al. 1987) in rats, and one of the developmental toxicity studies in mice (Conaway et al. 1985) did not include a dose that was minimally toxic to adult males and females. Little developmental or reproductive toxicity was reported in these studies, but it is difficult to interpret this lack of findings because the concentrations were not high enough to induce adult maternal and paternal toxicity.

Developmental Toxicity

Animal Developmental Toxicity Studies

Dose-dependent effects on fetal weight and fetal skeletal variations were reported in mice; no fetal effects were reported in the rats and rabbits. Notably, the rat developmental toxicity study

(Conaway et al. 1985, Bio/dynamics, Inc. 1984a) was conducted in a lower concentration range. In rabbits, maternal toxicity was reported at the highest concentration (8,000 ppm) as reduced maternal food intake, maternal weight loss, hypoactivity, and ataxia during treatment and increased relative liver weights at term. However, no fetal effects of treatment were reported in rabbits (Tyl 1989).

In mice (Bevan et al. 1997b, Tyl and Neeper-Bradley 1989), an 8,000 ppm concentration produced statistically significant lower pregnancy weight gain (approximately 30% lower compared to controls) as well as reduced corrected pregnancy weight gain. Food consumption of dams was lower during the exposure period only. Clinical signs of toxicity, statistically greater in incidence in the 8,000 ppm group on gestation day six to 15, were hypoactivity, ataxia, prostration, labored respiration, lacrimation and periocular encrustation. Group observations during daily exposures included hypoactivity, ataxia and forced respiration. Fetal toxicity endpoints at the 8,000 ppm concentration included: increased postimplantation loss, fewer live fetuses per litter, higher percent of litters with external and visceral malformations, increased incidence of cleft palate and partial atelectasis (absence of fetal lung inflation), reduced fetal body weight (21%), and increase in the frequency of a number of skeletal variations reflecting delayed ossification.

At the 4,000 ppm exposure, two of these fetal effects (reduced fetal body weight and delayed ossification) were also statistically significant and no maternal toxicity in the form of body weights or clinical signs of toxicity occurred. Group observations at the 4,000 ppm concentrations included hypoactivity and ataxia. The fetal body weight effects and delayed ossification were generally concentration-related at 4,000 and 8,000 ppm, with no indication of treatment related effects at 1,000 ppm, the NOAEL. The mouse developmental toxicity study (Conaway et al. 1985) reported a nonsignificant but apparently concentration-related pattern of increased fetal skeletal malformations in mice exposed to zero, 250, 1,000, or 2,500 ppm (seven, 11, 16, and 22% affected litters), including fused ribs and sternebrae. Conaway et al. (1985) also evaluated skeletal ossification variations (Bio/dynamics, Inc. 1984b), but data were not provided or discussed.

Animal Reproductive Toxicity Studies

As noted above, the two rat reproductive toxicity studies used longer exposures than the developmental toxicity studies, beginning prior to mating and continuing through pregnancy and lactation in the dams. Developmental toxicity in the two generation rat study included reduced pup viability and body weights in the postnatal period for both generations (Bevan et al. 1997a, Neeper-Bradley 1991). Viability, as indexed by the number of dead pups on postnatal day four, was lower than controls in the 8,000 ppm group of both the F_1 and F_2 generations; survival indices were not affected. Group difference in pup body weights was not significant on lactation day one; group differences in body weight appeared later in lactation. Pup weights were consistently lower than controls in the 8,000 ppm group after postnatal day 14 in the F_1 generation and after postnatal day seven in the F_2 generation, and in the 3,000 ppm group after postnatal day 14 in the F_2 generation.

The finding of reduced pup weight gain during lactation in the absence of reduced maternal weight gain is a distinctive finding of the study. Pups were not directly exposed to MTBE during the lactation period but may have been indirectly exposed via dam's milk or MTBE condensation on the dam's fur. The postnatal effects could also have been the result of MTBE effects on maternal behavior or lactation. The findings on postnatal effects are partially supported by the earlier rat single generation study (Biles et al. 1987), which described reduced pup survival and reduced postnatal weights at exposure concentrations of 250 to 2,500 ppm. The statistical

significance and dose-related characteristics of these effects varied in the single generation study (see Table 6).

Reproductive Toxicity

Fertility and general toxicity

The two rat reproductive toxicity studies used exposures beginning prior to mating and continuing through pregnancy and lactation in the dams. No indication of reduced fertility was reported in either study. No evaluations of ovarian cyclicity or sperm parameters were included in either study.

As mentioned above, a concentration toxic to the adult breeders was not reached in the single generation study (Biles et al. 1987), but was included in the two generation study (Bevan et al. 1997a, Neeper-Bradley 1991). Increased absolute liver weights (8,000 ppm males and females) and increased relative liver weights (3,000 and 8,000 ppm males and 8,000 ppm females) were reported in the F_1 generation. Liver weights of the F_1 generation were the only organ weights reported.

An unexplained effect was greater lactational body weight gain in the 3,000 ppm dams (F_1) and 8,000 ppm dams (F_0 and F_1) relative to controls. This was due to less maternal weight loss at the end of the lactation period, postnatal days 14 to 28. Lactational weight gain through postnatal day 14 did not differ from controls. Maternal body weight had not been reduced during gestation or at term. However, pups in the 3,000 and 8,000 ppm groups were smaller than controls at some postnatal ages (see section on developmental toxicity above) and this may have resulted in lower energy requirements for lactation.

Reproductive organs

Information on reproductive organs of rats from single and multi-generation studies is varied and incomplete. No effects on reproductive organ weights (testes, epididymides, seminal vesicles, prostate, ovaries) or pathology (testes, epididymides, ovaries) were reported in the rat single generation study (Biles et al. 1987). Reproductive organ weights were not obtained in the rat multi-generation study; no exposure related histopathology of reproductive organs (vagina, uterus, ovaries, epididymides, seminal vesicles, testes, prostate) was reported when 25 rats per sex per generation in the control and 8,000 ppm group were examined (Bevan et al. 1997a, Neeper-Bradley 1991).

Reproductive organ weights and pathology were sometimes reported in subchronic and chronic toxicity and oncogenicity studies in rats. No effects on weight or histopathology of gonads (ovaries and testes) were noted in 14 and 90-day gavage studies in rats (n = 10/sex/group) (Robinson et al. 1990). No effects on histopathology (testes, ovaries, prostate, uterus) were reported in a lifetime (eight weeks to natural death) gavage study in rats (n = 60/sex/group) (Belpoggi et al. 1995). Organ weights were not reported in this oncogenicity study.

Endocrine effects

Moser et al. (1996b, 1998) conducted studies in mice of potential antiestrogenic effects of MTBE. Endocrine modulating effects of MTBE were suggested by the rodent tumor profile of endocrine sensitive organs in oncogenicity studies. An additional suggestive finding was reduced incidence of uterine endometrial hyperplasia in the mouse inhalation cancer bioassays (Burleigh-Flayer et al. 1991), which implies reduced estrogen action on the endometrium

throughout the lifetime. Moser et al. (1996b, 1998) demonstrated a number of adverse effects of MTBE on the reproductive system of mice:

- lower relative uterine and ovarian weights compared to controls
- increase in overall length of estrous cycle, as well as estrus and nonestrus stages
- lower rate of cell proliferation in the uterine, cervical and vaginal epithelium
- changes in histology of the uterus, cervix and vagina indicative of decreased estrogen action

Body weight gain was also lower in MTBE exposed mice than in controls.

In investigating the potential mechanism of MTBE-induced reduction in estrogen action, Moser et al. (1996b) found that estrogen metabolism was increased twofold in hepatocytes isolated from mice exposed to 1,800 mg MTBE/kg/day by gavage for three days. This change was associated with greater liver weight and P_{450} content. This series of experiments suggested that MTBE might lower circulating estrogen concentrations by increasing estrogen metabolism. However, later studies failed to confirm effects on serum estrogen when female mice were exposed to 8,000 ppm MTBE for four or eight months (Moser et al., 1998). A further series of experiments (Moser et al. 1998) failed to find evidence that MTBE endocrine effects were mediated by the estrogen receptor by studying binding of MTBE and its metabolites to the estrogen receptor, changes in expression of estrogen receptor in MTBE exposed mice, and alterations of estrogen receptor activation and translocation in a transfection assay. The authors suggest that MTBE may exert an antiestrogenic action by a mechanism that does not involve a change in circulating estrogen or estrogen receptor binding.

The consequences of reduced estrogen action induced by MTBE in mice are not known; no fertility studies have been conducted in mice. It is also not clear whether similar effects occur in other species, at other doses, or with other exposure durations, since parallel studies have not been done. The specificity of the effect also needs to be determined. Unleaded gasoline has been found to have some antiestrogenic effects similar to MTBE (MacGregor et al. 1993, Moser et al. 1996b, Standeven et al. 1994). Also, an in vivo study reported recently in abstract form (Okahara et al. 1998) described mild estrogenic and antiestrogenic effects in pubertal mice (21 to 25 days old) gavaged with 600 or 1,500 mg MTBE/kg body weight for five days.

Other Relevant Data

As discussed in the section on metabolism and pharmacokinetics, MTBE is distributed to all major tissues studied in the rat. MTBE is metabolized in the liver to TBA. TBA appears to be widely distributed (Aarstad et al. 1985, Borghoff et al. 1996a, Savolainen et al. 1985). No studies specifically examining distribution of MTBE or TBA to male or female reproductive organs, or the placenta, embryo, or fetus were located in the general published literature. In view of the general widespread distribution, it is plausible that MTBE and TBA distribute to these tissues.

Several studies have examined the developmental toxicity of TBA in mice (oral) and rats (inhalation and oral). No reproductive studies of TBA were located. NTP conducted subchronic and carcinogenesis studies in mice and rats by drinking water that examined some reproductive endpoints. There is also an in vitro study of TBA and mouse sperm.

The specific studies located were:

- one developmental toxicity study in mice, oral (liquid food), zero, 0.5, 0.75, or one % weight to volume, gestation days six to 20 (Daniel and Evans 1982),
- one developmental toxicity study in mice, oral (gavage), zero or 780 mg/kg, twice per day, gestation days six to 18 (Faulkner et al. 1989),

- one developmental toxicity study in rats, inhalation, zero, 2,000, 3,500, or 5,000 ppm, seven hours per day, gestation days one to 19 (Nelson et al. 1989a),
- one developmental toxicity study in rats, inhalation, zero, 6,000, 12,000 mg/m^3 (zero, 1,660, or 3,330 ppm), seven hours per day, gestation days one to 19 (abstract only) (Nelson et al. 1989b),
- one developmental toxicity study in rats, oral (liquid food), zero, 0.65, 1.3, or 10.9% volume to volume, gestation days eight to 22 (abstract only) (Abel and Bilitzke 1992),
- one developmental toxicity study in rats, gastric cannula, zero, or 0.6 to 2.7 g/kg/day, postnatal day four to seven (Grant and Samson 1982),
- subchronic (13 weeks) and carcinogenesis (two years) studies in rats and mice (both sexes), oral (water), various concentrations (NTP 1995),
- one in vitro study of mouse sperm fertilization capacity (Anderson et al. 1982).

With the exception of Nelson et al. (1989a), reporting of the data in the developmental studies was incomplete. Developmentally toxic effects were observed in mice and rats orally administered TBA, including prenatal and postnatal death (Abel and Bilitzke 1992, Faulkner et al. 1989, Daniel and Evans 1982) and postnatal developmental retardation (Daniel and Evans 1982). Malformations were not observed (Faulkner et al. 1989). The inhalation study in rats by Nelson et al. (1989a) found developmental retardation, as manifested in lower fetal weights, at concentrations of 2,000, 3,500 and 5,000 ppm TBA, and a higher percent of skeletal variations compared to controls at 3,500 and 5,000 ppm. No increases in resorptions or malformations were observed. Lower maternal weight was reported at 5,000 ppm. Maternal neurobehavioral effects associated with the exposures (narcosis at 5,000 ppm, unsteady gait at 3,500 and 5,000 ppm, unsteady at 2,000 ppm) were also observed in the Nelson et al. (1989a) study.

The NTP subchronic and carcinogenesis studies in mice and rats by drinking water used various concentrations of TBA. In these studies, systemic toxicity was observed at the high concentration, usually including death, reduced weight gain, and altered kidney weight. The studies found little indication of potential reproductive toxicity. Specifically, no effects on testis weight or sperm were observed. Minor and inconsistent effects on testis histopathology and estrous cyclicity were observed at the high concentrations. The in vitro study found no effect of TBA on mouse sperm fertilization capacity.

Table 6. MTBE: Developmental and Reproductive Toxic Effects (studies in alphabetical order by author)

Study design[1]	Reported effects[2]	Reference
Rat (Sprague-Dawley) oral (gavage) Male and female 104 weeks, 4 days/week 0, 250, 1,000 mg/kg/day	Male: No increased death, reduced body weight gain, or reduced food consumption. No testicular histopathological effects. Female: No reduced body weight gain, or reduced food consumption. 250, 1,000 mg/kg/day: Increased death (dose-responsive, SS not addressed). No ovarian histopathological effects.	Belpoggi et al. 1995
Mouse (CD-1) inhalation gd 6-15, 6 hours/day Target concentrations: 0, 1,000, 4,000, 8,000 ppm Analytical concentrations: 0, 1,035, 4,076, 8,153 ppm	No maternal death, or altered liver weight. 8,000 ppm: Reduced maternal body weight (SS), reduced body weight gain (SS), reduced food consumption during treatment period (SS). Clinical signs (individual observations): maternal, hypoactivity (SS), ataxia (SS), prostration (SS), labored respiration (SS), lacrimation (SS), periocular encrustation (SS). Clinical signs (group observations during daily exposure periods): maternal hypoactivity, ataxia, labored breathing. 4,000 ppm: Clinical signs (group observations during daily exposure periods): maternal hypoactivity, ataxia. No increased pre-implant loss, early resorptions, or skeletal malformations. 8,000 ppm: Increased post-implant loss (late resorptions and dead fetuses) (SS), reduced live litter size (SS), altered sex ratio (less males) (SS), increased cleft palate (SS) (resulting in increased pooled external malformations, soft tissue malformations, and total malformations (SS)), reduced fetal weight (SS), increased incidence of some skeletal variations (mainly reduced ossification) (SS). 4,000 ppm: Reduced fetal weight (SS), increased incidence of some skeletal variations (mainly reduced ossification) (SS).	Bevan et al. 1997b, Tyl and Neeper-Bradley 1989

Study design[1]	Reported effects[2]	Reference
Rabbit (New Zealand White) Inhalation gd 6-18, 6 hours/day Target concentrations: 0, 1,000, 4,000, 8,000 ppm Analytical concentrations: 0, 1,021, 4,058, 8,021 ppm	No maternal death, reduced body weight, or clinical signs of toxicity before or after daily exposure periods. 8,000 ppm: Reduced maternal body weight gain (gd 6-12) (SS) (resulting in reduced body weight gain gd 6-18 (SS)), reduced food consumption (gd 6-11, 13-14) (SS) (resulting in reduced food consumption gd 6-18 (SS)), increased relative liver weight (SS). Clinical signs (group observations during daily exposure periods): hypoactivity, ataxia. 4,000 ppm: Reduced maternal body weight gain (gd 6-9) (SS), reduced food consumption (gd 6-8, 9-10) (SS). No increased pre- or post-implant loss, reduced litter size, altered sex ratio, reduced fetal weight, increased malformations, or increased skeletal variations.	Bevan et al. 1997b, Tyl 1989

Study design[1]	Reported effects[2]	Reference
Rat (Sprague-Dawley) Inhalation 2 generation reproductive Target concentrations: 0, 400, 3,000, 8,000 ppm Analytical concentrations: 0, 402, 3,019, 8,007 ppm Male: 6 hours/day, 10 weeks (5 days/ week) + mating + gestation Female: 6 hours/day, 10 weeks (5 days/ week) + mating + gestation (gd 1-19) + lactation (pnd 5-28) Exposures for F_0 starting at pnd 42, and F_1 starting on pnd 29-31. Pups not placed in inhalation chambers during lactation.	No adult male or female deaths (F_0 or F_1), reduced adult female body weight (F_0), reduced adult female body weight gain (F_1), or reduced adult female food consumption (F_0). 8,000 ppm: Reduced adult male body weight (F_0, F_1) (SS), reduced adult male body weight gain (F_0: weeks 0-3, 5-7; F_1: weeks 0-2, 5-6), reduced adult female body weight (F_1: weeks 0-8, not gestation or lactation) (SS), reduced adult female body weight gain (F_0: weeks 0-1, 5-6, not gestation or lactation) (SS), increased female body weight gain during lactation (F_0, F_1) (SS), increased adult male and female absolute and relative liver weights (F_1) (SS), reduced adult female food consumption (F_1: lactation days 7-14, not pre-breed or gestation) (SS). Clinical signs (individual observations): adult male, perioral wetness (F_0, F_1), perioral encrusation and salivation (F_1); adult female, perioral wetness (F_0, F_1), perioral encrusation, salivation and urine stains (F_1). Clinical signs (group observations during daily exposure periods): adult male and female, ataxia (F_0, F_1), hypoactivity (F_0, F_1), blepharospasm (F_0, F_1), lack of startle reflex (F_0, F_1). 3,000 ppm: Increased adult male relative liver weights (F_1) (SS), increased adult female body weight gain (F_1: lactation) (SS). Clinical signs (group observations during daily exposure periods): adult male and female, hypoactivity (F_0, F_1), blepharospasm (F_0, F_1), lack of startle reflex (F_0, F_1). No ovarian, uterine, or vaginal histopathological effects, testicular or other male reproductive organ histopathological effects, reduced mating (F_0, F_1), reduced fertility (F_0, F_1), reduced live litter size (F_1, F_2), reduced postnatal survival after pnd 4 (F_1, F_2), reduced live birth, four-day survival, or lactation indices (F_1, F_2), or reduced lactation day one weight (F_1, F_2). 8,000 ppm: Increased dead pups pnd 4 (F_1, F_2) (SS), reduced litter size at end of lactation (F_2) (SS), reduced postnatal weight (F_1: pnd 14-28, F_2: pnd 7-28) (SS), reduced postnatal weight gain (F_1: pnd 7-21, F_2: pnd 1-21) (SS). 3,000 ppm: Increased dead pups pnd 4-28 (F_1) (SS) (NOT at 8,000 ppm), reduced postnatal weight (F_1: pnd 4, 14, F_2: pnd 14-28) (SS), reduced postnatal weight gain (F_1: pnd 1-4, 7-14, F_2: pnd 7-21) (SS).	Bevan et al. 1997a, Neeper-Bradley 1991

Study design[1]	Reported effects[2]	Reference
Rat (Sprague-Dawley) Inhalation Reproductive: 1 generation, 2 litter Male: 6 hours/day, 12 weeks (5 days/week), + first mating (2 weeks, daily), + 8 weeks (5 days/week), + second mating (2 weeks, daily) Female: 6 hours/day, 3 weeks (5 days/week), + first mating (daily) + first gestation (gd 0-20) + first lactation (pnd 5-21) + 2 weeks (5 days/week) + second mating (daily) + second gestation (gd 0-20) + second lactation (pnd 5-21) Target concentrations in text: 0, 250, 1,000, 2,500 ppm Target concentrations in abstract: 0, 300, 1,300, 3,400 ppm Nominal concentrations, Male/Female: 0/0, 290/300, 1,300/1,300, 3,400/3,400 ppm Analytical concentrations, Male/Female: 0/0, 290/300, 1,180/1,240, 2,860/2,980 ppm	No adult male or female death, or reduced male or female body weight (F_0). 2,500, 250 ppm: Increased incidence dilated renal pelves in females (NOT 1,000 ppm). No altered testes or ovary weight (F_0), adverse histopathological effects on ovaries or testes (F_0), reduced mating, reduced male fertility, reduced female fertility (pregnancy rate), reduced litter size (live or total) (F_{1a}, F_{1b}), altered sex ratio (F_{1a}, F_{1b}), reduced pup viability at birth (live/total) (F_{1a}), reduced birth weight (F_{1a}, F_{1b}), reduced pup survival on pnd 4 (F_{1b}), or reduced pup survival on pnd 21 (F_{1a}, F_{1b}). 2,500 ppm: Reduced pup viability at birth (live/total) (F_{1b}) (SS) (Note high in controls: control 99%, 1,000 and 2,500 ppm 95.5%. Authors discount biological significance), reduced postnatal weight on pnd 14, 21 (F_{1a}, F_{1b}) (NOT SS). 1,000 ppm: Reduced pup viability at birth (live/total) (F_{1b}) (SS) (Note high in controls: control 99%, 1,000 and 2,500 ppm 95.5%. Authors discount biological significance), reduced pup survival from pnd 0-4 (F_{1a}) (NOT 2,500 ppm), reduced postnatal weight on pnd 14, 21 (F_{1a}, F_{1b}) (NOT SS). 250 ppm: Reduced pup survival from pnd 0-4 (F_{1a}) (NOT 2,500 ppm) (SS).	Biles et al. 1987, Bio/ dynamics 1984c

Study design[1]	Reported effects[2]	Reference
Mouse (CD-1) Inhalation Male and female 6 hours/day, 5 days/week, 18 months 0, 400, 3,000, 8,000 ppm	Male: 8,000 ppm: Increased death (SS), reduced body weight (SS), increased liver weight (SS), blepharospasm, hypoactivity, ataxia, lack of startle reflex, prostration. 3,000 ppm: Increased liver weight (SS), blepharospasm, hypoactivity, ataxia, lack of startle reflex, stereotypy. 400 ppm: Increased liver weight (SS). No alteration in testes weight, testicular (or other reproductive organ) histopathological effects. Female: No increased death. 8,000 ppm: Reduced body weight (SS), increased liver weight (SS), blepharospasm, hypoactivity, ataxia, lack of startle reflex, prostration. 3,000 ppm: Increased liver weight (SS), blepharospasm, hypoactivity, ataxia, lack of startle reflex, stereotypy. No ovarian (or other reproductive organ) histopathological effects.	Burleigh-Flayer et al. 1992

Study design[1]	Reported effects[2]	Reference
Rat (Fischer 344) Inhalation Male and female 6 hours/day, 5 days/week Male: 0, 400 ppm, 104 weeks Male: 3,000 ppm, 97 weeks Male: 8,000 ppm, 82 weeks Female: 0, 400, 3,000, 8,000 ppm, 104 weeks	Male: No altered liver weight to 400 ppm (see note). 8,000 ppm: Increased death (SS), reduced body weight (SS), (increased) nephropathy, ataxia, hypoactivity, blepharospasm, lack of startle reflex. 3,000 ppm: Increased death (SS), nephropathy, ataxia, hypoactivity, blepharospasm, lack of startle reflex. 400 ppm: Increased death (SS), nephropathy. No altered testes weight to 400 ppm (see note). 8,000, 3,000, 400 ppm: Increased testicular mineralization (see note). Note: Remaining males in 8,000 and 3,000 ppm groups were sacrificed early due to high group mortality. Authors attribute mortality and mineralization of "numerous tissues" to nephropathy. No statistical evaluation of testes or other organ weight, or, apparently, histopathological changes, was performed by the authors for the 8,000 or 3,000 ppm groups. Female: No increased death. 8,000 ppm: Reduced body weight (SS), increased liver weight (SS), ataxia, hypoactivity, blepharospasm, lack of startle reflex, nephropathy. 3,000 ppm: Increased liver weight (SS), ataxia, hypoactivity, blepharospasm, lack of startle reflex, nephropathy. No ovarian (or other reproductive organ) histopathological effects.	Chun et al. 1992

Study design[1]	Reported effects[2]	Reference
Rat (Sprague-Dawley) Inhalation gd 6-15, 6 hours/day Target concentrations: 0, 250, 1,000, 2,500 ppm Analytical concentrations: 0, 250, 1,000, 2,430 ppm Nominal concentrations: 0, 260, 1,100, 3,300 ppm	No maternal death, reduced maternal body weight, altered water consumption, or altered liver weight. 2,500, 1,000, 250 ppm: Reduced maternal food consumption on gd 9-12 (SS). No increased pre- or post-implant loss, reduced live litter size, reduced fetal weight, reduced crown-rump distance, altered sex ratio, increased malformations, or increased ossification variations.	Conaway et al. 1985, Bio/ dynamics, Inc. 1984a
Mouse (CD-1) Inhalation gd 6-15, 6 hours/day Target concentrations: 0, 250, 1,000, 2,500 ppm Analytical concentrations: 0, 280, 1,110, 2,710 ppm Nominal concentrations: 0, 280, 1,200, 3,500 ppm	No maternal death, reduced maternal body weight, altered food or water consumption, altered liver weight. No increased pre- or post-implant losses, reduced live litter size, reduced fetal weight, reduced crown-rump distance, altered sex ratio, increased malformations. [Fetuses with skeletal malformations: control, 1.6%; 250 ppm, 1.7%; 1,000 ppm, 2.4%; 2,500 ppm, 3.1% (NOT SS). Litters with skeletal malformations: control, 7.4%; 250 ppm, 11.5%; 1,000 ppm, 16%; 2,500 ppm, 22.2% (NOT SS).]	Conaway et al. 1985, Bio/ dynamics, Inc. 1984b

Study design[1]	Reported effects[2]	Reference
Rat (Sprague-Dawley) oral (gavage) Male and female 14 days 0, 357, 714, 1,071, 1,428 mg/kg/day	Male: No increased death. 1,428 mg/kg/day: Reduced body weight gain (SS), anesthesia, loose stools. 1,071, 714 mg/kg/day: Reduced body weight gain (SS), loose stools. 357 mg/kg/day: Loose stools. No altered absolute testes weight, or testicular histopathological effects. 1,071, 714 mg/kg/day: Increased relative testes weight (NOT at 1,428 mg/kg/day) (SS). Female: No increased death. 1,428 mg/kg/day: Reduced body weight gain (SS), anesthesia, loose stools. 1,071 mg/kg/day: Reduced body weight gain (SS), loose stools. 714, 357 mg/kg/day: Loose stools. No altered ovary weight, or ovarian histopathological effects.	Robinson et al. 1990

Study design[1]	Reported effects[2]	Reference
Rat (Sprague-Dawley) oral (gavage) Male and female 90 days 0, 100, 300, 900, 1,200 mg/kg/day	Male: No increased death. 1,200 mg/kg/day: Reduced body weight (NOT SS), increased relative liver weight (SS), increased absolute and relative kidney weight (SS), anesthesia, diarrhea. 900 mg/kg/day: Increased relative liver weight (SS), increased absolute and relative kidney weight (SS), diarrhea. 300, 100 mg/kg/day: Diarrhea. No altered testes weight, or testicular histopathological effects. Female: No increased death. 1,200 mg/kg/day: Reduced body weight (SS), anesthesia, diarrhea. 900, 300 mg/kg/day: Reduced body weight (NOT SS), diarrhea. 100 mg/kg/day: Diarrhea. No altered ovary weight, or ovarian histopathological effects.	Robinson et al. 1990

(1) Abbreviations: gd = gestation day, pnd = postnatal day.
(2) Effects reported by authors to be statistically significant (SS) or biologically noteworthy.

Immunotoxicity

Oral administration of 1,428 mg MTBE/kg/day for 14 days reduced absolute spleen weights and absolute and relative thymus weights in female rats but not in males and did not produce histopathological lesions in the spleen or thymus. Similar results were observed following 90 days treatment with an oral dose of 100 to 1,200 mg MTBE/kg/day (Robinson et al. 1990). An increased incidence of dysplastic proliferation of lymphoreticular tissues was observed in female rats gavaged with 250 or 1,000 mg MTBE /kg/day, four days per week for 104 weeks (Belpoggi et al. 1995). The authors discussed the possibility that these lesions had the potential to develop into the lymphomas and leukemias also observed in this study.

Administration of MTBE to Sprague-Dawley male rats by daily gavage for 28 days with 40, 400, or 800 mg MTBE/kg/day produced an overall increased percentage of apoptotic-type comets in peripheral blood lymphocytes but no dose produced a statistical increase over vehicle controls. DNA strand breakage was significantly increased in the 800 mg/kg/day group and depressed body weight gain and high corticosterone levels were observed at 28 days (Lee et al. 1998).

Neurotoxicity

Acute oral exposure in rats caused marked CNS depression at doses greater than 1,900 mg/kg, ataxia at doses greater than 2,450 mg/kg, loss of righting reflex at doses greater than 3,160 mg/kg, and tremors and labored breathing at doses greater than 4,080 mg/kg. A no observed effect level (NOEL) of 40 mg/kg for adverse but reversible neurological effects for acute oral exposure was identified (Bioresearch Laboratories 1990b) and an acute oral MRL of 0.4 mg/kg/day was calculated by ATSDR (1996).

Scholl et al. (1996) measured the duration of ataxia and hypnosis in male Fischer 344 rats pretreated with P_{450} inducers following a single sub-hypnotic (0.5 mg/kg) and hypnotic (1.2 mg/kg) i.p. dose of MTBE. Pretreatment with phenobarbital, and to a lesser extent clofibrate but not beta-naphthoflavone, prolonged the duration of ataxia or narcosis from MTBE compared with the vehicle control. The data suggested that the biotransformation status is a major potential determinant of sensitivity to the CNS depression effects of MTBE.

Two inhalation studies indicated that MTBE might be a weak neurotoxicant in adult rats with primary effects of acute impairment. A six-hour inhalation study and a 13-week repeated vapor inhalation study produced signs of reversible CNS depression following exposure to 8,000 ppm and, to a lesser extent, to 4,000 ppm vapor with a NOAEL of 800 ppm (Dodd and Kintigh 1989, Daughtrey et al. 1997). MTBE induced some mild and reversible CNS toxicity but did not appear to be a neurotoxicant under the conditions of these studies (Fueta et al. 1994).

Chronic Toxicity

Sprague-Dawley rats (60 animals per sex, per dose group) were given zero, 250 or 1,000 mg MTBE/kg/day in olive oil via gavage, four days per week, for 104 weeks. This dosing regimen gives a seven-day time-weighted average daily dose of zero, 143, and 571 mg/kg/day. Survival appeared to be decreased in female rats after 16 weeks, but no statistical treatments on data were reported. There was no reporting of hematological, clinical chemistry or urinalysis parameters, or any indication as to whether or not these endpoints were evaluated. The authors did not observe any differences in food consumption or final body weights in the various groups. In addition, they did not report any noncancer histopathological changes (Belpoggi et al. 1995, 1997, 1998). Due to the limited scope, intermittent treatment schedule and scant data reporting on noncancer endpoints in this study, it is not possible to identify an adequate NOAEL or LOAEL.

Kidney toxicity was observed in both males and females in the two-year inhalation study in Fischer 344 rats by Chun et al. (1992) discussed in the next section on carcinogenicity. U.S. EPA derived a RfC of three mg/m^3 based on the kidney and liver effects of MTBE (U.S. EPA 1993, 1997c). These data support the conclusion that, after MTBE exposure, kidney toxicity is of toxicological concern. However, the use of the Robinson et al. (1990) study for evaluation of kidney effects, as detailed in the previous section on subchronic toxicity, has two significant uncertainties. One is that the study was for 90 days and not for a lifetime, and the second is the extrapolation of dose from a single daily bolus dose in corn oil to the continuous small doses from drinking water exposure. In general, it would be anticipated that a 90-day exposure period would tend to underestimate the toxicity, while the bolus dose (a NOAEL of 100 mg/kg/day) would be more likely to overestimate the toxic response. However, the relative effects of these two factors are uncertain.

Animal studies conducted at very high levels of exposure to MTBE, i.e., at greater than 1,000 ppm, through inhalation caused increased liver, kidney, spleen, and adrenal weights; decreased brain weight, body weight, and body weight gain; swollen periocular tissue; and ataxia in rodents. Increased prostration (lying flat) or exhaustion was reported in female rodents only.

Carcinogenicity

No data on long-term effects of human exposure to MTBE relevant to cancer risk were found in recent literature searches performed by OEHHA.

The carcinogenic activity of MTBE has been investigated in male and female Sprague-Dawley rats administered MTBE by gavage (Belpoggi et al. 1995, 1997, 1998) and in male and female Fischer 344 rats (Chun et al. 1992, Bird et al. 1997) and CD-1 mice (Burleigh-Flayer et al. 1992, Bird et al. 1997) exposed to MTBE by inhalation. In rats receiving MTBE by gavage for 24 months, statistically significant increases in Leydig interstitial cell tumors of the testes were observed in males, and statistically significant increases in lymphomas and leukemias (combined) were observed in females. An increase in the incidence of uterine sarcomas was also observed in MTBE-exposed female rats, but was not statistically significant at the $p < 0.05$ level. In rats exposed to MTBE by inhalation for up to 24 months, statistically significant increases in the incidences of renal tubular tumors and Leydig interstitial cell tumors of the testes were observed in males. In mice exposed to MTBE by inhalation for up to 18 months, statistically significant increases in the incidences of liver tumors were observed in females (hepatocellular adenomas; hepatocellular adenomas and carcinomas combined) and males (hepatocellular carcinomas). These studies are described in more detail below.

Oral Exposure Studies

Rat gavage exposure studies: Belpoggi et al. (1995, 1997, 1998)

Groups of 60 male and 60 female eight-week old Sprague-Dawley rats were administered MTBE in olive oil by gavage at doses of zero (oil only), 250 or 1,000 mg/kg body weight/day, four days per week for 104 weeks. Animals were maintained until natural death; the last animal died at 174 weeks of age. No difference in water or food consumption, or in mean body weights was observed between treated and control animals of either sex. A dose-related decrease in survival was observed in females. At 56 weeks of age, survival was approximately 98%, 85%, and 78% in controls, low- and high-dose females, respectively; at 88 weeks of age, survival in those same groups was approximately 76%, 60%, and 43%. In males, there was no difference in survival between the controls and the low-dose animals. However, after 88 weeks, survival in high-dose males exceeded that of low-dose and control males. At 104 weeks of age, survival was approximately 30% in low-dose and control males and 43% in high-dose males; at 120 weeks of age, survival in those same groups was approximately 11% and 32%.

A dose-related increase in the combined incidence of lymphomas and leukemia was observed in female rats (Table 7). The authors reported that the increase was highly significant ($p < 0.01$) in the high-dose group and marginally significant in the low-dose group, when analyzed using a log-ranked test as described by Mantel (1966) and Cox (1972). When analyzed using the Fisher Exact test, the combined incidence of lymphomas and leukemia in high-dose females was significantly different from controls at the $p = 0.001$ level. Historical control incidence rates in this laboratory for lymphomas and leukemias (combined) was < 10% in female Sprague-Dawley

rats (Belpoggi et al. 1995). The authors also noted an increase in uterine sarcomas in the low-dose females (5/60 versus 1/60 in controls), however, this increase did not reach statistical significance ($p = 0.1$ by Fisher's Exact test). In males, a statistically significant increased incidence of Leydig cell tumors of the testes was observed in the high-dose group (Table 7). The authors reported that this increase was significant at the $p = 0.05$ level using a prevalence analysis for nonlethal tumors (Hoel and Walburg 1972).

Subsequent to the initial report of this study, a pathology review was undertaken (Belpoggi et al. 1998) in which slides from the original study were re-examined, and diagnostic criteria reviewed. This was undertaken by an independent panel of the Cancer Research Centre (where the study authors are based), assisted by an outside pathologist. Tumor incidences according to the review are also presented in Table 7. Both observed types of tumor were re-examined:

1. Testicular tumors

   Diagnosis was carried out according to criteria developed by NTP, and adenomas and hyperplasia were reported separately. In addition, adenomas were further characterized as single or multiple histiotype, and the number of multifocal adenomas in each dose group was reported. The results confirmed the diagnosis of the Leydig cell tumors as adenomas, as reported in the initial papers. According to the NTP diagnostic criteria, the incidence of Leydig cell adenomas was three, five, and 11 in the control, low- and high-dose groups, respectively. Hyperplasia was found in four, eight, and nine animals of the three dose groups. This compares with the originally reported incidences of two, two, and 11 in control, low- and high-dose animals. The latest report indicated that all four multifocal adenomas observed occurred in the high-dose group. No dose related increase of atrophy or degeneration of testicular tissue was observed, although these pathologies were reported. Thus, the tumors were not considered likely to be secondary to cell death.

2. Lymphoid tumors

   The cell type of origin and tumor sites were reported. All neoplasms were of lymphoid origin. Corrected incidences were two, seven, and 12 in the control, low- and high-dose groups, respectively. For comparison, the previously reported incidence data were two, six, and 12 in the same groups. Cancers were classified as lymphoblastic lymphomas, lymphoblastic leukemias and lymphoimmunoblastic lymphomas. The latter category was the most prevalent, accounting for one, six, and eight of the tumors observed in the respective dose groups. The data on distribution by site indicated that most animals with lymphoid cancers were affected at multiple sites. The tissues involved in treated animals were lung, liver, spleen and lymph node, and “other”, with the lung being the most commonly affected site in treated animals.

Table 7. Tumors in Sprague-Dawley Rats Receiving MTBE by Gavage, zero, 250 or 1,000 mg/kg/day, Four days/week for 104 Weeks (Belpoggi et al. 1995, 1997, 1998)

Tumor site and type		Dose[a] (mg/kg/day)		
		0	250	1,000
Females				
Hemolympho-reticular tissues (including mesenteric lymph nodes)	Lymphomas and leukemias (Belpoggi et al. 1995)	2/58[b] (3.4%)	6/51[b] (11.8%)	12/47[b,c,d, e] (25.5%)
	Lymphomas and leukemias of lymphoid origin (Belpoggi et al. 1998)	2/58[b] (3.4%)	7/51[b] (13.7%)	12/47[b,d, e] (25.5%)
Males				
Testes	Leydig interstitial cell tumors (Belpoggi et al. 1995)	2/26[f] (7.7%)	2/25[f] (8.0%)	11/32[f, g, h] (34.4%)
	Leydig interstitial cell adenomas (Belpoggi et al. 1998)	3/26[f] (11.5%)	5/25[f] (20.0%)	11/32[f, h] (34.4%)

[a] Administered in olive oil, four days per week, for 104 weeks.
[b] Number of lesion-bearing animals/total alive at 56 weeks of age, when the first leukemia was observed.
[c] Incidence relative to control group was significant ($p < 0.01$) using a log-ranked test (Mantel 1966, Cox 1972), as reported by Belpoggi et al. (1995).
[d] Incidence relative to control group was significant by the Fisher Exact test ($p = 0.001$).
[e] Dose-related trend was significant by the Cochran-Armitage trend test ($p < 0.01$).
[f] Number of lesion-bearing animals/total alive at 96 weeks of age, when the first Leydig cell tumor was observed.
[g] Incidence relative to control group was significant at the $p = 0.05$ level using prevalence analysis for nonlethal tumors (Hoel and Walburg 1972), as reported by Belpoggi et al. (1995).
[h] Incidence relative to control group was significant by the Fisher Exact test ($p < 0.05$).

Inhalation Exposure Studies

Rat inhalation exposure: Chun et al. (1992), Bird et al. (1997)

Groups of 50 male and 50 female eight-week old Fischer 344 rats were exposed to zero, 400, 3,000, or 8,000 ppm MTBE vapor by inhalation (corresponding to analytical mean concentrations of 403, 3,023, or 7,977 ppm, or 1,453, 10,899, 28,760 mg/m^3). The animals were exposed for six hours per day, five days per week for 24 months, except for the mid- and high-dose males, which were terminated at 97 and 82 weeks, respectively, due to a dose-dependent increased mortality rate from chronic progressive nephropathy. Low-dose males also experienced an increase in nephropathy that was associated with a slight increase in mortality and a decrease in survival. Survival times for females were not significantly different between exposed and control rats. However, there were slightly more deaths due to chronic progressive nephropathy in the mid- and high-dose females than in the low-dose and control females. Body weight gain and absolute body weight were decreased in both sexes of the high-dose group. Exposure-related increases in kidney and liver weights were reported in mid- and high-dose females, but not in males. Chun et al. (1992) concluded that the maximum tolerated dose (MTD) was exceeded in both sexes at high- and mid-dose levels, based on increased mortality. Other observed effects of MTBE exposure included anesthetic effects in rats of both sexes in the mid- and high-dose groups.

A detailed histopathology examination was performed on all animals in the control and high-dose groups, and on all animals that died or were sacrificed moribund. Only a limited histopathology examination was performed on non-moribund animals from the low- and mid-dose groups that survived to terminal sacrifice; for males, only the liver, kidneys, testes and gross lesions were evaluated, while for females, only the liver and gross lesions were examined microscopically (Bird et al. 1997). At the request of the MTBE Task Force, Experimental Pathology Laboratories, Inc. (1993) re-evaluated the histopathologic slides of kidneys from all male and female rats used in the Chun et al. (1992) study, and confirmed the study pathologist's conclusion that MTBE increased the severity of chronic progressive nephropathy in rats of both sexes. No histopathologic re-evaluation of the kidney tumors was performed.

In males, a statistically significant increase in renal tubular adenoma and carcinoma (combined) was observed in the mid-dose group (Table 8). In high-dose males renal tubular adenomas were increased, however, this increase did not reach statistical significance (Table 8). The sensitivity of the bioassay to detect a dose-related increase in renal tumors in the high-dose group is likely to have been reduced by the high rate of early mortality, and the early termination of this treatment group at week 82. Despite the reduced sensitivity of the bioassay, a statistically significant increase in Leydig interstitial cell testicular tumors was observed in mid- and high-dose males, with a clear dose-response evident (Table 8). Historical laboratory control values for Leydig testicular tumors in Fischer rats ranged from 64 to 98% (Bird et al. 1997).

In female Fischer 344 rats exposed to MTBE vapor, a single rare renal tubular cell adenoma was observed in one mid-dose animal; no treatment-related increases in tumor incidence were observed (Chun et al. 1992, Bird et al. 1997). MTBE treatment of females was associated with several nonneoplastic kidney lesions, however. Both female and male rats exposed to MTBE experienced a dose-related increase in mortality from chronic progressive nephropathy. Increases in microscopic kidney changes indicative of chronic nephropathy were seen in all treated males and in mid- and high-dose females. All treated males had increases in the severity

of mineralization and interstitial fibrosis of the kidney, while increases in mild to moderate glomerulosclerosis, interstitial fibrosis, and tubular proteinosis were observed in females.

Table 8. Tumors in Male Fischer 344 Rats Receiving MTBE by Inhalation, zero, 400, 3,000, or 8,000 ppm, for up to 24 Months[a] (Chun et al. 1992, Bird et al. 1997)

Tumor site and type		Concentration[b] (ppm)			
		0	400	3,000	8,000
Kidney	renal tubular adenoma	1/35[c]	0/32[c]	5/31[c]	3/20[c]
	renal tubular carcinoma	0/35[c]	0/32[c]	3/31[c]	0/20[c]
	renal tubular adenoma and carcinoma (combined)	1/35[c] (3%)	0/32[c] (0%)	8/31[c,d] (26%)	3/20[c] (15%)
Testes	Leydig interstitial cell tumors	32/50 (64%)	35/50 (70%)	41/50[e] (82%)	47/50[f] (94%)

[a] Mid- and high-dose animals were terminated at 97 and 82 weeks, respectively, due to a dose-dependent increased mortality rate from chronic progressive nephropathy.

[b] Administered as MTBE vapor six hours per day, five days per week.

[c] Survival-adjusted tumor incidence rates were used to attempt to control for excess early mortality in the mid- and high-dose groups (U.S. EPA, 1995c).

[d, e, f] Incidence relative to control group was significant by the Fisher Exact test ([d]$p < 0.01$, [e]$p < 0.05$, [f]$p < 0.001$).

Mouse inhalation exposure: Burleigh-Flayer et al. (1992), Bird et al. (1997)

Groups of 50 male and 50 female eight-week old CD-1 mice were exposed to zero, 400, 3,000, or 8,000 ppm MTBE vapor by inhalation (corresponding to analytical mean concentrations of 402, 3,014, or 7,973 ppm or 1,442, 10,816, or 28,843 mg/m^3). The animals were exposed for six hours per day, five days per week, for 18 months. Increased mortality and decreased mean survival time were observed only for male mice in the high-dose group. A slightly increased frequency of obstructive uropathy, a condition that occurs spontaneously in this mouse strain, was observed in high-dose males, however, deaths due to the condition were within the range noted for historical controls. Body weight gain and absolute body weights were decreased in high-dose males and females. Dose-dependent increases in liver weights were observed in both sexes. Kidney weights were increased in high-dose females and in low- and mid-dose males. Burleigh-Flayer et al. (1992) concluded that the MTD was exceeded in both sexes at the high-dose level. Other observed effects of MTBE exposure included anesthetic effects in mice of both sexes in the mid- and high-dose groups.

A detailed histopathology examination was performed on all animals in the control and high-dose groups, and on all animals that died or were sacrificed moribund. Only a limited histopathology examination was performed on non-moribund animals from the low- and mid-dose groups that survived to terminal sacrifice; for males, only the liver, spleen and submandibular lymph nodes were evaluated, while for females, only the liver, uterus and stomach were examined microscopically (Bird et al. 1997).

In females, a statistically significant increased incidence of hepatocellular adenomas was observed in the high-dose group (Table 9). The incidence of hepatocellular adenomas and carcinomas (combined) was also increased in high-dose females, however, only two hepatocellular carcinomas were reported, one each in the low- and high-dose groups. In males, a statistically significant increase in hepatocellular carcinomas was observed in the high-dose group (Table 9). Bird et al. (1997) noted that the combined incidence of adenomas and carcinomas in high-dose males was similar to the historical incidence for male CD-1 mice of 33%. However, after correcting for the number of animals alive at 49 weeks, when the first hepatocellular adenoma was observed in males, the incidence in the high-dose group was 43% (16/37, see Table 9), representing a clear increase above the cited historical incidence in male CD-1 mice. Burleigh-Flayer et al. (1992) concluded that the increased incidence of liver tumors in the high-dose groups (adenomas in females and carcinomas in males) could be attributed to MTBE exposure. The ability of this study to detect increases in tumor incidence was likely decreased by the shortened study length (18 versus 24 months).

Table 9. Tumors in CD-1 Mice Receiving MTBE by Inhalation, zero, 400, 3,000 or 8,000 ppm, for up to 18 Months[a] (Burleigh-Flayer et al. 1992, Bird et al. 1997)

Tumor site and type		Dose[b] (ppm)			
		0	400	3,000	8,000
Females					
Liver	hepatocellular adenoma	2/50	1/50	2/50	10/50[c]
	hepatocellular carcinoma	0/50	1/50	0/50	1/50
	hepatocellular adenoma and carcinoma (combined)	2/50	2/50	2/50	11/50[d]
Males					
Liver	hepatocellular adenoma	11/47[e]	11/47[e]	9/46[e]	12/37[e]
	hepatocellular carcinoma	2/42[f]	4/45[f]	3/41[f]	8/34[c,f]
	hepatocellular adenoma and carcinoma (combined)	12/47[e]	12/47[e]	12/46[e]	16/37[e]

[a] Male mice in the high-dose group experienced early mortality.
[b] Administered as MTBE vapor six hours per day, five days per week.
[c,d] Incidence relative to control group was significant by the Fisher Exact test ([c]$p < 0.05$, [d]$p < 0.01$).
[e] Number of lesion-bearing animals per total alive at 49 weeks, when the first hepatocellular adenoma was observed.
[f] Number of lesion-bearing animals per total alive at 63 weeks, when the first hepatocellular carcinoma was observed.

Other Relevant Data

Structure-Activity Comparisons

MTBE and similar ethers generally undergo metabolism at the ethereal bond to form the corresponding alcohol and an aldehyde (Savolainen et al. 1985). Other structurally similar ethers include ETBE and tertiary-amyl methyl ether (TAME). No studies have been reported to date on the carcinogenicity of ETBE or TAME. Published data on the genotoxic potential of ETBE and TAME are few in number; ETBE and TAME tested negative in the Salmonella reverse mutation assay, and TAME did not induce micronuclei in mouse bone marrow cells following exposure in vivo (NSTC 1997). In a recent review of gasoline toxicity, Caprino and Togna (1998) briefly refer to an unpublished report in which TAME induced "chromosomal effects" in Chinese hamster ovary cells. MTBE is made by isobutene and methanol, or TBA and methanol. NTP

has documented some evidence of carcinogenic activity for isobutene in male rats (NTP 1997), and for TBA in male rats and female mice (NTP 1995).

Pathology

The tumors observed by Belpoggi et al. (1995, 1997, 1998) in hemolymphoreticular tissues in the female Sprague-Dawley rat were diagnosed as lymphomas and leukemias. The reanalysis of the pathology data (Belpoggi et al. 1998) confirmed that these neoplasms were all of lymphoid origin, and further identified them as lymphoblastic lymphomas, lymphoblastic leukemias, and lymphoimmunoblastic lymphomas. IARC (IARC, 1993) classifies all three of these tumor types as malignant lymphomas. The aggregation of these tumor types for carcinogen identification and risk assessment purposes is therefore appropriate.

The testicular tumors observed in both the Sprague-Dawley (Belpoggi et al. 1995, 1997, 1998) and Fischer 344 (Chun et al. 1992, Bird et al. 1997) rat strains were diagnosed as Leydig interstitial cell tumors. The spontaneous incidence of these tumors is typically much lower in the Sprague-Dawley rat, as compared to the Fischer 344 rat (approximately five % and 88%, respectively at 24 months) (Clegg et al. 1997). The control incidence of these tumors reported by Belpoggi et al. (1995) (i.e., 7.7%) is consistent with levels typically observed in the Sprague-Dawley strain. The control incidence observed by Chun et al. (1992), (i.e., 64%) was reported in the published study (Bird et al. 1997) as being lower than that typically observed in the Fischer 344 strain. However, this control incidence was similar to that (i.e., 64.9%) reported for male Fischer 344 rats in another oncogenicity study from the same laboratory (Burleigh-Flayer et al., 1997), the same as the historical control rate for male Fischer 344 rats in NTP inhalation studies (Nyska et al. 1998), and within the range (64 to 98%) reported for aged male rats of this strain (Bird et al. 1997, Haseman and Arnold 1990). The lower spontaneous Leydig cell tumor incidence observed in the Chun et al. (1992) study is likely to have facilitated the detection of the dose-dependent increase in Leydig cell tumors in MTBE-treated males, despite the early termination of the mid- and high-dose groups.

The tumors observed in male Fischer 344 rat kidney tissues (Chun et al. 1992, Bird et al. 1997) were diagnosed as renal tubular adenomas and carcinomas. These two tumor phenotypes are generally considered to be related in origin, with the possibility that adenomas may progress to carcinomas (Borghoff et al. 1996b). Therefore, they are normally aggregated for carcinogen identification and risk assessment purposes (U.S. EPA 1991). The possibility that the male rat-specific α_{2u}-globulin nephropathy plays a significant role in the pathogenesis of MTBE rat kidney tumors has been investigated, and reported to be unlikely (NSTC 1997, U.S. EPA 1997a). The data indicate that MTBE induces only mild accumulation of α_{2u}-globulin and mild or partial expression of α_{2u}-globulin associated nephropathy in male rats, while clearly exacerbating the expression of non-α_{2u}-globulin rat nephropathy in both males and females (NSTC 1997). Support for this conclusion includes the observation that a dose-dependent increase in mortality from chronic progressive nephropathy was observed in male rats at all dose levels, and in females at the mid- and high-dose levels in the rat inhalation bioassay (Bird et al. 1997). Observed microscopic kidney changes included increases in the severity of mineralization and interstitial fibrosis in all treated males, and increases in mild to moderate glomerulosclerosis, interstitial fibrosis, and tubular proteinosis in mid- and high-dose females (Chun et al. 1992). In addition, a rare renal tubular tumor was observed in one MTBE-treated female rat (Chun et al. 1992). In a separate analysis of a 13-week inhalation exposure study of male rats conducted at the Bushy Run Research Center laboratory, Swenberg and Dietrich (1991) measured the levels of α_{2u}-globulin associated with hyaline droplets in MTBE-treated and control kidney sections by

immunohistochemical staining techniques. Although a slight increase in renal cortex staining for α_{2u}-globulin was observed in MTBE-treated animals, as compared with controls, there was no relationship between the level of α_{2u}-globulin staining and the dose of MTBE received (U.S. EPA 1997c, Swenberg and Dietrich 1991). In a study by Lington et al. (1997), inhalation of 4,000 and 8,000 ppm MTBE for 13 weeks resulted in a moderate increase in the size of hyaline droplets in male rat kidney, but no MTBE-associated increase in the area or intensity of α_{2u}-globulin immunostaining was observed, as reported by Bird et al. (1997). In a four-week inhalation study, exposure to 3,000 and 8,000 ppm MTBE increased the levels of protein accumulated in male rat kidney tubule epithelial cells, but not the levels of α_{2u}-globulin, as compared with controls (Bird et al. 1997).

The tumors observed by Burleigh-Flayer et al. (1992) and Bird et al. (1997) in mouse liver were diagnosed as hepatocellular adenomas and carcinomas. These two tumor phenotypes are generally considered to be related in origin, with the possibility that adenomas may progress to carcinomas. They are normally therefore aggregated for carcinogen identification and risk assessment purposes. The sensitivity of the study to detect treatment-related tumors, especially in the low- and mid-dose groups, may have been compromised by the less-than-lifetime length of the study (18 months).

Mechanism

The mechanism(s) by which MTBE induces tumors at multiple sites in rats and mice is unknown at this time. It is unclear whether MTBE itself plays a direct role in the observed tumorigenesis, or whether metabolism to one or more active metabolites is required. The two major metabolites of MTBE, HCHO (Kerns et al. 1983, Sellakumar et al. 1985, Til et al. 1989, Woutersen et al. 1989) and TBA (NTP 1995), have both been shown to possess tumorigenic activity in animal studies. Interestingly, there is a commonality of tumor sites observed for MTBE, HCHO, and TBA. Leukemias were observed in male and female Sprague-Dawley rats administered HCHO in drinking water (Soffritti et al. 1989), and renal tubular cell adenomas and carcinomas were observed in male Fischer 344 rats administered TBA in drinking water (NTP 1995, Cirvello et al. 1995). IARC (1995) concluded that the evidence on the carcinogenicity of HCHO was sufficient in animals and limited in humans, and classified the agent in Group 2A probably carcinogenic to humans. NTP (1995) in reviewing the results of two-year drinking water studies with TBA concluded that "there was 'some' evidence of carcinogenic activity of TBA in male Fischer 344/N rats based on increased incidences of renal tubule adenoma or carcinoma (combined)".

It is presently unknown whether the nature or degree of MTBE metabolism is tissue- or sex-specific, or whether there is any relationship between the site of metabolism and target tumor sites. Comparison of the target tumor sites in rats administered MTBE by two different routes of administration is inherently limited by the use of different rat strains in these studies; however, these findings suggest that route-specific distribution and metabolism of MTBE may be of importance in the development of some (e.g., leukemias and lymphomas, renal tumors), but not all treatment-associated tumors (e.g., testicular tumors). It has also been suggested that sex-specific differences in metabolism may underlie the development of leukemias and lymphomas in female, but not male rats (Belpoggi et al. 1995, 1997, 1998). This hypothesis remains untested, however.

MTBE was negative in a number of genotoxicity assays as noted in the section on genetic toxicity in this document and by ATSDR (1996), testing positive only in the activated mouse lymphoma forward mutation assay (ARCO 1980, Mackerer et al. 1996) and the rat lymphocyte

comet assay (Lee et al. 1998). The MTBE metabolite TBA was not mutagenic in either the Salmonella assay (Zeiger et al. 1987) or the mouse lymphoma assay (McGregor et al. 1988). HCHO is genotoxic, testing positive in numerous assay systems (IARC 1995). Data on HCHO-related genotoxicity in MTBE tumorigenesis are too limited to draw any conclusions at this time. Studies conducted in freshly isolated mouse hepatocytes from female CD-1 mice (Casanova and Heck 1997) did not find any dose-related increase in HCHO-associated DNA-protein cross-links or RNA-HCHO adducts following MTBE-treatment. Similar results were obtained with freshly isolated hepatocytes from male B6C3F1 mice and male Fischer 344 rats (Casanova and Heck 1997). These data suggest that HCHO is not the active species responsible for MTBE liver tumorigenesis in the mouse. In studies using the mouse lymphoma assay, however, HCHO has been implicated as the active species responsible for MTBE's mutagenic activity (Garnier et al. 1993, Mackerer et al. 1996). DNA-protein cross-link data and RNA-HCHO adduct data are not available for the other tumor sites noted after MTBE exposure in laboratory animals.

Several hypotheses have been put forward suggesting that MTBE may act via a variety of nongenotoxic mechanisms, such as the involvement of endocrine modulation in mouse liver and rat testicular tumorigenesis (Bird et al. 1997, Moser et al. 1996b) and α_{2u}-globulin nephropathy in male rat kidney tumorigenesis (Bird et al. 1997, Poet and Borghoff 1997a, 1997b, Prescott-Mathews et al. 1997a). While MTBE exposure of the mouse is associated with various endocrine-related tissue and cellular responses (see the section on developmental and reproductive toxicity in this document), the available data are insufficient to support an endocrine-mediated mode of action for MTBE-associated liver (Moser et al. 1996a, 1996b, Moser et al. 1998, Okahara et al. 1998) or testicular tumors (Day et al. 1998) at this time.

Data which suggest that α_{2u}-globulin nephropathy may be involved in MTBE kidney tumorigenesis include the following:

- A mild to moderate increase in the number and size of hyaline droplets in the renal proximal tubule cells of MTBE-treated male rats has been observed.
  - ◊ In a 10-day inhalation study, MTBE increased the number of protein droplets within the renal proximal tubules of male rats with a statistically significant concentration-related positive trend (Prescott-Mathews et al. 1997a).
  - ◊ In a 14-day gavage study, MTBE increased the formation of hyaline droplets in male rat kidney proximal tubular epithelial cells at the highest dose tested (Robinson et al. 1990).
  - ◊ In a 28-day inhalation study, MTBE slightly increased protein accumulation in male rat kidney tubular epithelial cells (Bird et al. 1997).
  - ◊ In a 13-week inhalation study, MTBE slightly increased hyaline droplet formation in male rat kidney (Swenberg and Dietrich 1991).
  - ◊ In another 13-week inhalation study, MTBE slightly increased the size of hyaline droplets in male rat kidney (Bird et al. 1997 reporting on findings of Lington et al. 1997).
  - ◊ In a 90-day gavage study, MTBE slightly increased the number of hyaline droplets in male rat kidney proximal tubular epithelial cells (Robinson et al. 1990).
- Protein in the renal proximal tubule cells of MTBE-treated male rats stains weakly for α_{2u}-globulin.
  - ◊ In a 13-week inhalation study, MTBE slightly increased hyaline droplet formation and staining for α_{2u}-globulin in male rat kidney but these increases were not dose-dependent (Swenberg and Dietrich 1991).

- ◊ In a 10-day inhalation study, no dose-related increase in α_{2u}-globulin staining could be detected in MTBE-treated male rat kidney by immunohistochemical staining (Prescott-Mathews et al. 1997a).

- Using an ELISA-based method, a mild dose-dependent increase in α_{2u}-globulin-immunoreactivity (approximately 150 µg α_{2u}-globulin/mg total protein in controls versus 200 µg α_{2u}-globulin/mg total protein in the high-dose animals) has been observed in rat kidney cytosol of male rats exposed to MTBE by inhalation for 10 days (Prescott-Mathews et al. 1997a).
- MTBE binds weakly to α_{2u}-globulin in vitro. Using a kidney homogenate system, only a very weak interaction between MTBE and male rat renal proteins was detected (Poet and Borghoff 1997a). This interaction did not survive dialysis or anion exchange chromatography (Poet and Borghoff 1997a).
- A dose-dependent increase in cell proliferation has been observed in the renal cortex of male rats exposed to MTBE by inhalation for 10 days (Prescott-Mathews et al. 1997a).
- Agents which are thought to induce renal tubular tumors via an α_{2u}-globulin-mediated mechanism are nongenotoxic. MTBE has demonstrated little or no genotoxicity in vitro or in vivo.

Data which argue against a significant role for α_{2u}-globulin nephropathy in MTBE kidney tumorigenesis include the following:

- Male rat specificity for nephropathy and renal tumorigenicity has not been observed.
  - ◊ In a two-year inhalation study, MTBE exacerbated chronic progressive nephropathy and increased mortality associated with chronic progressive nephropathy in a dose-dependent manner in both in female and male rats (Chun et al. 1992, Bird et al. 1997).
  - ◊ A rare kidney tumor was observed in one MTBE-treated female rat in the two-year inhalation study (Chun et al. 1992, Bird et al. 1997).
- A clear exposure-related increase in staining for α_{2u}-globulin, an effect typical of classical α_{2u}-globulin nephropathy-inducing agents, has not been observed in male rats treated with MTBE.
  - ◊ In a 13-week inhalation study, MTBE slightly increased hyaline droplet formation and staining for α_{2u}-globulin in male rat kidney but these increases were not dose-dependent (Swenberg and Dietrich 1991).
  - ◊ In another 13-week inhalation study, MTBE slightly increased the size of hyaline droplets in male rat kidney, but no increase in the area or intensity of α_{2u}-globulin staining was observed (Bird et al. 1997 reporting on findings of Lington et al. 1997).
  - ◊ In a 28-day inhalation study, MTBE slightly increased protein accumulation in male rat kidney, but did not increase α_{2u}-globulin immunohistochemical staining (Bird et al. 1997).
  - ◊ In a 10-day inhalation study, no dose-related increase in α_{2u}-globulin staining could be detected in MTBE-treated male rat kidney by immunohistochemical staining, but using a more sensitive ELISA-based assay a mild increase in the concentration of α_{2u}-globulin (approximately 150 µg α_{2u}-globulin/mg total protein in controls versus 200 µg α_{2u}-globulin/mg total protein in the high-dose animals) was observed (Prescott-Mathews et al. 1997a). This small increase is in contrast to the marked increase seen with classical α_{2u}-globulin nephropathy-inducing agents, such as 2,2,4-trimethylpentane

(approximately 200 μg α_{2u}-globulin/mg total protein in controls versus 550 μg α_{2u}-globulin/mg total protein in treated animals) (Prescott-Mathews et al. 1997a).

- α_{2u}-Globulin-positive proteinaceous casts, another effect typical of classical α_{2u}-globulin nephropathy-inducing agents, were not seen at the junction of the proximal tubules and the thin loop of Henle in several short-term studies, including a 10-day inhalation study (Prescott-Mathews et al. 1997a), a 28-day inhalation study (Bird et al. 1997), or a 13-week inhalation study (Swenberg and Dietrich 1991, U.S. EPA 1997c). However, in a 90-day oral study a small number of granular casts were observed (Robinson et al. 1990).
- Linear mineralization of papillary tubules, another effect typical of classical α_{2u}-globulin nephropathy-inducing agents, has not been reported in rats exposed to MTBE to date.
- To date, published reports have not detected the binding of MTBE to α_{2u}-globulin or male rat renal proteins in vivo (Prescott-Mathews et al. 1997b), although Borhgoff and colleagues report indirect evidence for an in vivo association between MTBE and male rat renal proteins (Borghoff, personal communication). Only a very weak interaction between MTBE and male rat renal proteins has been detected in vitro, using a kidney homogenate system (Poet and Borghoff 1997a). This interaction did not survive dialysis or anion exchange chromatography (Poet and Borghoff 1997a), in contrast to observations with classical α_{2u} -globulin nephropathy-inducing agents, where typically 20 to 40% of bound ligand is retained after dialysis (NSTC 1997).

The available data on renal tumorigenesis indicate that MTBE induces only mild accumulation of α_{2u}-globulin and mild or partial expression of α_{2u}-globulin associated nephropathy in male rats, while clearly exacerbating the expression of non- α_{2u}-globulin rat nephropathy in both males and females (NSTC 1997). The U.S. EPA (1991) established three criteria for causation of an α_{2u}-globulin effect:

(1) increased number and size of hyaline droplets in renal proximal tubule cells of treated male rats;

(2) accumulating protein in the hyaline droplets is α_{2u}-globulin; and

(3) additional aspects of the pathological sequence of lesions associated with α_{2u}-globulin nephropathy are present.

If the response is mild all of the typical lesions may not be observed, however, some elements consistent with the pathological sequence must be demonstrated to be present.

Evaluation of the available data indicates that the first U.S. EPA criterion has been satisfied, but not the second or third (NSTC 1997, U.S. EPA 1997a).

In late 1997, IARC held a workshop to examine, among other issues, the scientific basis for possible species differences in mechanisms by which renal tubular cell tumors may be produced in male rats (IARC 1998b). The final draft of the consensus report from this workshop outlines seven criteria which all must be met by agents causing kidney tumors through an α_{2u}-globulin-associated response in male rats. These criteria are the following:

(1) Lack of genotoxic activity (agent and/or metabolite) based on an overall evaluation of in vitro and in vivo data

(2) Male rat specificity for nephropathy and renal tumorigenicity

(3) Induction of the characteristic sequence of histopathological changes in shorter-term studies, of which protein droplet accumulation is obligatory

(4) Identification of the protein accumulating in tubular cells as α_{2u}-globulin

(5) Reversible binding of the chemical or metabolite to α_{2u}-globulin

(6) Induction of sustained increased cell proliferation in the renal cortex

(7) Similarities in dose-response relationship of the tumor outcome with the histopathological end-points (protein droplets, α_{2u}-globulin accumulation, cell proliferation)

The data summarized above indicates that the second, fourth and seventh IARC (1998b) criteria have not been satisfied. With regard to the third criterion, the classical α_{2u}-globulin-associated accumulation of granular casts has not been observed in several shorter-term studies. Similarly, linear mineralization of papillary tubules, which is also part of the characteristic sequence of histopathological changes, has not been observed. With regard to the fifth criterion, MTBE appears to reversibly bind to α_{2u}-globulin only very weakly. As to the sixth criterion, there are no data available to evaluate whether MTBE induces a sustained increase in cell proliferation in the renal cortex.

Thus, based on both the U.S. EPA and IARC criteria, α_{2u}-globulin nephropathy does not appear to play a significant role in MTBE kidney tumorigenesis.

Summary of the Evidence

Epidemiological studies of the carcinogenic effects of MTBE are not available. Carcinogenicity of MTBE has been observed in both sexes of the rat in a lifetime gavage study (Belpoggi et al. 1995, 1997, 1998), in male rats of a different strain in a 24-month inhalation study (Chun et al. 1992, Bird et al. 1997), and in male and female mice in an 18-month inhalation study (Burleigh-Flayer et al. 1992, Bird et al. 1997). Statistically significant increases in Leydig interstitial cell tumors of the testes were observed in two different strains of rats by two separate routes of administration. Other statistically significant increases in the rat were leukemias and lymphomas (combined) in females and renal tubular tumors in males. Statistically significant increases in hepatocellular carcinomas were observed in male mice and statistically significant increases in adenomas and combined adenomas and carcinomas were observed in female mice. MTBE has demonstrated little or no genotoxicity in vitro or in vivo. The mechanism by which MTBE induces tumors at multiple sites in animals remains unknown (NSTC 1997, Mennear 1995, 1997a, 1997b). Additional supporting evidence is provided by the carcinogenic activity of HCHO and TBA, two primary metabolites of MTBE, which share target tumor sites in common with MTBE. Both TBA and MTBE cause renal tumors in one strain of rat, and both orally administered HCHO and MTBE were associated with lymphohematopoietic cancers in a different strain.

Conclusion

Based on the information reviewed in the preparation of this document, there is evidence for the carcinogenicity of MTBE at multiple sites in both sexes of the rat and the mouse in five of the six available studies; MTBE is a two-species, multi-strain, two-sex, two-route, and multi-site carcinogen. Positive animal carcinogenicity data for HCHO and TBA, metabolites of MTBE, provide support for this conclusion.

Ecotoxicity

Concern has been raised about the effects of MTBE in water on plants, animals and ecosystems (UC 1998). Rowe et al. (1997) summarized aquatic toxicity information and water quality criteria for VOCs including MTBE being monitored in the NAWQA Program by the USGS. The species tested so far for toxic effects of MTBE have high thresholds in the ppm or mg/L range indicating that MTBE has limited acute and chronic toxicity for aquatic species (Mancini 1997, Stubbleffield et al. 1997). Acute studies generated MTBE LC_{50} values with the freshwater green algae of 184 ppm, the freshwater Ceriodaphnia fleas of 348 ppm, the freshwater Daphnia water fleas of 542 and 681 ppm, the freshwater fathead minnows of 672, 706, 929 and 979 ppm, the freshwater rainbow trouts of 887 and 1237 ppm, the freshwater tadpoles of 2,500 ppm, the marine mysid shrimps of 44 and 136 ppm, the marine inland silverside of 574 ppm, the marine bleak of > 1,000 ppm, the marine copepod of > 1,000 ppm, and the marine sheepshead minnows of > 2,500 ppm.

Toxicity of MTBE to Daphnia magna and Photobacterium phosphoreum was reported (Gupta and Lin 1995). A recent laboratory toxicity study with three unicellular algae suggests that the dissolved MTBE may alter algal community composition in the natural environment (Rousch and Sommerfeld 1998). Research by the API and others on ecological hazards of MTBE exposure is continuing. Because of the large amount of MTBE usage in California, high water and lipid solubility of MTBE, and lack of information on toxic effects of long-term exposure to low doses of MTBE (e.g., reproductive impairment in plants or animals), Cal/EPA (1998) has a continuing interest in reviewing current and proposed research to fill in these data gaps.

Toxicological Effects in Humans

No studies were located regarding toxic effects of MTBE in humans following ingestion or skin contact. No studies were located regarding toxic effects of ingested or inhaled or skin-contacted MTBE in drinking water in humans. No studies were located regarding acute effects, subchronic effects, chronic effects, death, systemic effects including respiratory, gastrointestinal, cardiovascular, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or body weight effects, immunological or lymphoreticular effects, neurological effects, developmental or reproductive effects, genotoxic effects, or cancer in humans after oral exposure to MTBE alone (ATSDR 1996).

No epidemiological study data on long-term effects and the carcinogenic effects of human exposure to MTBE were found in an earlier search by ATSDR (1996) or more recently by OEHHA. The U.S. EPA has not classified MTBE with respect to potential human carcinogenicity based on animal studies. The NSTC (1997) report concluded that "there is sufficient evidence to indicate that MTBE is an animal carcinogen and to regard MTBE as having a human hazard potential." Nevertheless, health complaints from the public have raised the concern of federal and state health agencies (Begley 1994, Begley and Rotman 1993, CDC 1993a, 1993b, 1993c, Drew 1995, Joseph 1995, Mehlman 1995, 1996, 1998a, 1998b, 1998c, 1998d).

No studies were located regarding death, cardiovascular effects, hematological effects, musculoskeletal effects, hepatic effects, renal effects, endocrine effects, body weight effects, developmental and reproductive effects, genotoxic effects, or cancer in humans after inhalation exposure to MTBE. No studies were located regarding death, respiratory effects, gastrointestinal

effects, cardiovascular effects, hematological effects, musculoskeletal effects, hepatic effects, renal effects, endocrine effects, body weight effects, immunological or lymphoreticular effects, neurological effects, developmental and reproductive effects, genotoxic effects, or cancer in humans after dermal exposure to MTBE (ATSDR 1996).

Acute Toxicity

A recent literature review (Borak et al. 1998) summarizes the exposure to MTBE and acute human health effects including nine epidemiological studies, ten industrial hygiene studies, and 12 clinical studies. No studies were located regarding acute toxic effects of ingested or skin-contacted MTBE in humans. There are very limited data on the acute toxicity of MTBE in humans through inhalation exposure. Several studies undertaken over the past four to five years were unable to find any correlation between reported acute health effects and MTBE exposures experienced by the general public, mainly through inhalation, from the use of MTBE in gasoline (ATSDR 1996, Balter 1997, McCoy et al. 1995, NSTC 1996, 1997, U.S. EPA 1997a). The acute effects of combustion products and atmospheric chemistry of gasoline, and of gasoline formulated with MTBE, deserve further study within the context of sensitive populations (McConnell and Taber 1998).

Ingestion of gasoline-MTBE mixtures may result in aspiration and pneumonitis. Two recent reviews by Mehlman (1998a, 1998d) reported neurotoxic, allergic, and respiratory effects in humans from water and air contaminated by MTBE in gasoline. Symptoms reported by 82 participants ingesting water containing MTBE from a spill in North Carolina for approximately five years include headache, anxiety, inability to concentrate, lightheadedness, ear, nose and throat irritation, skin rashes, sneezing and breathing problems, shortness of breath and bronchitis. Similar acute illnesses in petroleum workers were reported. Acute symptoms in Alaska and New Jersey were summarized and allergic symptoms from one Alaska resident were detailed.

Complaints of acute effects from exposure to oxygenates such as MTBE in gasoline, mainly via inhalation, have been received by health authorities (Fiedler et al. 1994, McCoy et al. 1995, Raabe 1993). However, the limited epidemiological studies that have been conducted to date have not demonstrated a causal association between acute effects and inhalation exposure in a relatively small population (ATSDR 1996). Three human volunteer inhalation studies did not show increased symptoms among healthy adults (Cain et al. 1996, Johanson et al. 1995, Prah et al. 1994).

In 1993, the J. B. Pierce Laboratory of Yale University (Cain et al. 1996) and U.S. EPA (Prah et al. 1994), in two separate studies, exposed individuals to clean air and air mixed with MTBE. In cases where 37 or 43 human volunteers were exposed to low levels of MTBE in air (1.39 or 1.7 ppm) for one hour, there was no significant increase in symptoms of eye, nasal, or pulmonary irritation when the results for periods of exposure to MTBE were compared to results from exposure to ambient air. There were also no significant effects on mood or in the results from several performance-based neurobehavioral tests. In both studies, the females ranked the general quality of the air containing MTBE lower than the control atmosphere. However, in the study by Cain et al. (1996), where the subjects were also exposed to an atmosphere containing a total of 7.1 ppm mixture of 17 VOCs that are frequent air contaminants in areas around gasoline stations, the air quality of the MTBE-containing atmosphere ranked higher than that with the VOC mixture. No increase in acute symptoms was observed in individuals exposed to MTBE at concentrations that would be encountered while refueling a car.

The studies by Hakkola (1994), Hakkola et al. (1996, 1997) and White et al. (1995) compared the effects in two groups exposed to different concentrations of MTBE from treated gasoline because of their lifestyles. The moderately exposed individuals either drove a gasoline delivery truck, worked in a gasoline station, or worked on car repairs. The minimally exposed individuals merely used a gasoline-powered vehicle to go to and from work or as part of their job. In the study by White et al. (1995), the odds ratio was 8.9 (95% confidence interval = 1.2 to 75.6) for the reporting of one or more symptoms when 11 individuals with blood MTBE levels of > 2.4 µg/L were compared with 33 individuals with lower levels. The odds ratio increased to 21 (95% confidence interval = 1.8 to 539) when commuters were excluded from the population studied and eight workers with blood levels of > 3.8 µg/L were compared to 22 individuals with lower blood MTBE levels. All individuals lived and worked in the area around Stamford, Connecticut.

In a series of studies conducted in Finland where the gasoline contains 10% MTBE, Hakkola (1994) first evaluated neuropsychological symptoms among 61 male tanker drivers with exposure to organic solvents at work. The differences between the exposed group and the two control groups (56 males with occasional exposure at work and 31 male with no exposure) were found not to be statistically significant. Hakkola et al. (1996) again found that there were no statistically significant differences between the signs and symptoms reported by 101 drivers of tanker trucks and 100 milk truck drivers. Blood concentrations of MTBE or its metabolites were not monitored. However, the latest Hakkola et al. (1997) study comparing symptoms and moods among 101 road tanker drivers with 100 milk delivery drivers found results different from the previous studies. The tanker drivers with long exposure to gasoline during the work week reported significantly higher changes in fatigue scores than drivers with short exposure, and 20% of tanker drivers reported acute symptoms connected to MTBE exposure.

In the winter of 1992, the state of Alaska began using 15% MTBE in wintertime oxygenated gasoline as part of the federal requirements to reduce emissions of CO in Fairbanks and Anchorage. There were reports of headaches, dizziness, nausea, and spaciness after refueling and/or working around oxygenated gasoline (Smith and Duffy 1995). The Centers for Disease Control (CDC), U.S. EPA, and the state of Alaska investigated these complaints but were unable to associate them with MTBE exposure. Instead, it was suggested that the increase in price of the new federal RFG, the odor of MTBE, and the harsh climate of Alaska resulted in some of the public associating changes in fuel with the reported symptoms. The state is now using ethanol in its gasoline during the winter (Beller et al. 1992, Chandler and Middaugh 1992, CDC 1993a). Gordian et al. (1995) reported no increase in claims for respiratory illness in Anchorage or Fairbanks after introduction of MTBE in Alaska.

A study in Alaska (Moolenaar et al. 1994) compared effects and blood levels of MTBE from a time period when oxygenated fuels were in use (Phase I) to those after the oxygenated fuels use had stopped (Phase II). The subjects were volunteers who were occupationally exposed to motor vehicle exhaust or gasoline fumes. Eighteen workers participated in Phase I and 22 in Phase II. Twelve of those that participated in Phase I of the study also participated in Phase II. A questionnaire was used to gather information on signs and symptoms and blood samples were collected for measurement of MTBE at the beginning and end of a typical workday. In Phase I, the median post-shift MTBE level was higher than the pre-shift value (1.80 versus 1.15 ppb). During Phase II, the values were more comparable (0.25 versus 0.21 ppb). Median post-shift blood measurements of TBA were higher during Phase I than in Phase II (5.6 versus 3.9 ppb).

Signs and symptoms that could be associated with MTBE exposure were reported more frequently during Phase I than Phase II (Moolenaar et al. 1994). During Phase I, 50% or more of the participants reported headaches, eye irritations, and nose and throat irritations. Reporting of

these symptoms occurred in less than 10% of the participants during Phase II. However, it is difficult to evaluate if psychosomatic factors and individual sensitivity had influenced these results. The volunteers may have chosen to participate because of their sensitivity to contaminants in the atmosphere. A follow-up survey of workers exposed to oxygenated fuel in Fairbanks, Alaska (Moolenaar et al. 1997) detected higher blood benzene concentrations in mechanics than drivers and other garage workers.

Milwaukee, Wisconsin began to use MTBE in its gasoline as part of the federal RFG program in November 1994. Similar health complaints, as voiced in Alaska (Beller et al. 1992), were registered in Wisconsin. U.S. EPA, the Wisconsin Department of Health, CDC, and the University of Wisconsin investigated complaints from approximately 1,500 people. They wrote two reports (May and September 1995) and concluded that they could find no relationship between reported health effects and MTBE exposure. It was suggested that the odor of MTBE, increase in price of wintertime gasoline, and negative media coverage were responsible for the reports of health problems associated with exposure to gasoline (Anderson et al. 1995).

National Institute for Working Life in Sweden (Nihlen et al. 1998a, 1998b) assessed acute effects up to the Swedish occupational exposure limit value with both objective measurements and questionnaires. The healthy male volunteers were exposed to MTBE vapor for two hours at five, 25, and 50 ppm during light physical work. In the questionnaire, only the ratings of solvent smell increased up to 50% of the scale as the volunteers entered the chamber and declined slowly with time. No ocular effects were observed. Nasal airway resistance blockage index increased but was not related to exposure levels. Decreased nasal volume was seen but with no dose-effect relationship. The authors concluded no or minimal acute effects of MTBE vapor upon short-term exposure at these relatively high levels.

An interview questionnaire study (Fiedler et al. 1994) was conducted, first to assess exposure and the symptomatic responses of individuals with multiple chemical sensitivities (MCS) while using gasoline products with MTBE, second to compare their responses to individuals with chronic fatigue syndrome (CFS) which can not contribute to exposure to chemicals, and third to compare with normal controls. Fourteen MCS, five CFS, and six normal control subjects of comparable age, education, gender, and ethnicity completed several structured interview and assessment sessions. It was concluded that while the sample was limited, MTBE symptoms were not uniquely associated with chemical sensitivity or with situations where MTBE was more prevalent.

Several additional major literature reviews on the acute health effects of MTBE have been conducted. Reviews from studies in Connecticut (CDC 1993b, White et al. 1995), Montana (MCCHD 1993), New Jersey (Mohr et al. 1994), New York (CDC 1993c), Illinois and Wisconsin (Anderson et al. 1995) and the HEI (1996) could find no evidence linking acute health effects with exposure to MTBE from gasoline use. In 1993, the Environmental and Occupational Health Sciences Institute (EOHSI) surveyed New Jersey garage workers and service station attendants, some of whom were exposed to MTBE, and some of whom were not. No significant differences in the frequency of reported symptoms were observed between the two groups (Hartle 1993, Mohr et al. 1994). EOHSI is conducting a study on individuals who have reported sensitivity to MTBE and were recruited from the "Oxybuster" group in New Jersey. The Oxybuster group is a citizens' group which claims their members experience acute health effects from breathing MTBE (Joseph 1995). Those individuals will be exposed to gasoline with and without MTBE. Results are expected later in 1998.

In response to the negative publicity associated with the use of federal wintertime oxygenated fuel, the White House OSTP through the NSTC in September 1995 directed federal agencies to review fuel economy and engine performance issues, water quality, air quality benefits, and health effects of oxygenates in fuel with a final report issued in June 1997. NSTC (1997) concluded that with the information collected to date there was no evidence that MTBE is causing increases in acute symptoms or illnesses at concentrations experienced by the general population, but anecdotal reports of acute health symptoms among some individuals cannot yet be explained or dismissed. NSTC also recommended that greater attention should be given to the potential for increased symptom reporting among workers exposed to high concentrations of oxygenated gasoline containing MTBE. Regarding the issue of acute sensitivity to MTBE, NRC which peer-reviewed an earlier draft of the NSTC report, concluded that there was no reason to believe that some people have extreme sensitivity to MTBE. The final NSTC report concluded "an examination of possible predisposing factors might be useful to better understand the occurrence of various symptoms in the general public following exposure to MTBE-containing gasoline."

MTBE has had a limited use as a therapeutic drug for dissolving cholesterol gallbladder stones (ATSDR 1996, HSDB 1997). Perfusion of MTBE through the bile duct and gallbladder by a percutaneous transhepatic catheter under local anesthesia was once used as a medical treatment to dissolve gallstones as an alternative to surgery (Diaz et al. 1992, Edison et al. 1993, Lin et al. 1994). Leuschner et al. (1994) reported identical side effects of manual and automatic gallstone dissolution with MTBE in 228 patients. Hellstern et al. (1998) surveyed 268 European patients from one hospital comparing with 535 patients from 20 other centers and reported that method-related lethality amounted to zero percent and 30-day-lethality to 0.4%. Another solvent, ethyl propionate, has been suggested to be preferable to MTBE in this investigational procedure due to intestinal mucosa damages (Hofmann et al. 1997).

Acute exposure of humans to MTBE has occurred via injection through the catheter into the gallbladder. During this procedure, some of the MTBE enters the blood stream and is distributed systemically. Side effects reported in patients treated by this procedure included nausea, vomiting, coughing, bronchitis, sleepiness, sedation, perspiration, bradycardia (slow heart beat), elevation of liver enzymes, apnea, CNS depression, and respiratory depression (Allen et al. 1985, Juliani et al. 1985, Wyngaarden 1986). A case of acute renal failure was also reported (Ponchon et al. 1988). These signs cannot be attributed totally to MTBE because of the confounding effects of anesthesia and the infusion process itself. Borak et al. (1998) reviewed 12 dissolution studies and reported that the peak MTBE blood levels averaged 40,000 μg/L in one study and ranged up to 10,000 μg/L in another study.

Immunotoxicity

There are very limited human studies available on the immunotoxicity of MTBE-added fuels through inhalation or MTBE-contaminated water. Duffy (1994) concluded that single day exposures to oxyfuel and its combustion products did not show an immediate effect on the immune system as measured by serum plasma interleukin six (IL-6) levels. In this study, blood samples from 22 individuals exposed to auto emissions derived from oxyfuel were analyzed for effects on the immune system by monitoring IL-6 levels at the beginning and at the end of the eight-hour workday during a four-week period in late November and early December 1992 (Duffy 1994).

Vojdani et al. (1997b) reported the detection of MTBE antibodies in seven out of 24 gasoline station attendants (six females and 18 males ranging in age from 21 to 58 years) who were employed for more than two years in service stations, and none out of the 12 healthy control subjects (four females and eight males 24 to 60 years of age). The results indicated that these IgG and IgM antibodies were produced against the methyl or tert-butyl group of MTBE. They also indicated that the immune reactions to MTBE occurred through hapten carrier reactions that could be related to airborne exposures to TBF. However, the antibody response did not correlate with claimed symptoms.

The same group (Mordechai et al. 1997, Vojdani et al. 1997a) also reported reversible but statistically significant increased rates of abnormal apoptosis (programmed cell death) and cell cycle progression in peripheral blood lymphocytes in 20 Southern California residents exposed to MTBE and benzene contaminated water as compared to ten healthy human controls. Similar observations on 80 patients were reported again by the same group (Vojdani and Brautbar, 1998). Apoptosis is an organism's way of maintaining healthy cell populations, the process can lead to the development of disease if it is unduly suppressed or stimulated (Thompson 1995). For example, cancer may be the result of a failure in the apoptotic process, in which mutant cells are allowed to proliferate freely rather than being recognized as damaged and destroyed.

Neurotoxicity

Burbacher (1993) reviewed gasoline and its constituents as neuroactive substances and recommended future studies to focus on examining the dose-response relationship between chronic low-level exposure and subtle toxic effects in CNS functions. The results from human studies of neurological effects, e.g. headache, dizziness, disorientation, fatigue, emotional distress, gastrointestinal problems, e.g. nausea or diarrhea, and symptoms of respiratory irritation in individuals exposed to MTBE vapors through MTBE-containing fuels are inconclusive (Hakkola et al. 1996, Hakkola and Saarinen 1996, Moolenaar et al. 1994, White et al. 1995). The three studies cited were different in their design and utilized slightly different parameters for monitoring effects. All studies evaluated exposure to an MTBE-gasoline mixture and not MTBE alone.

However, in the most recent study by Hakkola et al. (1997) comparing neuropsychological symptoms and moods among 101 road tanker drivers from three Finnish oil companies with 100 milk delivery drivers from two milk companies, the tanker drivers with long exposure to gasoline during the work week reported significantly higher changes in fatigue scores than drivers with short exposure, and 20% of tanker drivers reported acute symptoms of headache, dizziness, nausea, dyspnoea, and irritation of saliva excretion. These symptoms have been connected to MTBE exposure. The authors suggested that exposure to MTBE during the workweek could be reason for acute symptoms among the tanker drivers in this study.

DOSE-RESPONSE ASSESSMENT

Internal Dose Estimation

Due to the lack of a clear mode of action of TBA or other MTBE metabolites in MTBE-induced carcinogenesis in experimental animals, OEHHA has necessarily had to treat the parent compound MTBE as the cause of the observed effects in animal studies for the purpose of

determining dose metrics. In order to estimate internal doses of MTBE, in addition to simple continuous applied doses, a simplified PBPK model was employed. This model is based on both the Borghoff et al. (1996a) model, in that it has five compartments for MTBE and five compartments for TBA, and the Rao and Ginsberg (1997) model with its MTBE metabolic parameters and slowly perfused compartment/blood partition coefficient for TBA. The PBPK model employs compartments loosely representing "Fat, Liver, Kidneys, Muscle, and rapidly perfused tissues termed as Vessel Rich Group (VRG)". The model's fundamental structure is based on that developed by Hattis et al. (1986) for perchloroethylene and was formulated in Stella® software (ithink® v. 3.0.6b for the Power Macintosh, High Performance Systems Inc., Hanover, New Hampshire 03755). The model units for the whole animal are moles, L, moles/L, hour, moles/hour, L/hour, and ppm in alveolar air. Simulations of up to 32 hours were run at approximately 1,000 steps per simulated hour, using the Runge-Kutta four computation method on a Power Macintosh 7100/80. The model parameters were obtained from Borghoff et al. (1996a) or Rao and Ginsberg (1997) and are listed in Table 10. In addition to simulations of the pharmacokinetic data of Miller et al. (1997) with a model 0.22 kg rat, simulations of cancer bioassay doses were conducted assuming 0.35 kg for female and 0.5 kg for male lifetime average body weights. Physiological and metabolic parameters were scaled to these body weights as described in Borghoff et al. (1996a).

Table 10. Parameters Used in the PBPK Model Simulations for MTBE and TBA

Parameter	Female rat	Male rat	Source
Body weight (kg)	0.35	0.5	Estimated from Belpoggi et al. 1995
Compartment volumes (L)			
Liver	0.014	0.020	Borghoff et al. 1996a
Kidney	0.00245	0.0035	Borghoff et al. 1996a
Muscle	0.2625	0.375	Borghoff et al. 1996a
Fat	0.0245	0.035	Borghoff et al. 1996a
Vessel Rich Group (VRG)	0.01505	0.0215	Borghoff et al. 1996a
Flows (L/hour)			
Alveolar ventilation	6.4	8.32	Borghoff et al. 1996a
Cardiac output	6.4	8.32	Borghoff et al. 1996a
Liver	1.6	2.88	Borghoff et al. 1996a
Kidney	1.6	2.88	Borghoff et al. 1996a
Muscle	0.96	1.248	Borghoff et al. 1996a
Fat	0.576	0.7488	Borghoff et al. 1996a
VRG	1.664	2.1632	Borghoff et al. 1996a
Partition coefficients (MTBE)			
Blood/Air	11.5	11.5	Borghoff et al. 1996a
Liver/Blood	1.1826	1.1826	Borghoff et al. 1996a
Kidney/Blood	3.113	3.113	Borghoff et al. 1996a
Muscle/Blood	0.565	0.565	Borghoff et al. 1996a
Fat/Blood	10.05	10.05	Borghoff et al. 1996a
VRG/Blood	3.113	3.113	Borghoff et al. 1996a
Partition coefficients (TBA)			
Blood/Air	481-75	481-75	Borghoff et al. 1996a*
Liver/Blood	0.8316	0.8316	Borghoff et al. 1996a
Kidney/Blood	1.1289	1.1289	Borghoff et al. 1996a
Muscle/Blood	0.4	0.4	Rao & Ginsberg 1997
Fat/Blood	0.3971	0.3971	Borghoff et al. 1996a
VRG/Blood	1.1289	1.1289	Borghoff et al. 1996a
Metabolism (MTBE)			
$Vmax_1$ (mole/hour)	2.05×10^{-6}	2.66×10^{-6}	Rao & Ginsberg 1997
$Vmax_2$ (mole/hour)	2.27×10^{-4}	2.94×10^{-4}	Rao & Ginsberg 1997
Km_1 (*M*)	2.27×10^{-6}	2.27×10^{-6}	Rao & Ginsberg 1997
Km_2 (*M*)	1.25×10^{-3}	1.25×10^{-3}	Rao & Ginsberg 1997
Metabolism (TBA)			
Vmax (mole/hour)	2.46×10^{-5}	3.21×10^{-5}	Rao & Ginsberg 1997
Km (*M*)	3.79×10^{-4}	3.79×10^{-4}	Rao & Ginsberg 1997
GI absorption ($hour^{-1}$)	0.8	0.8	Model assumption

* Note: see text

The PBPK model simulation results for oral exposures to MTBE are summarized in Table 11. The italic boldface values are observed experimental data from Miller et al. (1997). The simulated or predicted values for 0.215 kg, 0.35 kg female, and 0.5 kg male rats are shown in normal type. In general, better predictions were obtained for MTBE than for TBA both for maximum blood concentration and the area under the blood concentration x time curve, or AUC.

Adequate simulation of TBA blood kinetics became increasingly difficult with increased body size and lower TBA blood-air partition coefficients of 150 and 75 had to be employed to achieve stable simulations. In all cases MTBE doses were cleared within 24 hours and there was no need for multi-day simulations to estimate an average daily MTBE AUC for the bioassays. In all cases MTBE AUC was linear with applied dose for a particular body size.

Table 11. Comparison of PBPK Predictions with Experimental Data from Oral MTBE Administrations*

Oral dose/ Body weight	MTBE mM Cmax	TBA mM Cmax	MTBE AUC mM hour	TBA AUC mM hour	Blood:Air MTBE/TBA
40 mg/kg					
0.215 kg rat	0.068	0.176	0.150	0.863	11.5/481
Observed					
Frat	***0.127***	***0.12***	***0.142***	***0.495***	
Mrat	***0.195***	***0.135***	***0.193***	***0.526***	
250 mg/kg					
0.35 kg Frat	0.527	0.974	1.03	6.3	11.5/75
0.5 kg Mrat	0.813	1.42	2.32	10.7	
400 mg/kg					
0.215 kg rat	0.801	2.26	1.88	30.7	11.5/150
Observed					
Frat	***1.30***	***0.66***	***2.19***	***3.90***	
Mrat	***1.41***	***0.68***	***2.61***	***4.10***	
1,000 mg/kg					
0.35 kg Frat	2.36	3.03	6.08	30.9	11.5/75
0.5 kg Mrat	3.81	3.26	11.9	30.6	

*Note: Mrat = male rat; Frat = female rat, in both cases values are for assumed lifetime average body weights. Simulation values are single day results and not averaged over a week.

Table 12 gives the average daily doses based on the blood MTBE AUC values for male and female rat simulations and the linear relations for each with applied oral dose.

Table 12. MTBE AUC Based PBPK Doses

Nominal dose mg/kg/day	Average applied dose mg/kg/day	MTBE AUC females mg/kg/day	MTBE AUC males mg/kg/day
0	0	0	0
250	143	116.1	124.2
1,000	571	576.0	575.1

Males: mg/kg/day = 26.28 + 82.36(mM hour) , r = 0.998;
females: mg/kg/day = 38.95 + 159.37(mM hour), r = 0.996.

Table 13 presents similar simulation results for inhalation exposures with the observed experimental values in italic boldface. The results are similar to the oral exposures with predictions of MTBE blood concentrations and AUCs being closer to observed values than TBA predictions. On the basis of comparison of MTBE AUC values, a 3,000 ppm × six-hour exposure appeared to be equivalent to a 1,000 mg/kg oral gavage dose to a 0.5 kg rat. As seen in the oral exposures, the MTBE AUC in mM hour varied linearly with applied dose [ppm × six-hour/day = 145.84 + 255.17 (mM hour), r = 0.999]. Also given in the lower part of Table 13 are dose conversions from MTBE AUC to oral mg/kg/day averaged for lifetime daily intake. This conversion assumes that the same relation exists between AUC and mg/kg/day as seen above in the oral simulations. If this assumption holds, the oral equivalent male doses from the inhalation bioassay would be zero, 82.9, 618.8, and 1,848.3 mg/kg/day. The male oral doses from the gavage bioassay study would be zero, 124.2, and 575.1 mg/kg/day.

Table 13. Comparison of MTBE PBPK Predictions with Experimental Data: Rat Inhalation

Inhalation dose/ Body weight	MTBE mM Cmax	TBA mM Cmax	MTBE AUC mM hour	TBA AUC mM hour	Blood:Air MTBE/TBA
400 ppm × 6 hours 0.215 kg rat	0.219	1.34	1.31	15.8	11.5/350
Observed 400 ppm					
Mrat	***0.169***	***0.535***	***0.956***	***5.45***	
Frat	***0.171***	***0.531***	***0.884***	***5.05***	
400 ppm × 6 hours 0.5 kg Mrat	0.182	0.914	1.09	12.2	11.5/350
3,000 ppm × 6 hours 0.5 kg Mrat	1.7	5.4	10.2	125est	11.5/150
8,000 ppm × 6 hours 0.215 kg rat	5.65	9.83	33.9	22.6	11.5/150
Observed 8,000 ppm					
Mrat	***6.3***	***7.2***	***33.6***	***81.0***	
Frat	***6.4***	***3.3***	***32.6***	***34.4***	
8,000 ppm × 6 hours 0.5 kg Mrat	5.2	9.6	31.1	487est	11.5/150

Male rats	**Nominal dose ppm × 6 hours**	**MTBE AUC mM hour**	**Dose from MTBE AUC ppm**	**Dose from MTBE AUC* mg/kg/day**
	400	1.09	424	82.9
	3,000	10.2	2,749	618.8
	8,000	31.1	8,082	1,848.3

*Note: This conversion assumes the same relation between AUC and mg/kg/day as seen in oral studies or what single oral dose would give the predicted MTBE AUC seen during the six-hour inhalation exposures. See also Dourson and Felter (1997) for alternative route-to-route extrapolation.

Overall, the PBPK pharmacokinetic correction for delivered dose when based on MTBE blood AUC is relatively modest compared to the simple applied dose. It is presently uncertain whether other dose metrics would be superior to MTBE AUC and will probably remain so until a more definitive mode(s) of action of MTBE carcinogenesis develops.

Noncarcinogenic Effects

The most sensitive noncarcinogenic effect by oral route is in the kidney based on the Robinson et al. (1990) 90-day gavage study with a NOAEL of 100 mg/kg/day. As noted above this value was used by U.S. EPA (1996a) to derive a proposed lifetime HA of 70 ppb (or 0.07 mg/L) in drinking water for MTBE. In its more recent document (U.S. EPA 1997a), U.S. EPA employed this toxicity endpoint along with two other noncancer endpoints, neurological and reproductive and developmental, as well as three cancer endpoints in a margin of exposure (MOE) analysis to develop longer-term HAs. Other states also used this toxicity endpoint to develop regulatory guidelines for MTBE as described later in this document.

Carcinogenic Effects

Possible Modes of Action

There are limited data available on the mechanism of action of MTBE. It remains unknown whether biotransformation is required for expression of MTBE's carcinogenic activity. The data from several in vitro and in vivo tests indicate that MTBE lacks significant genotoxic activity and suggest that a genotoxic mode of action is unlikely. It has been proposed that MTBE's induction of renal tubular cell tumors in the male rat is the result of α_{2u}-globulin nephropathy. Although some characteristic features of α_{2u}-globulin nephropathy have been associated with MTBE, the absence of others leads to the overall conclusion that α_{2u}-globulin nephropathy is not likely to account for the induction of kidney tumors by MTBE. Although endocrine-mediated modes of action have been suggested for MTBE's induction of testicular tumors in rats and liver tumors in mice, there are insufficient data to support these hypotheses. In summary, the data available at this time do not provide sufficient evidence in support of a specific mode of action of MTBE carcinogenicity.

Estimation of Carcinogenic Potency

According to the proposed guidelines for carcinogen risk assessment (U.S.EPA 1996f) the type of extrapolation employed for a given chemical depends on the existence of data supporting linearity or nonlinearity or a biologically based or case-specific model. When insufficient data are available supporting either approach the default is to use a linear extrapolation. MTBE seems to fit this category, since no mode of action is known (U.S. EPA 1994a, 1994c). Although the lack of genotoxicity and the nonlinearity of the carcinogenic response in some studies might be argued as supportive of a mechanism other than direct genotoxicity via covalent modification of DNA, attempts to identify positively an alternative mechanism have not so far succeeded. Dourson and Felter (1997) attempted to perform an extrapolation of the cancer potency of MTBE from inhalation route (Chun et al. 1992) to oral route.

Cancer potency or cancer potency factor (CPF) is a slope derived from a mathematical function used to extrapolate the probability of incidence of cancer from a bioassay in animals using high doses to that expected to be observed at the low doses which are likely to be found in chronic human exposure. The mathematical model, such as the LMS model, is commonly used in quantitative carcinogenic risk assessments in which the chemical agent is assumed to be a

complete carcinogen and the risk is assumed to be proportional to the dose at very low doses. q_1* is the upper 95% confidence limit on the cancer potency slope calculated by the LMS model. Or another cancer slope factor (CSF) is a potency value derived from the lower 95% confidence limit on the 10% tumor dose (LED_{10}). LED_{10} is the 95% lower bound on the dose that is predicted to give a 10% tumor incidence. The CSF equals to 10% dividing by LED_{10}.

Earlier guidelines for cancer risk assessment, including those formerly used by OEHHA (DHS 1985) have required the use of the LMS model to estimate an upper bound on the low-dose potency (q_1*). However, more recent OEHHA methodologies, and the draft proposed U.S. EPA (1996f) guidelines for carcinogen risk assessment, recommend a linear extrapolation approach based on the LED_{10}. A multistage polynomial is used to fit data in the observable range, unless some other dose-response curve is specifically indicated by the available data. Because adequate data do not exist for MTBE, the default curve-fitting approach is appropriate. Interspecies scaling for oral doses (and internal doses calculated from a single-species pharmacokinetic model) is based on $(\text{body weight})^{3/4}$ as proposed by U.S. EPA (1996f, 1992b) instead of the $(\text{body weight})^{2/3}$ used previously. For inhalation exposures U.S. EPA has in the past used an assumption of equivalence between different species of exposures to a given atmospheric concentration. This provides roughly similar scaling in effect, due to the way that breathing rate and related parameters affecting uptake scale with body weight. More recently PBPK modeling has been seen as a preferable approach to both dose estimation and interspecies scaling of inhalation exposures, where data are available to support this. Since pharmacokinetic data are available for MTBE in the rat, the modeling approach was feasible in this case for that species only.

Table 14 summarizes the cancer potency values derived by both the LED_{10} method and the LMS model (for comparison with earlier results) from the available statistically significant rodent cancer bioassay data sets for MTBE described earlier in the section on carcinogenicity. In all cases the Tox_Risk v.3.5 (Crump et al. 1993) program was used to fit the multistage model to the quantal data sets. The q_1* cancer potencies or the 95% upper bound on the LMS linear slope at low dose were calculated directly by the program. CSF's are based on the LED_{10}. The CSF is $0.1/LED_{10}$, in units of $(\text{mg/kg-day})^{-1}$. For the curve fitting to estimate the LED_{10}, we have employed a $p \geq 0.05$ criterion for the Chi-squared goodness of fit statistic of the optimized polynomial. In order to obtain an adequate fit it was necessary to exclude the data for kidney tumors in the high dose (8,000 ppm) males rats in the study by Chun et al. (1992). As can be seen from Table 14, the potency estimates for all tumors are similar whether based on the q_1* or the CSF. Results in the inhalation studies (Chun et al. 1992, Burleigh-Flayer et al. 1992) are effectively the same (within a factor of two) for the different sites in rats and mice, except that the potency for testicular interstitial cell tumors in male rats is about five times higher. Comparison between different routes and experiments for the rat is easiest by examining the data calculated using the pharmacokinetic model to convert the inhalation exposures to equivalent oral doses. In this case it is apparent that all the results are comparable, with the testicular interstitial cell tumors in the Chun et al. (1992) males again showing a slightly higher value than those found at other sites or in the testis in the Belpoggi et al. (1995, 1997, 1998) oral study.

Table 14. Dose Response Parameters for MTBE Carcinogenicity Studies

a) Inhalation studies - ppm in air as dose metric

Species	Sex	Tumor site and type	q_1^* (ppm^{-1})	LED_{10} (ppm)	CSF (ppm^{-1})
Mouse	Female	hepatocellular adenoma + carcinoma	3.2×10^{-4}	320	3.2×10^{-4}
	Male	hepatocellular adenoma + carcinoma	7.3×10^{-4}	140	7.0×10^{-4}
Rat	Male	renal tubular cell adenoma + carcinoma	4.4×10^{-4}	240	4.2×10^{-4}
		testicular interstitial cell tumors	2.3×10^{-3}	46	2.2×10^{-3}

Assumed:
Data reassessment by U.S. EPA (1994c, 1995c).
Duration correction based on $(t_e/t_l)^3$: t_l = 104 weeks for both rats and mice.
Interspecies correction: ppm equivalency.

b) Rat oral study - Administered dose as dose metric

Study	Sex	Tumor site and type	q_1^* $(mg/kg\text{-}day)^{-1}$	LED_{10} mg/kg/day	CSF $(mg/kg\text{-}day)^{-1}$
Belpoggi et al. 1995, 1998	Male	Leydig cell tumors:			
		Original 1995 report	1.38×10^{-3}	76	1.38×10^{-3}
		Revised 1998 data	1.63×10^{-3}	64	1.55×10^{-3}
	Female	Leukemia/lymphoma:			
		Original 1995 report	2.13×10^{-3}	49	2.03×10^{-3}
		Revised 1998 data	2.20×10^{-3}	48	2.09×10^{-3}

Assumed:
No duration correction: $t_e = t_l$.
Interspecies correction: $BW^{3/4}$.

c) Rat oral and inhalation studies - AUC as dose metric

Route	Sex	Tumor site and type	q_1* $(mM.hour/day)^{-1}$	LED_{10} mM.hour/day	CSF $(mM.hour/day)^{-1}$
Inhalation (Chun et al. 1992)	Male	renal tubular cell adenoma + carcinoma	0.037	2.9	0.035
	Male	testicular interstitial cell tumors	0.16	0.66	0.15
Gavage (Belpoggi et al. 1995, 1998)	Male	Leydig cell tumors:			
		Original 1995 report	0.044	2.4	0.041
		Revised 1998 data	0.044	2.4	0.041
	Female	Leukemia/lymphoma:			
		Original 1995 report	0.051	2.1	0.048
		Revised 1998 data	0.051	2.1	0.048

Assumed:
Data reassessment by U.S. EPA (1994c, 1995c) for Chun et al. (1992) study.
Duration correction based on $(t_e/t_l)^3$: t_l = 104 weeks for rats.
Interspecies correction: AUC equivalency.

d) Rat oral and inhalation studies - Equivalent oral dose as dose metric

Route	Sex	Tumor site and type	q_1* $(mg/kg\text{-}day)^{-1}$	LED_{10} mg/kg/day	CSF $(mg/kg\text{-}day)^{-1}$
Inhalation (Chun et al. 1992)	Male	renal tubular cell adenoma + carcinoma	1.9×10^{-3}	55	1.8×10^{-3}
	Male	testicular interstitial cell tumors	9.2×10^{-3}	11	8.7×10^{-3}
Gavage (Belpoggi et al. 1995, 1998)	Male	Leydig cell tumors:			
		Original 1995 report	1.38×10^{-3}	76	1.38×10^{-3}
		Revised 1998 data	1.63×10^{-3}	64	1.55×10^{-3}
	Female	Leukemia/lymphoma:			
		Original 1995 report	2.13×10^{-3}	49	2.03×10^{-3}
		Revised 1998 data	2.20×10^{-3}	48	2.09×10^{-3}

Assumed:
Data reassessment by U.S. EPA (1994c, 1995c) for Chun et al. (1992) study.
Duration correction based on $(t_e/t_l)^3$: t_l = 104 weeks for rats.
Interspecies correction: $BW^{3/4}$.

e) Oral and inhalation studies -Study design

Spe-cies	Route	Sex	Body weight	Study duration	Lifetime assumed	Dosing schedule	Concen-trations	Study
Rat	Inhalation	Male	500 g	97 weeks	104 weeks	6 hour/day, 5 day/week	0, 400, 3,000, 8,000* ppm	Chun et al. 1992
Mouse	Inhalation	Male	35 g	68 weeks	104 weeks	6 hour/day, 5 day/week	0, 400, 3,000, 8,000* ppm	Chun et al. 1992
		Female	30 g	68 weeks	104 weeks	6 hour/day, 5 day/week	0, 400, 3,000, 8,000* ppm	
Rat	Gavage	Male	500 g	lifetime	104 weeks	4 day/week	0, 250, 1,000 mg/kg/day	Belpoggi et al. 1995
		Female	350 g	lifetime	104 weeks	4 day/week	0, 250, 1,000 mg/kg/day	

*8,000 ppm dose group not used in analysis of male rat renal tubule tumors due to inability of multistage polynomial to achieve adequate fit.

Carcinogen risk assessment guidelines used by OEHHA normally recommend selection of human cancer potency estimates based on the most sensitive site and species, unless there is evidence to indicate that the most sensitive site(s) are not relevant to human cancer induction, or represent data sets with unusually wide error bounds. As an alternative, where several equally plausible results are available and are sufficiently close to be regarded as concordant, the geometric mean of all such estimates may be used.

The pharmacokinetic model, that allows comparison of different routes and corrects for nonlinearities in the relationship between applied and internal dose, is not available for the mouse. Therefore, the potency estimates obtained in the rat are preferred for risk assessment purposes. Because the results in rats and mice are comparable, the use of the rat data is consistent with the policy of selecting appropriately sensitive species as the basis for the estimate of potency in humans.

In terms of the relevance to human cancer and the mechanism of the observed effects, the results of the studies by Chun et al. (1992) and Burleigh-Flayer et al. (1992) are limited by the relatively severe mortality seen in the highest dose groups, and the less-than lifetime exposure given the mice and the male rats. These experimental flaws are not so severe as to exclude the use of the data in risk assessment, nor more prohibitive than the experimental flaws associated with many studies on other compounds that have been successfully used for this purpose. There are, however, additional problems in the case of the testicular interstitial cell tumors observed in

male rats by Chun et al. (1992). The study authors stated that the control incidence of these tumors was lower than the historical incidence observed in animals from the colony from which these experimental animals were obtained. In view of this, the slightly divergent value for the potency estimate obtained with this data set is regarded with lower confidence than the other values obtained in this analysis.

An attempt was made to allow for the severe impact of mortality on the male rat kidney adenoma and carcinoma incidence in the study by Chun et al. (1992) by applying the time-dependent version of the LMS model to the individual time-to-tumor incidence data in this study. A suitable model available in the Tox_Risk program (multistage in dose, Weibull in time) was used, and an adequate fit was obtained. The program provided an estimate of $q_1^* = 7.6 \times 10^{-2}$ $(mg/kg\text{-}day)^{-1}$, which is substantially higher than the value estimated from the quantal data. The calculated end-of-life LED_{10} indicated a CSF of 7.2×10^{-2} $(mg/kg\text{-}day)^{-1}$. However, the fit obtained involved a large Weibull exponent (z = 8.7, whereas more usual values are in the range of three to six), implying a very late appearance of this tumor. This observation may be of interest in addressing the unsolved question of the mechanism of induction of this tumor by MTBE. However it implies a marked reduction in the confidence which can be placed in the potency estimate using this model. Few tumor data were obtained during the final third of the expected lifetime of the exposed rats (due to the early death of all the rats dosed with 8,000 ppm, and most of the rats dosed with 3,000 ppm by this time). The potency estimate therefore involves a substantial extrapolation outside the range of the observed data, even using the LED_{10}/CSF methodology that is designed to avoid such problems. The extreme time dependency, deficiency in genotoxicity data, and other uncertainties described previously also raise the question of how appropriate it is to use this particular model to fit these data. Its use for extrapolation outside the range of observed data (as opposed to merely as a curve-fitting device within the range of observed data) implies an acceptance of the classic Armitage-Doll theory of action for genotoxic carcinogens, which may not be warranted in the case of MTBE. Because the mechanistic information and the technical resources which would be required to undertake a more appropriate analysis of these time-to-tumor data are lacking, it was decided not to include the results of the time-dependent analysis in the final risk estimate.

In view of the closeness of the other values obtained in the rat, and their similar confidence levels, the preferred value for the cancer potency is therefore the geometric mean of the potency estimates obtained for the male rat kidney adenomas and carcinomas combined (1.8×10^{-3}) (Chun et al. 1992), and the male rat Leydig interstitial cell tumors (1.55×10^{-3}) and the leukemia and lymphomas in female rats (2.09×10^{-3}) (Belpoggi et al. 1995, 1998). The combined use of these data yields an estimated CSF of 1.8×10^{-3} $(mg/kg\text{-}day)^{-1}$. While it is theoretically possible that the true human CSF could exceed this value, that is considered unlikely. On the other hand it is plausible that the lower bound on the human CSF includes zero. This is a result of statistical uncertainty with a zero lower bound estimate on q_1 by the LMS method with some MTBE data sets and biological uncertainties due to interspecies extrapolation and mode of action.

A unit risk value is similarly derived from the geometric mean of the respective LED_{10} values for the blood MTBE AUC (Table 14c) as follows:

a) the geometric mean of 2.1 mM × hour is converted to external concentration (in ppm) using the regression expression derived above i.e., 145.84 + 225.17(2.1) = 618.7 = 619 ppm;

b) this value is converted to mg/m^3 using the 3.6 mg/m^3/ppm conversion factor, or 619 ppm × 3.6 mg/m^3/ppm = 2,230 mg/m^3,

c) the unit risk is calculated as 0.1/2230 mg/m^3 or 4.5×10^{-5} $(mg/m^3)^{-1}$ or 4.5×10^{-8} $(\mu g/m^3)^{-1}$.

Since the LED values were in human equivalent doses no additional interspecies scaling is required. This unit risk would indicate negligible theoretical lifetime cancer risk at ambient MTBE air concentrations below about 6.2 ppbv (ppb by volume).

CALCULATION OF PHG

Calculations of public health-protective concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets, and other household uses resulting in potential dermal and inhalation exposures.

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for MTBE in drinking water for noncarcinogenic endpoints uses the following general equation adopted by U.S. EPA (1990, 1992a, 1996c):

$$C = \frac{NOAEL/LOAEL \times BW \times RSC}{UF \times DWC}$$

where,

NOAEL/LOAEL	=	no observable adverse effect level or lowest observed adverse effect level.
BW	=	body weight (a default of 70 kg for a male or 60 kg for a female adult).
RSC	=	relative source contribution (a default of 20% to 80% as explained below).
UF	=	Uncertainty factors (UFs) are included to account for gaps in our knowledge (uncertainty) about the toxicity of chemicals and for recognized variability in human responses to toxic chemicals.

In determining UFs for chronic effects it is conventional to apply an UF where data are only available from short- or medium-term exposures of animals, rather than full lifetime exposures. In the case of MTBE noncarcinogenic effects, there is no adequate chronic study in experimental animals of the critical effect (increase in kidney weight in rats): the key study is of 90 days duration or about 10% the life span of a rat. Because of this, we consider that a 10-fold UF is justified.

For interspecies extrapolation of toxic effects seen in experimental animals to what might occur in exposed humans an UF of up to 10-fold is generally recommended. This is usually considered as consisting of two parts: one that accounts for metabolic or pharmacokinetic differences between the species; and another that addresses pharmacodynamic differences, i.e. differences between the response of human and animal tissues to the chemical exposure. Based on

the limited metabolic studies of MTBE in humans that indicate possible differences from metabolism in rodents, and unresolved questions of its toxic potential for neurological, immunological and endocrine effects we believe a 10-fold UF for interspecies differences is appropriate.

Exposed humans are known to vary considerably in their response to toxic chemical and drug exposures due to age, disease states, and genetic makeup, particularly in genetic polymorphisms for enzymes (isozymes) for detoxifying chemicals. While little is known about individual variation of MTBE metabolism and toxicity the use of a 10-fold UF seems prudent considering the widespread use of tap water in the population.

Finally an additional 10-fold UF is used to account for possible carcinogenicity. This follows an U.S. EPA policy applied to their Group C contaminants. OEHHA has previously employed this additional UF for other PHGs in situations where either a nonlinear dose response was applied to a carcinogen or where both linear and nonlinear approaches were used.

DWC = daily water consumption rate (a default of two L/day for an adult has been used by the U.S. EPA (1996b), or L equivalent/day (Leq/day) to account for additional inhalation and dermal exposures from household use of drinking water as explained below).

Based on the NOAEL of 100 mg/kg/day of the most sensitive noncarcinogenic effect in the kidney from the 90-day gavage (Robinson et al. 1990) study, the following calculation can be made:

$$C = \frac{100 \text{ mg/kg/day} \times 70 \text{ kg} \times 0.2}{10 \times 1{,}000 \times 3 \text{ Leq/day}} = 0.0467 \text{ mg/L} = 47 \text{ ppb (rounded)}$$

In this calculation an additional UF of 10 is employed to account for potential carcinogenicity and a DWC value of three Leq/day is used to account for inhalation exposures via typical household use as well as ingestion of tap water. The RSC addresses other non-drinking-water sources, principally airborne MTBE from vehicular exhaust. Support for these values is presented below in a discussion of exposure factors.

Exposure Factors

The U.S. EPA (1994b) estimated scenarios of potential human exposure to MTBE related to RFG. In terms of the equation for calculating the public health-protective concentrations of chemical contaminants in drinking water as shown above, the first exposure factor to be considered is the RSC (OEHHA 1996, U.S. EPA 1994b). The RSC is a factor that is based on an estimate of the contribution of drinking water exposure relative to other sources such as food, air, etc. While food is often a significant source of chronic chemical exposure, in the case of MTBE, airborne exposures are likely to be most significant, if highly variable. U.S. EPA typically uses 20% as the default RSC. Maine Department of Human Services used 10% RSC for their proposed MCL for MTBE of 35 ppb (Smith and Kemp 1998) based on the same renal toxicity (Robinson et al. 1990) NOAEL in the 90-day oral study.

Estimates for combined population's airborne exposures and occupational subpopulations' exposures vary by three orders of magnitude or more and include few California data sets. Some of these estimates are collected in Table 15 where RSC values are calculated for a range of drinking water concentrations. The analyses of Brown (1997) include a combined population grand average of 0.00185 mg/kg/day for various activity associated airborne exposures and an average ambient water concentration of 0.36 ppb. The NSTC (1997) report gives MTBE concentrations in groundwater and surface water ranging from 0.2 to 8.7 ppb with a median value of 1.5 ppb, presumably resulting from nonpoint sources. Although the air exposure analysis of Brown (1997) is the most comprehensive it may underestimate MTBE exposures to the general public in local areas in California (e.g., the Los Angeles basin), possibly by a factor of two. Also due to the year-round and universal use of MTBE in California gasoline, commuters, other drivers, gasoline station customers and neighbors, and the general public are likely to receive greater exposures than elsewhere in the U.S. For this reason a health-protective value of 0.2 (or 20%), equal to the default value used by U.S. EPA (1994a, 1994b, 1996a), is used here for the RSC.

The other exposure factor in the equation to calculate the public health-protective concentrations of chemical contaminants in drinking water as shown above is DWC, the daily water intake in Leq/day. DWC represents the amount of tap water consumed as drinking water as well as that mixed with beverages and used in cooking. The default for an adult is two L/day. For children a default value of one Leq/day is used. For VOCs, additional exposures occur via the inhalation and dermal routes (i.e., multi-route) during and after showering, bathing, flushing of toilets, washing clothes and dishes, and other domestic uses (OEHHA 1996, U.S. EPA 1994b).

Estimates of inhalation and dermal exposure of MTBE relative to ingestion exposure vary from 15% at 0.36 ppb in water (Brown 1997) to 45% to 110% at 70 ppb in water based on predictions of the CalTox™ Model (DTSC 1994) assuming only 50% of inhaled MTBE is absorbed. Nihlen et al. (1998a) observed a respiratory uptake of 42% to 49% in human subjects exposed to MTBE for two hours at five, 25, and 50 ppm. A value of 50% inhalation absorption seems supported by actual human data. Based on this assumption and a range of values for Henry's Law constant, the estimated total MTBE intake ranges from 2.5 Leq/day to four Leq/day as shown in Table 16. For this analysis, OEHHA scientists concluded that one liter of additional exposure would incorporate the expected exposure to MTBE volatilized from water and inhaled. Therefore, three Leq/day for total MTBE exposure would appear to be a reasonable estimate for the purpose of calculating the PHG. The Henry's Law constant for MTBE is about 6×10^{-4} atm-m^3/mole at 25 °C which is approximately one quarter (1/4) that of benzene and one fourteenth (1/14) that of perchloroethylene, the two common VOCs that have been studied previously (Robbins et al. 1993). MTBE is less volatile and its solubility in water is significantly higher than these VOCs. Accordingly, the correction for showering and other activities for assumed daily water consumption for MTBE is smaller than these other common VOCs. This is consistent with the conclusions of Johnson (1998) as documented in the UC (1998) MTBE report.

Table 15. Relative Source Contribution (RSC) Estimates (%) for Different Combinations of Air and Drinking Water Exposures to MTBE*

Air exposure estimate (mg/kg/day)	Air exposure scenario	RSC (%) 0.36 ppb*	2 ppb*	12 ppb*	70 ppb*	Reference
0.00185	Combined U. S. population grand average	0.6	3	16	52	Brown 1997
0.01	One million exposed U. S. nationwide	0.1	0.6	3.3	17	Brown 1997
0.002	Los Angeles basin at 4 ppbv ambient	0.5	2.8	15	50	ARB 1996
0.0093	Scenario I annual	0.1	0.6	3.6	18	NSTC 1996
0.0182	Scenario II annual	0.06	0.3	1.8	10	NSTC 1996
6.7×10^{-5}	Milwaukee, Wisconsin Air	13	46	84	97	HEI 1996
0.37	MTBE distribution of fuel mixture Time-Weighted-Average (TWA) for workers	0.003	0.02	0.09	27	HEI 1996
1.3×10^{-4}	Albany, New York air	7	30	72	94	NSTC 1997
Geometric mean		0.28	1.5	6.4	34	
Arithmetic mean		2.6	10.4	24.5	45.6	

Note:
RSC = (I_{water} x 100) / (I_{water} + I_{air}). Food and soil sources are considered negligible for MTBE.
I_{water} = uptake by ingestion of tap water containing MTBE at the concentrations noted assuming two L/day and 100% intestinal absorption.
I_{air} = uptake by inhalation of airborne MTBE assuming 20 m^3 air inhaled/day and 50% absorption.
Both I_{water} and I_{air} are assumed for a 70 kg human.

*The concentrations of MTBE in drinking water were taken from the reports noted rather than using arbitrary values: 0.36 ppb (Brown 1997); two ppb (NSTC 1997 rounded); 12 ppb (rounded 10^{-6} risk estimate, U.S. EPA 1996a); and 70 ppb (proposed Longer-Term and Lifetime HA, U.S. EPA 1996a). However, any plausible range could have been used, e.g., five, 10, 20, 40, etc.

Table 16. CalTox™ Predictions of Inhalation (I), Oral (O) and Dermal (D) Exposures (mg/kg/day) from 70 ppb MTBE Contaminated Tap Water: Effects of Varying Henry's Law Constant and Drinking Water Intake Level

Henry's Law constant ($Pa\ m^3/mole$)		Water intake (mL/kg/day)		
		19.4	33.3	43.9
66.5	I=	1.16×10^{-3}	1.16×10^{-3}	1.16×10^{-3}
	O=	1.11×10^{-3}	1.91×10^{-3}	2.52×10^{-3}
	D=	4.41×10^{-6}	4.41×10^{-6}	4.41×10^{-6}
		2.28×10^{-3}	3.08×10^{-3}	3.69×10^{-3}
	All	2.46 Leq/day	3.30 Leq/day	3.97 Leq/day
142	I=	1.17×10^{-3}	ND	ND
	O=	1.09×10^{-3}		
	D=	4.43×10^{-6}		
		2.26×10^{-3}		
	All	2.48 Leq/day		
228	I=	1.18×10^{-3}	1.18×10^{-3}	1.18×10^{-3}
	O=	1.09×10^{-3}	1.88×10^{-3}	2.47×10^{-3}
	D=	4.34×10^{-6}	4.3×10^{-6}	4.34×10^{-6}
		2.27×10^{-3}	3.06×10^{-3}	3.65×10^{-3}
	All	2.51 Leq/day	3.33 Leq/day	4.03 Leq/day

Note:
The CalTox™ model vadose and root zone compartments were loaded to predict 70 ppb MTBE in the groundwater used for residential drinking water. Various values for Henry's Law constant and water intake in mL/kg/day for a 62 kg female were used. MTBE parameters for molecular weight, octanol-water partition coefficient, melting point, vapor pressure, and water solubility were entered. Water intake values (mL/kg/day) correspond to median tap water for 20 to 64 year old females (19.4), median total water intake for 20 to 64 year old females (33.3), and average total water intake for all females (43.9) based on the Western Regional data (Ershow and Cantor 1989). Inhalation (I) value assumes 50% of inhaled MTBE is absorbed. Oral (O) and dermal (D) values assume 100% absorption. Total intakes by all routes are also expressed as L equivalents (Leq) per day.

Carcinogenic Effects

For carcinogens, the following general equation can be used to calculate the public health-protective concentration (C) for a chemical in drinking water (in mg/L):

$$C = \frac{BW \times R}{q_1^* \text{ or } CSF \times DWC} = mg/L$$

where,

BW	=	adult body weight (a default of 70 kg).
R	=	de minimis level for lifetime excess individual cancer risk (a default of 10^{-6}).
q_1^* or CSF	=	cancer slope factor. The q_1^* is the upper 95% confidence limit on the cancer potency slope calculated by the LMS model, and CSF is a potency derived from the lower 95% confidence limit on the 10% (0.1) tumor dose (LED_{10}). CSF = 0.1/ LED_{10}. Both potency estimates are converted to human equivalent [in $(mg/kg\text{-}day)^{-1}$] using $BW^{3/4}$ scaling.
DWC	=	daily volume of water consumed by an adult (a default of two L/day or other volume in Leq/day to account for additional inhalation and dermal exposures from household use of drinking water as explained above).

Two cancer potency estimates, q_1^* or CSF, were calculated because our current experience with the LMS model is extensive whereas the new methodology proposed by U.S. EPA (1996f) in its draft guidelines for carcinogen risk assessment is based on the LED_{10} for which little is known about the problems and outcome of using this procedure. The LMS model focuses on the linear low dose extrapolation and analysts (e.g., U.S. EPA) have often accepted relatively poor fits to the observed tumor incidence data. The new method places a higher premium on fitting the observed data to estimate the ED_{10} and the 95% lower bound LED_{10}, the point from which the low dose extrapolation is made (U.S. EPA 1996a). In the case of the estimates obtained for carcinogenic potency of MTBE, the values calculated using the LMS model are not significantly different from that obtained using the preferred LED_{10} approach.

The calculated public health-protective concentration accounting for carcinogenic effects of MTBE is based on a carcinogenic potency of 1.8×10^{-3} $(mg/kg\text{-}day)^{-1}$. This estimate is the geometric mean of the potency estimates (CSFs) obtained for the combined male rat kidney adenomas and carcinomas in the inhalation study by Chun et al. (1992), the male rat Leydig cell tumors in the oral study by Belpoggi et al. (1995, 1998), and the leukemia and lymphomas in female rats, also in the study by Belpoggi et al. (1995, 1998). It is consistent with potencies obtained at other sites in another species (mice). The estimate for the inhalation route was converted to an oral intake using the pharmacokinetic model described earlier. The public health-protective concentration was therefore calculated using the following values:

BW = 70 kg (the default male adult human body weight).

R = 10^{-6} (default de minimis lifetime excess individual cancer risk).

q_1^* or CSF = 1.8×10^{-3} $(mg/kg\text{-}day)^{-1}$ (CSF estimated as above).

DWC = 3 Leq/day (daily water consumption. As described previously in the section on RSCs, there are various probable routes of exposure in addition to ingestion that would result from contamination of water supplies. To allow for these additional exposures as shown in calculations in Table 16, the assumed daily volume of water consumed by an adult is increased from the default of two L/day to three Leq/day).

Thus,

$$C = \frac{70 \times 10^{-6}}{1.8 \times 10^{-3} \times 3} = 13 \times 10^{-3} \text{ mg/L} = 13 \text{ µg/L} = 13 \text{ ppb}$$

Since the calculated public health-protective concentration based on noncancer toxicity of 47 ppb is less protective of public health than the above cancer based value of 13 ppb, the recommended PHG level for MTBE is therefore 13 ppb (0.013 mg/L or 13 µg/L). The adopted PHG is considered to contain an adequate margin of safety for the potential noncarcinogenic adverse effects including adverse effects on the renal, neurological and reproductive systems.

RISK CHARACTERIZATION

MTBE is used as an additive in cleaner burning automotive fuel in California. This results in opportunities for airborne exposures as well as drinking water exposures through leaking USTs and to a lesser extent from certain powered watercraft and air deposition. The public health risks of exposure to MTBE can be characterized as follows:

Acute Health Effects

Acute health effects are not expected to result from typical exposure to MTBE in drinking water. This includes household airborne exposures from showering, flushing toilets, etc. Reports of health complaints of various nonspecific symptoms (e.g., headache, nausea, cough) associated with exposure to gasoline containing MTBE have not been confirmed in controlled studies and remain to be fully evaluated.

Carcinogenic Effects

Inhalation exposure to MTBE produced increased incidences of kidney and testicular tumors in male rats and liver tumors in mice. Oral administration of MTBE produced leukemia and lymphoma in female rats and testicular tumors in male rats. A summary of our evaluation is listed below.

- As a result of this assessment OEHHA considers MTBE to be an animal carcinogen and a possible human carcinogen.
- Three cancer bioassays have shown MTBE induced tumors at several sites, in two species, in both sexes, by oral and inhalation routes of exposure; five of six studies were positive.
- Cancer study results exhibit consistency. For example, testicular tumors were induced in rats by both routes of MTBE administration.

- The oral rat study by Belpoggi et al. (1995, 1997, 1998) was found to be adequate for risk assessment purposes despite early mortality in the females.
- The inhalation studies in rats and mice were also considered adequate for risk assessment despite early mortality in both studies.
- In general the quality of the three studies was as good or better than those typically available for chemical risk assessment.
- While there are varying degrees of uncertainty as to the relevance to human cancer causation for each of the tumor types induced by MTBE in rodents (i.e., hepatocellular adenoma and carcinoma, renal tubular adenoma and carcinoma, Leydig interstitial cell tumors of the testes, leukemias and lymphomas), the occurrence of tumors at all of these sites adds considerably to the weight of evidence supporting the conclusion that MTBE should be considered a possible human carcinogen.
- MTBE genotoxicity data is weak, and there is no clear evidence that genotoxicity of its metabolites is involved in the carcinogenicity observed.
- There is no evidence to support a specific nongenotoxic mode of action (e.g., hormone receptor binding) and no evidence that metabolism of MTBE is required for carcinogenicity. In the absence of sufficient evidence, dose metrics based on the parent compound, MTBE, were necessarily chosen for the dose-response assessment.
- In the absence of specific scientific information explaining why the animal tumors are irrelevant to humans at environmental exposure levels, a standard health protective approach was taken to estimate cancer risk.
- Cancer potency estimates derived from different studies, sites, and routes of administration are similar.
- Cancer potency estimates are low compared to other known carcinogens despite the health conservative default assumptions employed.
- The adopted PHG of 13 ppb is based on an average of three quantitatively similar CSFs for three sites (kidney tumors, testicular tumors, leukemia and lymphoma). If the PHG value was based on individual tumor sites instead of an average, the values would range from 2.7 to 15 ppb.
- The CSFs are upper-bound estimates defined by the 95% confidence limit on the ED_{10}. It is theoretically possible that the true value of the cancer potency of MTBE in humans could exceed these values, but that is considered unlikely. It is plausible that the true value of the human cancer potency for MTBE has a lower bound of zero based on statistical and biological uncertainties including interspecies extrapolation and mode of action.
- The estimate of multi-route exposure employed in the PHG calculation was three Leq/day. The range of exposure estimates based on different Henry's Law constants and water ingestion rates was 2.5 to four Leq/day. The range of possible PHGs based on this range and the average CSF of 0.0018 $(mg/kg\text{-}day)^{-1}$ is 10 to 16 ppb.
- Additional peer review of all the cancer bioassays would be useful, as would be a separate bioassay of MTBE in drinking water. However, these supplemental data should be seen in the context of the data already available, which are substantial and of better quality than is available for some other compounds for which risk assessments have been undertaken.
- Lack of knowledge of the mode(s) of action of MTBE or its metabolites is a major limitation of this risk assessment.

- Lack of evidence of cancer causation in humans is also a significant limitation, although widespread use and potential exposure is relatively recent in California and the rest of the U.S.
- Additional pharmacokinetic data in humans and improved PBPK models in animals and humans are desirable.
- Lack of information on the role that interindividual variability (i.e., stemming from metabolic polymorphisms, age-related differences, and concurrent disease conditions) may play in determining susceptibility to the carcinogenicity of MTBE severely hinders identification of sensitive subgroups in the California population.

The cancer potency estimate derived from the geometric mean of the CSFs of the combined male rat kidney adenomas and carcinomas, the male rat Leydig cell tumors, and the leukemia and lymphomas in female rats was 1.8×10^{-3} $(mg/kg\text{-}day)^{-1}$. Individual tumor endpoint CSFs ranged from 1.55×10^{-3} $(mg/kg\text{-}day)^{-1}$ to 8.7×10^{-3} $(mg/kg\text{-}day)^{-1}$, or a range of about six-fold. Potencies based on the LMS model were similar ranging from 1.63×10^{-3} $(mg/kg\text{-}day)^{-1}$ to 9.2×10^{-3} $(mg/kg\text{-}day)^{-1}$, also a range of six-fold. A time-to-tumor analysis gave much higher values of 0.076 $(mg/kg\text{-}day)^{-1}$ and 0.072 $(mg/kg\text{-}day)^{-1}$ for the LMS and LED_{10} approaches, respectively. However this latter estimate has a low degree of confidence.

The findings of the oral gavage studies conducted by Belpoggi and colleagues have been given less weight by some reviewers, based on criticisms of various aspects of the study design, study reporting, and data analysis employed. The NAS (NRC 1996) review of the studies of Belpoggi et al. (1995) noted the following as study deficiencies: (1) the dosage schedule of Monday, Tuesday, Thursday, and Friday, rather than five consecutive days; (2) use of doses in apparent excess of the Maximum Tolerated Dose (MTD), based on a dose-related decrease in survival among treated females; (3) the combining of leukemia and lymphoma incidence; (4) incomplete description of tumor pathology and diagnostic criteria; and (5) lack of mortality adjusted analysis to account for differences in survival times. As noted above, OEHHA has considered these criticisms and considers that, although these experiments, like the others available for MTBE, do have certain limitations or difficulties of interpretation, they contribute considerably to the overall evidence available for MTBE risk assessment. Further, our conclusion is that the study is valid, not critically flawed, and is consistent with other reported results.

In criticizing the dosing schedule, NAS (NRC 1996) is correct in pointing out that five days per week is more usual. However, there is no evidence from the pharmacokinetic analyses that the proportionately higher peak dose and longer recovery periods would make any difference relative to the same time-averaged dose given over five days. The criticism that the MTD was exceeded appears misguided, in that a substantial proportion of the animals in all groups survived for a major part of the standard lifetime. The authors specifically noted no dose-related differences between control and exposed animals in food and water consumption or mean body weights (important indicators of non-specific toxicity). In any event, such a flaw, if real, would reduce rather than enhance the power of the studies to detect a positive response. The questions as to the advisability of combining leukemias and lymphomas, and the desire for clarification of the diagnostic criteria for these and the Leydig cell tumors, have been addressed by pathology review undertaken by Belpoggi et al. (1998), and reviewed elsewhere in this document. OEHHA shares the NAS preference for availability of full mortality data whenever possible, but notes that extensive quantal statistical analyses were undertaken by Belpoggi et al. (1998), as well as by OEHHA for this report, and considers that the data as presented provide an adequate basis for use in this risk assessment.

In its critique of the Belpoggi et al. studies, the NAS (NRC 1996) also stated that "an in-depth review of the data, especially the pathology (microscopic slides) of the critical lesions, is warranted (as was done with the inhalation studies) before the data are used for risk assessment." As mentioned above, Belpoggi and colleagues have recently published the results of a pathology review in which slides from the original study were re-examined, and diagnostic criteria reviewed by an independent panel of pathologists from the Cancer Research Centre, with the participation of an outside pathologist (Belpoggi et al. 1998). This review confirmed the authors' previous findings, and addressed the concerns expressed in the NAS report. As was correctly pointed out in the NSTC report (1997), the pathological findings of the MTBE inhalation studies (Burleigh-Flayer et al. 1992, Chun et al. 1992) have not undergone peer review, moreover, "independent peer review of pathological findings are not routinely performed in carcinogenesis studies used by the risk assessing community and (U.S.) EPA."

The water concentration associated with a 10^{-6} negligible theoretical extra lifetime cancer risk calculated from this analysis is 13 ppb. This includes an estimate of inhalation exposure from showering in MTBE contaminated water, flushing toilets, and other household activities involving tap water. The estimate of one Leq/day of additional exposure via the inhalation route is lower than the default value of two Leq/day of additional exposure suggested by U.S. EPA (1996b) based on average estimated showering exposures of a number of typical VOCs. This reflects the fact that MTBE is less volatile and more water-soluble than other VOCs commonly found in drinking water. The adopted PHG value of 13 ppb also compares favorably with the Provisional Health and Consumer Acceptability Advisory range of 20 to 40 ppb established by U.S. EPA (1997a) using a MOE approach. Since the adopted value of 13 ppb was calculated for a 1×10^{-6} theoretical lifetime extra risk from a linear extrapolation, the values of 130 ppb and 1,300 ppb (1.3 ppm or 1.3 mg/L) would be associated with the higher risk estimates of 1×10^{-5} and 1×10^{-4}, respectively.

For PHGs, our use of the RSC has, with a few exceptions, followed U.S. EPA drinking water risk assessment methodology. U.S. EPA has treated carcinogens differently from noncarcinogens with respect to the use of RSCs. For noncarcinogens, RfDs (in mg/kg/day), DWELs (in mg/L) and MCLGs (in mg/L) are calculated using UFs, body weights and DWC (in Leq/day) and RSC, respectively. The typical RSC range is 20% to 80% (0.2 to 0.8), depending on the scientific evidence.

U.S. EPA follows a general procedure in promulgating MCLGs:

- if Group A and B carcinogens (i.e., strong evidence of carcinogenicity) MCLGs are set to zero;
- if Group C (i.e., limited evidence of carcinogenicity), either an RfD approach is used (as with a noncarcinogen) but an additional UF of one to 10 (usually 10) is applied to account for the limited evidence of carcinogenicity, or a quantitative method (potency and low-dose extrapolation) is used and the MCLG is set in the 10^{-5} to 10^{-6} cancer risk range;
- if Group D (i.e., inadequate or no animal evidence) a RfD approach is used to promulgate the MCLG.

For approaches that use low-dose extrapolation based on quantitative risk assessment, U.S. EPA does not factor in a RSC. The use of low-dose extrapolation is considered by U.S. EPA to be adequately health-protective without the additional source contributions. In developing PHGs, we have used the assumption that RSCs should not be factored in for carcinogens grouped in U.S. EPA categories A and B, and for C carcinogens for which we have calculated a cancer

potency value based on low-dose extrapolation. This is an area of uncertainty and scientific debate and it is not clear how this assumption impacts the overall health risk assessment.

OTHER REGULATORY STANDARDS

The IPCS of WHO is issuing the final version of an environmental health criteria document on MTBE (IPCS 1997). The Dutch Expert Committee on Occupational Standards (Wibowo 1994) recommended a health-based eight hour-Time-Weighted Average (TWA) exposure limit for MTBE of 180 mg/m^3 or 50 ppm to be averaged over an eight-hour working day, and a short-term 15-minute-TWA limit of 360 mg/m^3 or 100 ppm in the Netherlands. Czechoslovakia has an Occupational Exposure Limit (OEL) TWA of 100 mg/m^3 and a Short-Term OEL (STEL) of 200 mg/m^3 since January 1993. Russia has a STEL of 100 mg/m^3 since January 1993 (RTECS 1997). Sweden established a TWA of 50 ppm and a 15-minute STEL of 75 ppm in 1988 (ACGIH 1996). The British Industrial Biological Research Association (BIBRA) compiled a toxicological profile on MTBE in 1990. The Danish Environmental Protection Administration is considering setting a 30 ppb limit of MTBE in groundwater. More recently, ECETOC (1997) recommended an occupational exposure limit of 90 mg/m^3 or 25 ppm to be eight hour-TWA and a short-term peak 15-minute-TWA limit of 270 mg/m^3 or 75 ppm.

In the U.S., the OSHA and NIOSH established the TLV-TWA as 40 ppm in air (144 mg/m^3) in 1994 as proposed by ACGIH in 1993. ACGIH (1996) also lists MTBE as an A3 animal carcinogen in 1995 as proposed in 1994. MTBE is on the Emergency Preparedness and Community Right-to-Know Section of the Superfund Amendments and Reauthorization Act of 1986 (SARA Title III) Extremely Hazardous Substances (EHS) list and in the TSCA Test Submission (TSCATS) Database. It is one of the TRI chemicals to be routinely inventoried. MTBE is on the Hazardous Air Pollutant (HAP) list with 189 other chemicals to be regulated under the Air Toxics Program of the 1990 CAAA. Article 211(b) of Title III of the CAAA requires that oil companies conduct gasoline inhalation studies and U.S. EPA sent the testing requirement notification on August 20, 1997. Negotiations with industry on the extent of these studies are ongoing. Animal research will focus on short and long-term inhalation effects of conventional gasoline and gasoline with MTBE. The Article 211 studies will also include human exposure research. The research will be completed at varying intervals over the next five years. HEI is funding three new studies designed to answer key questions on the metabolism of MTBE and other ethers in animals and humans.

MTBE is listed as a California TAC mandated under AB 1807 by virtue of its status as a HAP. It is one of the California Air Toxics “Hot Spots” chemicals mandated under AB 2588. ARB is proposing to place MTBE into subcategory b as substances nominated for review for development of health values. A chronic Reference Exposure Level, which is the same as the three mg/m^3 RfC for inhalation of MTBE in air as listed in the U.S. EPA (1997c) IRIS database, is being developed in the draft Hot Spots document by OEHHA mandated under SB 1731. Texas established a half-hour limit in ambient air of 0.6 mg/m^3 and an annual limit of 0.288 mg/m^3 in 1992 (Sittig 1994).

MTBE is not a priority pollutant under the Clean Water Act and is not a target analyte in routine water quality monitoring and assessment programs. MTBE is included in the draft and final Drinking Water Contaminant Candidate List (CCL) required by the Safe Drinking Water Act (U.S. EPA 1997b, 1997d, 1998b). The final list is published on March 2, 1998 with descriptions on how to make decisions on whether to establish a standard on the contaminants. CCL is divided into categories representing next steps and data needs for each contaminant. U.S. EPA

will choose at least five contaminants from the Regulatory Determination Priorities category and determine by August 2001 whether or not to regulate them based on occurrence, exposure and risk. If regulations are deemed necessary they must be proposed by August 2003 and promulgated by February 2005. MTBE is proposed for inclusion on the federal "National Drinking Water Contaminant Occurrence Data Base".

In the interim, the Office of Water has initiated a database based on voluntary reporting from some states, USGS data, and other available sources. MTBE is on the U.S. EPA Drinking Water Priority List for future regulation. The U.S. EPA's Office of Research and Development is working to identify MTBE research needs, including monitoring, exposure, health effects, and remediation. A workshop was held on October 7, 1997 to present an initial assessment of research needs to industry and academic groups. A draft report (U.S. EPA 1998b) has been issued for public comment ending by August 28, 1998. Other U.S. EPA activities include development of a protocol to collect data on potential CO reductions using federal oxygenated gasoline. USGS is conducting urban land use studies this year to characterize VOCs, including MTBE contamination as a part of the larger national NAWQA program.

Since the early 1990s, U.S. EPA has evaluated MTBE to quantify its toxic effects (Farland 1990, Hiremath and Parker 1994, Klan and Carpenter 1994, Gomez-Taylor et al. 1997). U.S. EPA (1996a) proposed a 70 ppb HA for MTBE in its December 1996 draft report based on noncarcinogenic kidney and liver effects in laboratory animals with large uncertainty factors (U.S. EPA 1996f). U.S. EPA also included an extra uncertainty factor in its draft report to account for the possible carcinogenicity of the substance. The laboratory animal cancer bioassays of MTBE by the inhalation route were performed by Bushy Run Research Center (Burleigh-Flayer et al. 1992, Chun et al. 1992) and the ones by the oral route were performed by Cancer Research Centre of the European Foundation for Oncology and Environmental Sciences “B. Ramazzini” in Italy (Belpoggi et al. 1995, 1997, 1998). U.S. EPA has not had an opportunity to audit the studies even though reviews of pathological findings are not routinely performed (NSTC 1997). Nevertheless, in the 1996 draft, U.S. EPA indicated that the animal studies would suggest that 12.5 ppb would equate to a theoretical risk level of one excess fatal case of cancer per million people per 70-year lifetime (a 10^{-6} risk), a level usually viewed as de minimis, for MTBE as a Group B2 probable human carcinogen. The 12.5 ppb was calculated based on an oral cancer potency estimate (q_1*) of 3×10^{-3} $(mg/kg\text{-}day)^{-1}$ derived from the default LMS method and a scaling factor of body weight raised to ¾ power using the combined lymphoma and leukemia in the female rats in the gavage study.

The U.S. EPA (1997c) IRIS database lists the RfC for inhalation of MTBE in air as three mg/m^3 as last revised on September 1, 1993. The RfC is based on increased liver and kidney weights, increased prostration in females, and swollen periocular tissues in male and female rats. The RfD for oral exposure to MTBE is under review by U.S. EPA (1997c). In 1992, U.S. EPA derived a draft long-term HA range for MTBE in drinking water of 20 to 200 ppb (or 0.02 to 0.2 mg/L) based on a RfD of 0.1 mg/kg/day from a 90-day rat drinking water study with dose-related increases in relative kidney weights in both sexes (Robinson et al. 1990). The range is due to the uncertainty for the carcinogen classification. The guideline would be either 20 ppb if MTBE were classified as a Group B2 or C carcinogen, or 200 ppb if MTBE is a Group D carcinogen. In 1994, U.S. EPA drafted a proposal in reviewing data from animal studies for the possibility of listing MTBE as a Group B2 probable human carcinogen, and derived an oral cancer potency estimate (q_1*) of 8.6×10^{-3} $(mg/kg\text{-}day)^{-1}$ and a HA of four ppb for a 10^{-6} risk.

The States of Vermont and Florida established drinking water standards for MTBE of 40 ppb and 50 ppb, respectively. The New York State Department of Public Water promulgated a MCL of

50 ppb in 1988. The New York State Department of Health is drafting an ambient water quality value for protection of human health and sources of potable water for MTBE based on the evaluation of animal oncogenicity data. The New Jersey Department of Environmental Protection (NJDEP) proposed in 1994 and established in 1996 a health-based MCL for MTBE in drinking water of 70 ppb, reducing from 700 ppb. This is in agreement with the 1993 evaluation of the U.S. EPA except for an uncertainty factor of 10,000 used by NJDEP instead of the 3,000 applied by the U.S. EPA (NJDWQI 1994, Post 1994). The Illinois Environmental Protection Agency listed a human threshold toxicant advisory concentration of 230 ppb in 1994 and has proposed a health-based MCL for MTBE in drinking water ranging from 70 to 2,000 ppb. The Massachusetts Department of Environmental Protection in 1995 proposed to decrease the guideline for MTBE in drinking water from 700 ppb to 70 ppb (MORS 1995). The Maine Department of Human Services listed a drinking water threshold of 50 ppb in 1995 and is considering to adopt 35 ppb based on noncancer health effects with a RSC of 10% (Smith and Kemp 1998). NCDEHNR has proposed a primary MCL of 70 ppb. The Wisconsin Department of Natural Resources in 1995 established a groundwater enforcement standard for MTBE of 60 ppb (WDOH 1995). The guideline for MTBE in drinking water is 35 ppb in Arizona, 40 ppb in Michigan, 50 ppb in Rhode Island, and 100 ppb in Connecticut and New Hampshire (ATSDR 1996, HSDB 1997, Sittig 1994).

The UC report mandated under SB521 concluded that MTBE is an animal carcinogen with the potential to cause cancers in humans (Froines et al. 1998). Using several models for exposure analysis, Johnson (1998) calculated a de minimis theoretical excess individual cancer risk level of 10^{-6} from exposure to MTBE of 10 ppb which, the author concluded, is comparable to the level recommended in this report.

DHS has added MTBE to a list of unregulated chemicals that require monitoring by drinking water suppliers in California in compliance with the California Safe Drinking Water Act, Sections 116300 to 116750. An interim Action Level of 35 ppb or 0.035 mg/L for drinking water was adopted by the DHS in 1991. The level was recommended by OEHHA (1991) using the oral RfD of 0.005 mg/kg/day then reported on the U.S. EPA IRIS database for an anesthetic effect in rats in a 13-week inhalation study performed in Europe (Greenough et al. 1980). DHS is proceeding with establishing drinking water standards for MTBE in California.

The initial standard to be developed for MTBE is a secondary MCL. The secondary MCL of five ppb is adopted by DHS as a regulation effective January 7, 1999. Secondary MCLs address aesthetic qualities of drinking water supplies. In the case of MTBE, the focus is on its organoleptic qualities, that is, its odor and taste. The purpose of the secondary MCL is to protect the public from exposure to MTBE in drinking water at levels that can be smelled or tasted. Secondary MCLs in California are enforceable standards, which means that drinking water should not be served by public water systems if it contains MTBE higher than the secondary standard. Enforceable secondary standards are unique to California. The proposed secondary MCL for MTBE is based on data from experiments that have been performed by researchers, using panels of subjects who were exposed to varying concentrations of MTBE in water to determine levels at which it could be smelled or tasted. As part of the process by which regulations are adopted under California's Administrative Procedures Act, the proposed regulation (R-44-97) was available for public comment since July 3, 1998, and September 8, 1998 was the close of the written comment period (DHS 1998).

The next standard to be developed is a primary MCL that protects the public from MTBE at levels that can affect public health. A primary MCL for MTBE will include consideration of the health risk assessment, the technical feasibility of meeting the MCL (in terms of monitoring and

water treatment requirements for MTBE) and costs associated with compliance. DHS has requested the OEHHA to provide a risk assessment for MTBE that is required for the development of the primary standard. DHS requested that the risk assessment be completed in order to meet the scheduled adoption of this regulation by July 1999. The proposed primary MCL is anticipated to be available for public comment in early 1999.

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