Second Revised Draft
Environmental Impact Report

Adoption of Statewide Regulations Allowing the Use of PEX Tubing

Prepared by:

Ascent Environmental, Inc.
455 Capitol Mall, Suite 210
Sacramento, CA 95814

May 2010

Second Revised Draft Environmental Impact Report
Adoption of Statewide Regulations Allowing the Use of PEX Tubing

Prepared for:
California Building Standards Commission
2525 Natomas Park Drive, Suite 130
Sacramento, CA 95833

Attn: Mr. David Walls, Executive Director
916/263-0916

Prepared by:

Ascent Environmental, Inc.
455 Capitol Mall, Suite 210
Sacramento, CA 95814

Contact:

Sydney Coatsworth
Project Manager
916/930-3185

May 2010

TABLE OF CONTENTS

ACRONYMS AND ABBREVIATIONS iii

1 INTRODUCTION 1-1
1.1 Background and Purpose of the Second Revised Draft Environmental Impact Report 1-1
1.2 Content of the Second Revised Draft EIR 1-1
1.3 Relationship to the DEIR and Revised Draft EIR 1-2

3 DESCRIPTION OF THE PROPOSED PROJECT 3-1
3.1 Location and Setting 3-1
3.2 Project Background 3-1
3.3 Project Objectives 3-3
3.4 Project Description 3-3
3.5 Regulatory Requirements, Permits, and Approvals 3-7
3.6 Scope of this EIR 3-7

4.2 Public Health and Hazards—Revised 4.2-1
4.2.1 Regulatory Setting 4.2-1
4.2.2 Existing Setting 4.2-3
4.2.3 Environmental Impacts 4.2-5
4.2.4 Significant and unavoidable 4.2-15

4.4 Water Quality—Revised 4.4-1
4.4.1 Regulatory Setting 4.4-1
4.4.2 Existing Setting 4.4-7
4.4.3 Environmental Impacts 4.4-12
4.4.4 Significant and Unavoidable Impacts 4.4-28

8 PREPARERS OF THE ENVIRONMENTAL DOCUMENT 8-1
8.1 Lead Agency 8-1
8.2 EIR Consultants 8-1

9 REFERENCES 9-1

Appendices

A Curriculum Vitae of Dr. Jonathan Borak
B MTBE Oral Risk Assessment—NSF International
C Addendum to MTBE Oral Risk Assessment—NSF International
D Public Health Goal for MTBE in Drinking Water—California Office of Environmental Health Hazard Assessment (OEHHA)
E Multiple Time Point Testing of MTBE and TBA—NSF International
F Calculations of Maximum Lifetime Dose of MTBE from PEX and Associated Cancer Risk

TABLE OF CONTENTS

Exhibits

3-1 Proposed Project Area 3-1

4.2-1 Heat Damaged Plastic Pipe 4.2-8

Tables

6-4 UPC 3-4

4.2-1 Testing Standards Related to Oxidative or Chlorine Resistance of PEX 4.2-4
4.2-2 Testing Standards Related to Firestop Materials 4.2-8

4.4-1 Chemicals Possibly Present in PEX Tubing and Comparison between NSF Criteria and California Drinking Water Standards (in mg/L) 4.4-9
4.4-2 Single Time Point Extraction Levels of MTBE as a Percentage of All Products Tested 1 ..... 4.4-15

ACRONYMS AND ABBREVIATIONS

µg/L	micrograms per liter
ANSI	American National Standards Institute
ATSDR	Agency for Toxic Substances and Disease Registry
BSC	California Building Standards Commission
CCR	California Code of Regulations
CEQA	California Environmental Quality Act
CO	carbon monoxide
CO_2	carbon dioxide
Coalition	Coalition for Safe Building Materials
CPC	California Plumbing Code
CPVC	chlorinated polyvinyl chloride
dbps	disinfection by-products
DEIR	Draft Environmental Impact Report
DFA	Department of Food and Agriculture
DHS	California Department of Health Services
DPH	California Department of Public Health
DSA	Division of the State Architect
DWSAP	Drinking Water Source and Assessment Program
EIR	environmental impact report
EPA	U.S. Environmental Protection Agency
ETBE	2-Ethoxy-2-methylpropane
FEIR	Final EIR
GHG	greenhouse gas
HAA	haloacetic acids
HCD	California Department of Housing and Community Development
HDPE	high-density polyethylene
IAPMO	International Association of Plumbing and Mechanical Officials
L/day	liters per day
LADDs	lifetime average daily doses
LCR	Lead and Copper Rule

MADL	Maximum Allowable Dose Level
MCLs	maximum contaminant levels
mg/kg-day	milligrams per kilogram of body mass per day
mg/L	milligrams per liter
MRL	Minimal Risk Level
MTBE	methyl tertiary-butyl ether
NOAEL/UF	no observed adverse effect level/uncertainty factor
NO_X	oxides of nitrogen
OEHHA	California Office of Environmental Health Hazard Assessment
OSHPD	Office of Statewide Health Planning and Development
PB	polybutylene
PE	polyethylene
PEX	cross-linked polyethylene
PEX-AL-PEX	polyethylene with an aluminum layer
PHGs	public health goals
PM_{10}	fine particulate matter, respirable particulate mater
PP	polypropylene
ppb	parts per billion
ppm	parts per million
PPFA	Plastic Pipe and Fittings Association
PVC	polyvinyl chloride
ROG	reactive organic gas
STEL	short-term exposure limit
TAC	total allowable concentration
TBA	tertiary butyl alcohol
TCE	trichloroethylene
THM	trihalomethane
TMDL	total maximum daily load
UPC	Uniform Plumbing Code
VOC	volatile organic compound

1 INTRODUCTION

1.1 BACKGROUND AND PURPOSE OF THE SECOND REVISED DRAFT ENVIRONMENTAL IMPACT REPORT

In May 2008, the California Building Standards Commission (BSC) published the Draft Environmental Impact Report (DEIR) for the Adoption of Statewide Regulations Allowing the Use of PEX Tubing. The DEIR assessed the potential environmental impacts of implementing the proposed regulations. The regulations would remove from the California Plumbing Code the prohibition against the use of cross-linked polyethylene (PEX) tubing, a type of plastic pipe, for potable water uses, allowing the statewide use of PEX tubing for hot and cold water (including potable water) distribution for applications under the jurisdiction of the Responsible Agencies that adopt the regulations. This includes applications such as drinking water, irrigation, and wastewater. The proposed PEX tubing regulations would apply to all occupancies, including commercial, residential, and institutional building construction, rehabilitation, and repair under the jurisdiction of BSC and the Responsible Agencies in all areas of the state.

The DEIR was circulated for public review and comment for a period of 45 days that ended June 23, 2008. During and until the end of the review period, comments were received on the DEIR. The BSC reviewed those comments to identify specific environmental concerns and determine whether any additional environmental analysis would be required to respond to issues raised in the comments. The comment letters raised issues that resulted in the addition of significant new information to the EIR related to: 1) the leaching of chemicals from PEX tubing, 2) the thresholds of significance for water quality, and 3) the determination that certain chemicals are no longer considered constituents of concern because they are not used in PEX, or are not present in a form that poses a threat to human health. Because significant new information was added to the EIR after public notice of availability of the DEIR, a revised EIR was prepared addressing the new information and circulated for public review on October 16, 2008. Comments were received on the Recirculated DEIR, evaluated by BSC, and responses to all comments received on the DEIR and Recirculated DEIR were prepared and included in the Final EIR (FEIR). The FEIR was certified and the regulations adopted on January 22, 2009. A lawsuit challenging the adequacy of the PEX EIR was filed by the Center for Environmental Health, et al. on February 19, 2009.

In a ruling issued by the Alameda County Superior Court on December 4, 2009, the BSC was directed to remedy specific issues in the EIR, including its analysis of: non-cancer health risks from leaching of constituents from PEX pipe; genotoxic cancer health risks; taste and odor impacts; and property damage impacts from premature failure from use in continuously recirculating hot water systems. This Second Revised Draft EIR addresses those issues as well as a minor revision to reflect updated regulatory standards applicable to fittings that may be used with PEX .

The superior court ruling was appealed by the Plastic Pipe and Fittings Association, which was a party to the lawsuit, and a cross appeal was filed by the Center for Environmental Health. The appeals are pending. The effect of the appeal is to leave in place the PEX regulations approved in January 2009. As discussed in section 1.2, below, after responding to any comments received on this Second Revised Draft EIR, the PEX EIR will be considered anew by the BSC to determine whether it should be certified as having been prepared in compliance with CEQA. Following certification of the EIR, the BSC will evaluate the action it will take with regard to the PEX regulations, which could include rescinding the current regulations and readopting the regulations in their current form or with modifications to reflect changes identified as a result of this additional round of CEQA review.

1.2 CONTENT OF THE SECOND REVISED DRAFT EIR

Consistent with the requirements of Section 15088.5(c) of the State CEQA Guidelines, this Second Revised Draft EIR contains only those sections of the EIR required to be recirculated (i.e., Water Quality, Public Health and Hazards), and the changes address only those issues required by the ruling to be remedied, with one exception relating to updated regulatory standards, as noted above in section 1.1. The document consists of the following chapters and sections. All chapter and section numbering is consistent with the chapter and section numbering outline in the DEIR (released May 2008).

Chapter 1, "Introduction." Chapter 1 describes the purpose and organization of the Second Revised DEIR.

Chapter 3, "Description of the Proposed Project." Chapter 3 describes project location, background, proposed actions by the BSC, project characteristics, and project objectives. This chapter also describes PEX tubing and project regulatory requirements. No changes to the project description have occurred since publication of the DEIR in May 2008 or since publication of the Recirculated DEIR in October 2008.

Section 4.2, "Public Health and Hazards." This section describes the project's potential impacts on public health: revisions from the DEIR and/or Recirculated DEIR address the risk of premature failure and flooding, potentially leading to formation of toxic mold, as it might occur from exposure to disinfectants, as well as changes in regulatory requirements relating to brass fittings that may be used with PEX.

Section 4.4, "Water Quality." This section describes the project's potential water quality impacts: revisions from the DEIR and/or Recirculated DEIR address non-cancer health risks from leaching of constituents from PEX pipe, genotoxic cancer health risks, and taste and odor impacts.

Chapter 8, "Preparers of the Environmental Document." This chapter identifies the Second Revised Draft EIR authors and consultants who provided analysis in support of the document's conclusions.

Chapter 9, "References." This chapter sets forth a listing of all sources of information used in the preparation of the Second Revised Draft EIR, including agencies or individuals consulted during its preparation.

Appendices. Appendices contain additional materials used or relied heavily upon during preparation of the Second Revised Draft EIR.

1.3 RELATIONSHIP TO THE DEIR AND REVISED DRAFT EIR

Consistent with the requirements of Section 15087 of the State CEQA Guidelines, this Second Revised Draft EIR is being made available on May 17, 2010, for public review for a period of 45 days. The public-review period ends on July 1, 2010. During this period, the general public, agencies, and organizations may submit written comments on the Second Revised Draft EIR to the BSC. Pursuant to procedures set forth in Section 15088.5(f)(2) of the State CEQA Guidelines, reviewers are directed to limit their comments to the information contained in the Second Revised Draft EIR that has changed from the Revised DEIR. Specifically, comments should be limited to the revised discussion of the project's potential impacts on public health through the risk of premature failure and flooding from exposure to disinfectants (contained in Section 4.2.2) and the discussion of regulatory changes applicable to fittings that may be used with PEX, potential water quality impacts relating to health risks and taste and odor impacts from leaching of chemicals from PEX (contained in Section 4.4).

As required under Sections 15087 and 15088.5(d) of the State CEQA Guidelines, the BSC has sent a notice of availability to all those who submitted comments on the DEIR and RDEIR, to all organizations and members of the public who were on the distribution list for the DEIR, and to any additional persons or organizations that have requested information about the EIR since the publication of the DEIR.

Copies of the Second Revised Draft EIR are available for review online at http://www.bsc.ca.gov/pex and at the following address:

California Building Standards Commission
2525 Natomas Park Drive, Suite 130
Sacramento, CA 95833

All written comments on this Second Revised Draft EIR should be addressed to:

California Building Standards Commission
Attention: Mr. David Walls, Executive Director
2525 Natomas Park Drive, Suite 130
Sacramento, CA 95833

Public notice of availability of the Second Revised Draft EIR has been published in the *Sacramento Bee* and the *Los Angeles Times* newspapers.

After close of the comment period, the BSC will consider all comments received on this Second Revised Draft EIR , and prepare responses as required. The FEIR will consist of the DEIR, RDEIR, and Second Revised Draft EIR , comments on the DEIR, RDEIR, and Second Revised Draft EIR , responses to comments, and any text changes. The FEIR will be considered anew by the BSC for certification if it is determined that the FEIR has been completed in compliance with CEQA. Following certification of the EIR, the BSC will consider the proposed project for approval.

3 DESCRIPTION OF THE PROPOSED PROJECT

As discussed in Chapter 1, the California Building Standards Commission (BSC) in January 2009 adopted new state plumbing code regulations that removed the prohibition against the use of cross-linked polyethylene (PEX) tubing, a type of plastic pipe, for potable water uses from the California Plumbing Code. The regulations authorize PEX tubing for use in various cold and hot water (including potable water) plumbing applications in residential, commercial, and institutional buildings. As a result of a legal challenge to the EIR evaluating those regulations, BSC was directed to remedy specific issues in the EIR. This Second Revised Draft EIR addresses those issues as well as a minor revision to reflect updated regulatory standards applicable to fittings that may be used with PEX. Because the court decision invalidating the PEX EIR is currently on appeal, the regulations adopted by the BSC in January 2009 remain in effect pending BSC's revisions to the EIR. Nevertheless, this Second Revised EIR evaluates the potential environmental effect of the regulations as they were originally proposed and makes no assumption about the future status of the PEX regulations, including what action BSC may take after considering this revised EIR.

This chapter presents the location and setting of the project, project background, and project goals and objectives. In addition, it provides an overview of the project, describes the different methods for cross-linking polyethylene, and presents project alternatives.

3.1 LOCATION AND SETTING

The adoption of regulations related to PEX tubing is a statewide regulatory change. As such, the project area is the State of California (Exhibit 3-1).

Source: Created by EDAW in 2008

Proposed Project Area **Exhibit 3-1**

3.2 PROJECT BACKGROUND

BSC is a state agency responsible for approving and adopting building standards adopted or proposed by other agencies and BSC staff. Building standards ordinarily are based on model codes with any amendments or deletions deemed appropriate. Model codes are created by nonprofit organizations made up of government officials and industry representatives from across the nation, or around the globe if the model code is international. The popularity of model building codes can be attributed to two factors: (1) proprietary building codes are prohibitively expensive to develop and (2) model codes can accommodate local conditions. Modern building regulations are very complex; therefore, most jurisdictions are not technically or financially capable of developing and effectively maintaining them. Rather than drafting its own building codes, a state might choose to use the model building codes instead. The model building codes are either adopted (accepted without modifications) or adapted (modified) to a particular jurisdiction and then enforced by the adopting authority. In California, building standards approved or adopted by BSC become part of the California Code of Regulations (CCR), Title 24, also known as the California Building Standards Code, of which the California Plumbing Code (CPC) is a part. The CPC is a compilation of three types of plumbing standards from three different origins:

- plumbing standards that have been adopted by state agencies without change from plumbing standards contained in national model codes;
- plumbing standards that have been adopted and adapted from the national model code standards to meet California conditions; and
- plumbing standards, authorized by the California legislature, that constitute extensive additions not covered by the model codes that have been adopted to address particular California concerns, which become part of the CPC.

Model building codes are developed by independent standards organizations. These organizations put together a network of development committees comprising representatives from the various affected entities, both government and private. This method allows the standards organizations to pool the financial and intellectual resources to produce codes that remain current and technically sound. The model code developers are constantly working to update their codes to incorporate the latest research results and building technologies. Normally, model building codes are updated and a new edition of the model building code is published every 3 years. The adopted code is based on the most recent version of the model building code. However, because of the length of time that it takes for a jurisdiction to review and approve a new code, the currently enforced version of the state code is often not the most recent edition of the model building code. Also, when any given jurisdiction adopts a model building code, it adopts a specific edition of the model code. For example, the 2007 California Building Code is the adoption of the 2006 International Building Code with modifications, which then becomes the law of that jurisdiction. As a result of this practice, the adopted codes are not automatically updated. When a new edition of the model code is released by the model code developer, BSC and other adopting authorities may choose to ignore it and continue using the older version of the model code it adopted. California and most other jurisdictions update their codes triennially. State law requires the BSC to adopt the latest version of the model codes triennially; however, unforeseen circumstances can cause a disruption in this effort.

The model codes may either be adopted or rejected outright, or they may be adopted with amendments, deletions, or additional rules. In some cases, the amendments or additional requirements and exemptions are issued as a separate document. The State of California contracts with the International Association of Plumbing and Mechanical Officials (IAPMO) to print the California Building Standards Code, Part 5 of which is known as the CPC. The 2007 edition of the CPC incorporates, by adoption (with modifications), the 2006 edition of the Uniform Plumbing Code (UPC) model building code with the California State revisions.

IAPMO, a nonprofit organization, published the 2000 UPC, a model code, in October 1999. It included, for the first time, provisions allowing the use of PEX tubing and fittings for hot and cold water distribution, including potable water uses. Membership in IAPMO is open to anyone who has an interest in promoting the installation of safe and efficient plumbing and mechanical products (e.g., heating, ventilating, cooling, and refrigeration systems). IAPMO members are located in over 40 U.S. states and in many foreign countries including Canada, Japan, New Zealand, Mexico, and Saudi Arabia. IAPMO develops the UPC and the Uniform Mechanical Code, the world's only plumbing and mechanical codes accredited by the American National Standards Institute (ANSI). Each iteration of the UPC from 2000 to the present has maintained the approval of PEX for hot and cold water distribution.

During the adoption cycle for the 2001 triennial code, BSC proposed to adopt regulations approving the use of PEX tubing for potable water uses along with other proposed regulatory changes. However, BSC received comment letters during the regulatory process that suggested a number of potentially adverse environmental and public health effects associated with the use of PEX for potable water distribution. Based on the information in those comment letters, BSC and the Responsible Agencies withheld approval of the PEX provisions by affirmatively not adopting it for most potable water applications under their jurisdictions, pending future environmental review in compliance with CEQA. In 2006, the California Department of Housing and Community Development (HCD) sought to adopt regulations allowing use of PEX and completed an initial study/negative declaration on September 9, 2006 (HCD 2006a). However, HCD withdrew the initial study/negative declaration on October 16, 2006 because of ongoing controversy and the perceived need for more in-depth analysis.

Each iteration of the UPC from 2000 to the present has maintained the approval of PEX for hot and cold water distribution. In January 2009, California removed the prohibition in the CPC against the use of PEX tubing and fittings for hot and cold potable water distribution. See Table 6-4, "UPC" in section 3.4.2, "PEX Regulations," below, for the regulatory changes (striking out the 2001 non-adoption language) that were approved in January 2009. The January 2009 approval is currently the subject of litigation, as mentioned above.

Based on substantial evidence in the record, BSC has determined that the project had the potential to have a significant effect on the environment and therefore concluded that an EIR was required. This CEQA analysis provides the information necessary for BSC to draw conclusions regarding the potential environmental and human health effects of PEX tubing and its appropriateness for a variety of hot and cold water applications.

3.3 PROJECT OBJECTIVES

The plumbing code regulations evaluated in this EIR authorize the statewide use of PEX tubing for various cold and hot water (including potable water) plumbing applications in residential, commercial, and institutional buildings. Responsible Agencies, each of which will rely on this CEQA analysis for its own adoption of regulations, include the California Department of Housing and Community Development (HCD), Division of the State Architect (DSA), Office of Statewide Health Planning and Development (OSHPD), Department of Public Health (DPH) (previously known as DHS), and the Department of Food and Agriculture (DFA). Cities and counties are not responsible agencies because they would not have any authority to approve the project or to disapprove or add requirements or restrictions relating to the use of PEX within their jurisdictions after it is approved by BSC, unless they make express findings for such additions or deletions based on climatic, topographical, or geological conditions (CPC 101.8.1). BSC's objective in proposing these regulations is to provide an alternative plastic hot and cold water plumbing material for use in California.

3.4 PROJECT DESCRIPTION

3.4.1 PROJECT OVERVIEW

The project is the adoption of regulations (i.e., building standards) pertaining to the use of PEX tubing. The regulations allow the statewide use of PEX tubing for hot and cold water (including potable water) distribution for applications under the jurisdiction of the Responsible Agencies that adopt regulations based on environmental information and conclusions in this CEQA analysis. This includes applications such as drinking water, irrigation, and wastewater. The PEX tubing regulations apply to all occupancies, including commercial, residential, and institutional building construction, rehabilitation, and repair in all areas of the state. Examples of commercial occupancies include retail establishments, restaurants, office buildings, salons, theaters, farms, ranches, and food processing plants. Residential buildings include, but are not limited to, single-family dwellings, apartment houses, hotels, motels, lodging houses, dwellings, dormitories, condominiums, shelters for homeless persons, congregate residences, employee housing, factory-build housing, permanent buildings and permanent accessory buildings or structures constructed within manufactured home parks and special occupancy parks, and other types of dwellings containing sleeping accommodations with or without common toilet or cooking facilities including accessory buildings and facilities. Institutional building examples include schools and hospitals.

In this analysis, the terms "PEX tubing" and "PEX" refer to cross-linked polyethylene (PE) tubing also known as PEX tubing unless the context clearly indicates otherwise. These regulations are a part of the CPC, which is a part of the California Building Standards Code. BSC is responsible for the final approval and adoption of the California Building Standards Code. BSC receives proposed code revisions from a number of public agencies that have statutory authority to propose codes for various types of occupancies. The Responsible Agencies for this project have regulatory authority over the commercial, residential, and institutional occupancies to which the PEX regulations would apply.

3.4.2 PEX REGULATIONS

California Health and Safety Code Sections 18928, 18938, 17922, and 19990 direct BSC and the Responsible Agencies to adopt building standards that are reasonably consistent with recognized and accepted standards contained in the most recent editions of the UPC. California adopts the UPC on a triennial basis with modifications in strikeout for deletions and italics and underline for additions. This revised code becomes the CPC; no finalized version (i.e., without changes shown in strikeout and underlined italics) is prepared. BSC selected the 2006 UPC published by IAPMO as the model code for this code adoption cycle. The project is a change to Part 5, Title 24, CCR (hereinafter referred to as CPC), which is applicable to buildings under the jurisdiction of BSC, DFA, DPH, DSA, HCD, and OSHPD. PEX is authorized for use in radiant heating systems, manufactured homes, certain approved institutional uses, and for hot and cold water distribution, including potable water uses in some local jurisdictions (as discussed in Section 3.4.4 below). However, PEX was specifically not adopted (i.e., it was deleted) in the 2007 CPC for uses under the jurisdiction of BSC and the Responsible Agencies.

The modifications to the existing plumbing code entail the following changes. Table 6-4, "UPC" and the following text are excerpted from "The Express Terms for the Building Standards of the Building Standards Commission Regarding the Adoption of Amendments into the 2007 California Plumbing Code, California Code of Regulations," Title 24, Part 5. The changes to the regulations involve deletion of exceptions to the adoption of PEX in the CPC and adding notes reflecting the requirements of the January 2009 FEIR. As no additions are proposed to the CPC, no text is in italics.

TABLE 6-4. UPC

Material	Water Distribution Pipe and Fittings		Building Supply Pipe and Fittings
	Hot	Cold	
Asbestos – Cement			X
Brass	X	X	X
Copper	X	X	X
Cast Iron	X	X	X
CPVC	X	X	X
Galvanized Malleable Iron	X	X	X
Galvanized Wrought Iron	X	X	X
Galvanized Steel	X	X	X
PE			X
PE-AL-PE	X	X	X
PEX [1,2]	X	X	X
PEX-AL-PEX[3]	X	X	X
PVC			X

[1] When PEX tubing is placed in soil and is used in potable water systems intended to supply drinking water to fixtures or appliances, the tubing or piping shall be sleeved with a material approved for potable water use in soil or other material that is impermeable to solvents or petroleum products.

[2] PEX tubing shall meet the requirements of ASTM F 876-08 or an equivalent or more stringent standard when used in continuously recirculating hot water systems where chlorinated water is supplied to the system and the PEX tubing is exposed to the hot water 100% of the time.

[3] [BSC, DSA/SS & HCD] The use of ~~PEX and~~ PEX-AL-PEX in potable water supply systems is not adopted ~~for applications under the authority of the California Building Standards Commission, the Division of State Architect and the Department of Housing and Community Development.~~

604.1
Exceptions:

~~**(2) [For OSHPD 1, 2, 3 & 4]** Use of PEX piping is not permitted for applications under the authority of the Office of Statewide Health Planning and Development.~~

~~**(4) [For BSC]** Use of PEX piping is not adopted for applications under the authority of the Department of Health Services and the Department of Food and Agriculture.~~

604.11 PEX. ~~***[Not Adopted by BSC, HCD, DSA/SS, DHS, AGR & OSHPD 1, 2, 3 & 4]***~~Crosslinked polyethylene (PEX) tubing shall be marked with the appropriate standard designation(s) listed in Table 14-1 for which the tubing has been listed or approved. PEX tubing shall be installed in compliance with the provisions of this section.

604.11.1 PEX Fittings. ~~***[Not Adopted by BSC, HCD, DSA/SS, DHS, AGR & OSHPD 1, 2, 3 & 4]***~~Metal insert fittings, metal compression fittings, and cold expansion fittings used with PEX tubing shall be manufactured to and marked in accordance with the standards for the fittings in Table 14-1.

604.11.2 Water Heater Connections. ~~***[Not Adopted by BSC, HCD, DSA/SS, DHS, AGR & OSHPD 1, 2, 3 & 4]***~~ PEX tubing shall not be installed within the first eighteen (18) inches (457mm) of piping connected to a water heater.

~~***(2) [For OSHPD 1, 2, 3 & 4]*** *Use of PEX piping is not permitted for applications under authority of the Office of Statewide Health Planning and Development.*~~

~~***(4) [For AGR, DHS]*** *Use of PEX piping is not adopted for applications under the authority of the Department of Health Services and the Department of Food and Agriculture.*~~

3.4.3 PEX DESCRIPTION

PEX is a form of plastic tubing. The materials used in the production of plastics are natural products such as cellulose, coal, natural gas, salt, and crude oil. Crude oil is a complex mixture of thousands of compounds. To become useful, it must be processed.

The production of plastic begins with a distillation process in an oil refinery. The distillation process involves the separation of heavy crude oil into lighter groups called fractions. Each fraction is a mixture of hydrocarbon chains (chemical compounds made up of carbon and hydrogen), which differ in terms of the size and structure of their molecules. One of these fractions, naphtha, is the crucial element for the production of plastics.

The two major processes used to produce plastics are called polymerisation and polycondensation, and they both require specific catalysts. In a polymerisation reactor, monomers like ethylene and propylene are linked together to form long polymer chains. (A polymer is a compound of high molecular weight that consists of long chains of repeated, linked units known as monomers). Each polymer has its own properties, structure, and size depending on the various types of basic monomers used.

There are many different types of plastics, and they can be grouped into two main polymer families: thermoplastics (which soften when heated and then harden again when cooled) and thermosets (which never soften when they have been molded). PEX is made of PE, often high-density PE (HDPE), which is a thermoplastic. PEX is a member of the polyolefin family of polymers along with normal PE, HDPE, polypropylene (PP), and polybutylene (PB). Polyolefins are produced from oil or natural gas. They can be processed in two ways to make products—by extrusion or molding.

To manufacture plastic tubing, a process known as profile extrusion is used. This process is used to manufacture plastic products with a continuous cross section, such as drinking straws, decorative molding, window trimming, plastic pipes, and a wide variety of other products. The plastic is fed in pellet form into the extruder machine's

hopper. Then a rotating screw inside a heated barrel conveys the material continuously forward. The pellets are thus softened by both friction and heat. The softened plastic is then forced out through a die and directly into cool water where the product solidifies. This is similar to soft-serve ice cream coming out of a machine, except that the ice cream will melt rather than harden. From here it is conveyed onward into the take-off rollers, which pull the softened plastic from the die.

The die is a metal plate placed at the end of the extruder with a section cut out of its interior. This cutout, and the speed of the take-off rollers, determines the cross section of the product being manufactured. A simple way to understand this concept is to consider the shape of toothpaste as it comes out of a squeezed tube. The product comes out in a solid rod because of the opening at the end of the tube. If that opening had a differently shaped cross section, the product would take on that new cross section. Extrusion produces an inherently strong finished product, stronger than is produced by the molding process. This is one of the reasons that plastic pipe is rated at higher pressures than plastic fittings that are injection molded.

Cross-linked PE, or PEX, is a high-density plastic that is an alternative to ferrous and nonferrous piping for water distribution, such as copper, enamel coated steel, and chlorinated polyvinyl chloride (CPVC) plastic piping. Normal PE is unsuitable for hot water uses because it softens at elevated temperatures. However, for PE to be suitable for hot water uses, the individual polymer chains must be “cross-linked” together with supplemental chemical bonds, which occurs during the PEX manufacturing process. In addition to cross-linking the polyethylene, other chemicals are added to the resin to prevent oxidation and ultraviolet light from weakening the tubing, which could lead to tubing failures. Such additives include antioxidants, ultraviolet blockers, fillers, and pigments.

3.4.4 CURRENT AND PROJECTED USES OF PEX

As indicated above, the following discussion of current and projected uses of PEX assumes conditions in place prior to approval of the PEX regulations and does not reflect the January 2009 approval by the BSC and Responsible Agencies of regulations authorizing statewide use of PEX, or any resulting actions by local agencies that may have occurred as a result of that action.

Use of PEX tubing is currently allowed throughout California for hydronic heating systems and all uses including potable water in manufactured homes. In the majority of existing buildings in California, including residential buildings, potable water pipe is made of metal, though CPVC plastic pipe was recently approved for statewide potable water uses, including use in residential buildings, beginning January 1, 2008. PEX tubing may also be used if it is approved by local ordinance or if the local agency with jurisdiction has approved it as an alternate material under the Alternate Materials, Methods of Design, and Methods of Construction provisions of the CPC. This provision authorizes local building officials to approve, on a project-by-project basis, alternate materials, provided the building official finds that the proposed design is satisfactory and complies with the provisions of the technical codes, and that the material, method, or work offered is, for the purpose intended, at least the equivalent of that prescribed in the technical codes in suitability, strength, effectiveness, fire resistance, durability, safety, and sanitation. (See California Health and Safety Code Section 17951[e], CPC 301.1 et seq. and CPC 108.7 et seq.) Such approval requires that the project proponent submit proof to support the building official’s findings. It also must be recorded and entered in the local building departments files. Under these provisions, building officials may require an applicant to arrange for an outside agency designated by the building official at the applicant’s expense to review an evaluation of the proposed alternate materials, methods of design, and methods of construction. In contrast, in the three jurisdictions that have approved the use of PEX by ordinance, no special approvals or submittals are needed to use PEX in a project.

Nearly 200 California cities and nearly 30 California counties have approved the use of PEX tubing in various cold and hot water plumbing (including potable water) applications in residential, commercial, and institutional buildings within their jurisdictions using the alternate materials provisions. In addition, at least three California cities (Palo Alto, Highland, and Santa Clarita) have adopted ordinances allowing the use of PEX tubing for all uses

approved in the UPC without requiring special documentation. PEX currently makes up approximately 37% of the market for plumbing materials in new single-family homes in California. If the PEX regulations are adopted, PEX would be used in cities and counties that do not currently allow its use, and use of PEX would be expected to increase in the cities and counties that already allow PEX as an alternate material.

As of 2005 the market share for plumbing materials for all types of uses (including hydronic radiant heating and potable water distribution) in new homes in California was approximately 29% PEX, 13% CPVC, 54% copper, and 4% for all other materials. Market share, in this instance, means the percentage of new single-family homes that were plumbed with PEX. Other plumbing materials include galvanized steel and PEX-AL-PEX (polyethylene with an aluminum layer). (HCD 2006b and Ash, pers. comm. 2008.) Though more current market share data for copper and CPVC is not available, the most current data for PEX (2006) indicates that its share of the market for plumbing materials in new homes in California was approximately 37% (Ash, pers. comm. 2008). The net effect of adoption of the proposed regulations would probably be an increase in the use of PEX tubing, with a proportionate decrease in the use of other piping materials, particularly copper, because of the reduced labor costs associated with installation of PEX and also because of corrosivity issues with copper piping resulting from the increased use of chloramines for drinking water disinfection.

3.5 REGULATORY REQUIREMENTS, PERMITS, AND APPROVALS

Two independent but related processes are taking place with regard to the PEX regulations: the regulatory process and the EIR process. If, after this EIR is certified, BSC determines that the EIR supports a decision to approve the PEX regulations, BSC may rely on the certified final EIR for subsequent approval of the regulatory changes. In addition, the certified EIR will be forwarded to the Responsible Agencies, which may also rely on the final EIR for changes to their regulations, to the extent that those changes are within the scope of this EIR.

3.6 SCOPE OF THIS EIR

The project is limited to the adoption of plumbing regulations to allow use of PEX tubing in a variety of hot and cold water applications (including potable water). These uses would apply to commercial, residential, and institutional building projects under the jurisdiction of the Lead Agency and Responsible Agencies in all California cities, cities and counties, and counties. The EIR does not assess any specific project that involves direct construction or modification to structures. Therefore, the environmental review does not include site specific analyses. In addition, the EIR does not evaluate the use of PEX-AL-PEX. PEX-AL-PEX is PEX tubing with a layer of aluminum embedded between the PEX layers. The regulations do not address certain other potential uses of PEX tubing, such as for specific industrial or medical devices or machines. Uses other than cold and hot water plumbing uses (including potable water uses) for commercial, residential, and institutional buildings are beyond the scope of this project and thus beyond the scope of this EIR.

4.2 PUBLIC HEALTH AND HAZARDS—REVISED

As described in Chapter 1, Introduction, a lawsuit was filed in early 2009 that challenged the adequacy of the EIR upon which the California Building Standards Commission (BSC) based its decision to approve use of PEX pipe for potable water uses in California. As a result, BSC was directed to remedy specific issues in the EIR regarding the analysis of public health and hazards. Consequently, this section includes revisions to the analysis of the potential for PEX to fail when used in continuously recirculating hot water systems; addresses regulatory changes adopted since publication of the draft environmental impact report (DEIR) that pertain to the standards used to test chlorine resistance of PEX under traditional and continuously recirculating hot water systems; and includes revised wording to requirements presented in Mitigation Measure 4.2-1 as a result of these changes. The section also has been updated to reflect regulatory changes adopted since publication of the DEIR that pertain to brass fittings that may be used with PEX.

This section evaluates potential public health and hazards impacts associated with the proposed project, specifically impacts related to biofilm, fire hazards, and mold. Background data and analyses are based primarily on technical studies submitted by the California Department of Housing and Community Development, the Plastic Pipe and Fittings Association, and the Coalition for Safe Building Materials. Particularly relevant studies and references are included in the appendices of this DEIR; all studies and references cited in this DEIR are available for review at the Building Standards Commission address included on page 1-3 . This analysis is limited to plumbing applications of PEX for use in a variety of hot and cold water (including potable water irrigation and wastewater) applications for commercial, residential, industrial, and institutional building projects. Water quality impacts associated with the proposed project are considered in Section 4.4, "Water Quality."

4.2.1 REGULATORY SETTING

FEDERAL PLANS, POLICIES, REGULATIONS, AND LAWS

Occupational Safety and Health Administration

The U.S. Congress created the federal Occupational Safety and Health Administration (OSHA) under the Occupational Safety and Health Act in 1970 (Title 29, U.S. Code, Section 651 et seq. [29 USC 651 et seq.]). The act was adopted in response to concerns for worker safety and encourages states to develop and operate their own job safety and health programs, which OSHA approves and monitors (29 USC 667). OSHA has approved the California state plan (OSHA 2008).

The *OSHA Technical Manual*, Section III, Chapter 2 (Davis 2001) refers to molds as a potential indoor air quality concern. This document suggests guidelines to employers on how to respond to employee complaints regarding indoor air quality, including recommendations for removal of offending organisms. Molds are one of several air contaminants mentioned as possible causes of building-related illnesses.

STATE PLANS, POLICIES, REGULATIONS, AND LAWS

State of California regulations related to the potential health and safety hazards of using PEX are described below. No State of California regulations pertain specifically to biofilm. However the federal and state Safe Drinking Water Acts address biofilm indirectly through the regulation of bacteria and the requirement for disinfection of most drinking water. For a discussion of drinking water disinfection requirements, please see Section 4.4, "Water Quality."

California Occupational Safety and Health Administration

The California Department of Industrial Relations enforces regulations governing workplace safety and health through the California Occupational Safety and Health Assessment Program (Cal/OSHA Program). Cal/OSHA sets regulations for acceptable exposure levels for airborne substances that can be harmful to workers. Some of

these substances are present in adhesives solvents commonly used in construction and required to join chlorinated polyvinyl chloride (CPVC) fittings. Installation of PEX does not require (and PEX is not compatible with) solvents or glues. Therefore, it does not generate airborne substances in the workplace that would be subject to these regulations.

The Occupational Health Branch of the Department of Public Health (OHB) is mandated to review new and emerging occupational hazards and propose new regulations to the California Division of Occupational Safety and Health (Cal/OSHA). As a result of a proposal by the OHB, Cal/OSHA is considering adding standards for molds to the sanitation standard for office buildings and workspaces (Davis 2001). OHB has created a "Molds in the Indoor Workplace" handout, which addresses these concerns (DPH 2008).

Toxic Mold Protection Act of 2001

The Toxic Mold Protection Act directs the Department of Health Services (now known as the Department of Public Health [DPH]), assisted by a task force of volunteer stakeholders, to undertake a series of tasks. These include determining the feasibility of adopting permissible exposure limits for indoor molds and the development of new standards or guidelines to:

- assess the health threat posed by the presence of indoor molds,
- determine valid methods for fungal sampling and identification,
- provide practical guidance for mold removal and abatement of water intrusion,
- disclose the presence of mold growth in real property at rental or sale, and
- assess the need for standards for mold assessment and remediation professionals.

However, the implementation of this statute depends on the provision of funding to accomplish these tasks. No funding has been provided by the state, and DPH has been soliciting donations from the public to raise the needed funding. Given the state budget situation and the current economic climate, it is unlikely that progress will be made on the implementation of this law in the near future.

The State of California does not have any regulations or thresholds that pertain to mold. In response to increasing queries about mold toxicity, the DPH Indoor Air Quality Program has developed a Web site that includes a variety of documents related to this issue. This section includes a document specific to residential exposure titled "Mold in My Home: What Do I Do?" (DHS 2001).

California Plumbing Code Firestop Standards (Title 24 of the California Code of Regulations, Part 5)

The California Plumbing Code (CPC) specifies standards for firestop protection and standards for plumbing that penetrates firestop structures. Firestops are structures within buildings that slow the spread of fire. A very common firestop structure consists of 2- x 4-inch horizontal wood blocking that is installed between vertical 2- x 4-inch studs inside wood-framed structures. The fire and heat retarding standard is normally expressed as the time that the structure may be exposed to specific fire conditions before allowing fire to spread or ambient temperatures to increase to a specified level. CPC Section 1501.0 et seq. specifies firestop standards for plumbing and plumbing assemblies that penetrate firestops.

Section 1505.2 specifies that when plumbing penetrates a firestop structure, the firestop capability of the structure shall be restored to its original rating. This means that the firestop structure through which the plumbing is installed must be able to withstand and retard the spread of fire for at least the same period of time at the same temperature as it would without the plumbing. This requires the use of a "penetration firestop system": an assembly of materials that surrounds the plumbing penetration of the firestop structure and is designed to retain the firestopping capabilities (Section 1504.1). The CPC specifies that these penetration firestop systems for plumbing structures meet standards of the American Society for Testing Materials Standard (ASTM), specifically the ASTM E 119 or E 814 tests for firestopping capability.

These tests are specific procedures for testing the firestopping capabilities of penetration firestop systems (or plumbing penetrations) by exposing the systems to fire and incineration. The CPC specifies that plumbing penetrations of floors must meet specific standards related to temperature retardation (T rating) and other penetrations must meet specific standards related to fire retardation (F rating). A T rating is the time period that the firestop and plumbing penetration takes to allow an increase in 325°F above ambient temperatures on one side of the structure when exposed to heat on the other side of the structure. Plumbing penetrations of floors must have a T rating of at least 1 hour (Section 1505.3). An F rating is the time period that the firestop and plumbing penetration can limit the spread of fire, under exposure to flame and heat. Plumbing penetrations must have an F rating of at least 1 hour (Section 1505.3).

4.2.2 EXISTING SETTING

As discussed above, in January 2009, the Building Standards Commission certified a Final EIR for this project and regulations removing the prohibition against the use of PEX were adopted. In February 2009, a lawsuit was filed challenging the adequacy of the January 2009 FEIR. The trial court rejected some of the challenges to the 2009 FEIR, and also found that the document did not contain substantial evidence to support certain findings that are further analyzed in this SRDEIR. The trial court's decision is presently on appeal, and as a result, the trial court's judgment is stayed, i.e., the regulations adopted in January 2009 remain in effect. Following the public comment period on this SRDEIR, the Building Standards Commission and the responsible agencies will exercise their discretion to determine the adequacy of this SRDEIR and subsequent actions with respect to the PEX regulations. Although the PEX regulations remain in effect, the following discussion of the existing setting assumes conditions in place prior to the January 2009 approval of the statewide PEX regulations, or any actions by local agencies that may have occurred as a result of that action.

The statewide use of PEX tubing is currently allowed in California for hydronic heating systems and potable water in manufactured homes. Additionally, nearly 200 California cities and nearly 30 California counties have approved the use of PEX tubing in various cold and hot water plumbing (including potable water irrigation and wastewater) applications in residential, commercial, and institutional buildings within their jurisdictions using the Alternate Materials, Designs, Tests and Methods of Construction provisions of the CPC (CPC 108.7 et seq.). In addition, at least three California cities (Palo Alto, Highland, and Santa Clarita) have adopted ordinances allowing the use of PEX tubing for a variety of cold and hot water applications. (Adoption by ordinance precludes the need for case-by-case assessment of PEX uses.) If the lead and responsible agencies approve this project, increased use of PEX is anticipated in the cities and counties that currently allow PEX as an alternate material, and use of PEX is expected in the city and county jurisdictions that do not currently allow it.

The current market share of other allowable plumbing materials establishes the context for existing hazards and public health concerns as they relate to the proposed project. As discussed in Chapter 3, "Description of the Proposed Project," as of 2005 the market share for various plumbing materials for all types of uses (including hydronic radiant heating, and potable water distribution) in new homes in California was 29% PEX, 13% CPVC, 54% copper, and 4% for all other materials. Other plumbing materials include galvanized steel and cross-linked polyethylene with an aluminum layer (PEX-AL-PEX). (HCD 2006; Ash, pers. comm., 2008). The most current data for PEX (2006) indicates that its share of the market for plumbing materials in new homes in California was 37% (Ash, pers. comm., 2008). The net effect of the regulations would probably be an increase in the use of PEX tubing, with a proportionate decrease in the use of other piping materials, particularly copper because of copper corrosion issues arising from using chloramines for disinfecting drinking water.

PEX is an approved pipe material in the Uniform Plumbing Code (UPC), International Plumbing Code (Church, pers. comm., 2007:1), and the International Residential Code (Brown, pers. comm., 2007:1). These plumbing codes require PEX piping to be third-party certified to applicable standards for various performance criteria, depending on the type of use. Performance standards are continually being updated to reflect the best available scientific information and to address issues related to product performance. Testing standards related to oxidative/chlorine resistance of PEX are listed below in Table 4.2-1.

Table 4.2-1 Testing Standards Related to Oxidative or Chlorine Resistance of PEX			
Testing Standard	Title	Purpose	Service Life
NSF International/American National Standards Institute[1]			
NSF/ANSI 14	Plastic Pipe System Components and Related Materials	Physical strength, performance, health effects	50 years
American Society for Testing Materials (ASTM)			
ASTM F2023-05[2]	Standard Test Method for Evaluating the Oxidative Resistance of Cross-linked Polyethylene (PEX) Tubing and Systems for Hot Chlorinated Water	Oxidative resistance test method	
ASTM F876-08[3]	Standard Specification for Cross-linked Polyethylene (PEX) Tubing	Product design, pressure strength, oxidative (chlorine) stability, environmental stress cracking	50 years
ASTM F877	Standard Specification for Cross-linked Polyethylene (PEX) Plastic Hot- and Cold-Water Distribution Systems	Product design, pressure strength, thermocycling resistance, bend strength	

Notes:
[1] Between 1999 and 2009, two non-consensus standards were available to test chlorine resistance under traditional and continuously recirculating systems—NSF P171-CL-TD and NSF P171-CL-R. Due to the promulgation in late 2008 of national consensus standard ASTM F876-08, which addresses chlorine resistance in both traditional and recirculating (100% hot water) systems, NSF P171-Cl-TD and NSF P171 CL-R were withdrawn.
[2] Applies to traditional domestic hot and cold potable water applications (assumes 25% hot water and 75% room temperature water).
[3] Applies to both traditional domestic applications and 100% hot water recirculation.
Source: Data compiled by Ascent in 2010

ASTM is an independent, nonprofit, standards-writing organization. It issues standards in many diverse technical disciplines. ASTM is the forum for a majority of standards in the United States, especially those related to plastic materials and products testing (NSF International 2008). ASTM standards are national consensus standards which are voluntary and developed by representatives of sectors that have an interest in the use of the standard. Represented sectors can include producers, users, and those having a general interest (representatives of government and academia), as well as ultimate consumers. While NSF standards are not national consensus standards, the actual physical testing methods and protocol are the same as ASTM standards. Testing of PEX piping is performed under conditions of continuously flowing hot water at 203°, 221°, and 239°F. The test results are then used in a regression analysis to extrapolate to water temperatures of 140°F (hot water) and 73°F (cold water).

NSF International, a nonprofit organization, is the most widely recognized agency for a listing of plumbing products in the United States. In a publicly searchable database, NSF indicates (i.e., lists) which products by which manufactures are certified under which standards. (See http://www.nsf.org/Certified/PwsComponents.)

Following are details about the various NSF International and ASTM standards that address product lifespan that may be applicable to PEX.

NSF/ANSI Standard 14: This standard establishes minimum requirements for physical performance, health effects, quality assurance, marking (labeling), quality control testing, test frequencies at each production location, and record keeping requirements for plastic piping components and related materials, including fittings used with PEX. Under NSF/ANSI Standard 14, PEX tubing must be marked (i.e., labeled) at intervals of no more than 5 feet and must include:

- the manufacturer's name or trademark;
- the testing standards to which it conforms;
- tube size;
- material designation code (i.e., PEX0006);
- pressure/temperature rating(s);
- Standard Dimension Ratio (SDR) (a formula that represents the pipe diameter divided by the wall thickness);
- if the tubing is for potable water, a laboratory seal or mark attesting to suitability for potable water; and
- ASTM fittings designations approved for use by the tubing manufacturer.

This standard also requires that materials used for pressure pipes, including PEX, meet a minimum 50-year, long-term strength requirement (Brown, pers. comm., 2007:2). The most recently adopted version of the California Plumbing Code, the 2010 CPC, requires that PEX comply with NSF/ANSI 14-2007. (2010 CPC Table 14-1; Walls, Pers. Comm. 2010). Since adoption of the 2010 CPC a more current version of NSF/ANSI 14, NSF 14-2009, has been adopted. All PEX tubing and related materials such as fittings will have to comply with NSF 14-2009 to be certified by NSF for carrying potable water.

ASTM F2023-05*, Standard Test Method for Evaluating the Oxidative Resistance of Cross-linked Polyethylene (PEX) Tubing and Systems to Hot Chlorinated Water:* This standard was most recently updated in 2005. This test procedure is designed to provide an estimate of the life expectancy of a hot-water plumbing pipe when used at a water temperature of 140°F and a pressure of 80 pounds per square inch (psi) (NAHB Research Center 2006:9). This standard lists the requirements and test methods for evaluating PEX tubing in long-term contact with hot, chlorinated water. Most plumbing systems are traditional domestic systems (Theilen, pers. comm., 2008). In these systems, the hot water pipes are exposed to hot water only when the tap is turned on and hot water is flowing through the system. The rest of the time, they are at room temperature (NSF International 1999). (Brown, pers. comm., 2007:3).

ASTM F876-08*, Standard Specification for Cross-linked Polyethylene (PEX) Tubing*: This is a national consensus standard adopted in 2008 designed to ensure the reliability of PEX piping systems in various hot and cold water applications. The standard requires that all PEX intended for use with potable water have a minimum extrapolated lifetime of 50 years when tested in accordance with test method ASTM F2023 (National Association of Home Builders [NAHB] Research Center 2006):9). This standard also addresses longevity of PEX in systems with continuous circulation of hot chlorinated water. This refers to systems in which hot water is recirculated through the hot water side of the plumbing system. In general, these systems are relatively rare and are mainly found in the commercial sector (e.g., hotels) and in some large homes (Theilen, pers. comm., 2008).

ASTM F877*, Specification for Cross-linked Polyethylene (PEX) Plastic Hot and Cold Water Distribution Systems*: This requires a pressurized flow-through test system, typical test pressures, test-fluid characteristics, failure type, and data analysis (ASTM 2008a). Additionally, PEX piping systems use fittings that also must comply with ASTM standards, and are made from brass, copper, or high-temperature engineered polymers that are chlorine resistant (NAHB Research Center 2006:9).

4.2.3 ENVIRONMENTAL IMPACTS

ANALYSIS METHODOLOGY

This analysis is based on a review and evaluation of existing information and reports documenting studies and conclusions from scientists, tubing manufacturers, and agencies. Relevant materials and information sources include:

- documents published by federal, state, and local agencies;
- consultation with California construction and plumbing industry experts;
- consultation with knowledgeable individuals of state and local agencies; and
- other documents and information contained in the project administrative record.

THRESHOLDS OF SIGNIFICANCE

For purposes of this analysis, the following applicable thresholds of significance were used to determine whether implementing the proposed project would result in a significant impact related to public health and hazards. The project would result in a significant impact if it would result in:

- a substantial increase in the public health risks associated with biofilm,
- substantial increase in fire hazard,
- substantial premature tubing failure and flooding that would lead to widespread incidences of mold infestation associated with significant health risks, or
- substantial safety hazards for plumbers.

IMPACT ANALYSIS

As described in Chapter 3, "Description of Proposed Project," the proposed project is a code change, adoption of regulations, and not a typical site-specific development project. As such, the project would not involve routine transport, use, or disposal of hazardous materials, and specific considerations of the initial study checklist (i.e., location near a public airport or school, interference with emergency plans) would not apply. These issues are not discussed further.

The potential for leaching of or permeation by toxic chemicals is assessed in Section 4.4, "Water Quality."

IMPACT 4.2-1 Public Health and Hazards—Potential Risk of Contact with Pathogens from Biofilm Growth. *Because biofilm could potentially harbor pathogenic bacteria such as* Legionella*, higher amounts of biofilm could lead to increased risk of human contact with pathogenic bacteria. All piping materials exhibit some biofilm formation (Chaudhuri, pers. comm., 2008). Although formation of biofilm is initially slower in copper tubing compared to PEX tubing, no substantial difference exists over longer periods. No direct quantitative correlation exists between measurements of biofilm and growth of* Legionella*. Therefore, increased biofilm growth does not correspond to higher amounts of* Legionella *bacteria, and the use of PEX would not lead to increased risk of human contact with pathogenic bacteria. Therefore, this is considered a* ***less-than-significant*** *impact.*

A concern exists that PEX promotes the growth of biofilm to a greater degree than other types of plumbing piping and tubing, such as copper. Because biofilm could potentially harbor pathogenic bacteria such as *Legionella*, higher amounts of biofilm could potentially lead to increased risk of human contact with pathogenic bacteria. *Legionella pneumonophila* causes Legionnaire's disease. Some studies show that PEX displayed the strongest biofilm formation and the strongest promotion of the growth of *Legionella* bacteria and that copper piping inhibits the growth of *Legionella* bacteria (Coalition for Safe Building Materials 2005:41–42).

Biofilms are a collection of microorganisms surrounded by the slime they secrete, attached to either an inert or living surface (Edstrom Industries 2008). Biofilms are common in nature. They are usually found on solid substrates submerged in or exposed to some aqueous solution. Biofilms may form on any surface exposed to bacteria and some amount of water. A biofilm can be formed by a single bacterial species, but more often biofilms consist of many species of bacteria, as well as fungi, algae, protozoa, debris, and corrosion products. Bacteria commonly have mechanisms by which they adhere to surfaces and to each other. In residential and commercial environments, biofilms can develop on the interiors of pipes and lead to clogs and corrosion. MNB Momba et al. 2000 define the term biofilm as a layer of microorganisms in an aquatic environment held together in a polymetric matrix attached to a substratum such as pipes or tubing. The matrix consists of organic polymers that are produced and excreted by the biofilm microorganisms. Biofilms are sometimes formed as continuous, evenly distributed layers but are often patchy in appearance. Biofilms in water distribution systems are thin, reaching a maximum thickness of perhaps a few hundred micrometers (MNB Momba et al. 2000). Biofilm is analyzed in studies as the number of total bacteria, heterotrophic plate counts (an indicator of bacteria cell counts), or the concentration of

adenosine triphosphate per surface area (which correlates with direct bacterial cell counts) of biofilm (Markku et al. 2005). Biofilms are a public health concern because they could potentially harbor pathogens, such as *Legionella pneumophila*, which causes Legionnaire's disease.

Although some studies show greater formation of biofilm in PEX tubing as compared to copper (Veenendaal and van der Kooij 1999) these results were reported after a relatively short duration (less than 250 days). Because plumbing pipes or tubing installed in buildings are generally used for many years, the studies evaluating biofilm formation over longer time periods (between 250 days and 2 years) provide more relevant results than studies evaluating biofilm formation over shorter time periods. Dick van der Kooij of KIWA Research presented the results of a study where bacteria were allowed to grow for an additional 300 days beyond the duration of the original study (described above) at a *Legionella* congress in Amsterdam (2006). The longer duration study showed that *Legionella* growth was approximately the same in copper as in PEX. The study authors hypothesize that the amount of *Legionella* on copper is low in the beginning because of the release of copper ions, which have a toxic effect on the *Legionella* bacteria. However, over a period of time a biofilm layer is created that may serve as a barrier, thus preventing or lessening the release of copper ions and ultimately reducing the toxic effect on the Legionella.

Perhaps more importantly from a public health perspective, the studies indicate that there does not appear to be a direct connection between quantities of biofilm and *Legionella,* nor does *Legionella* occur at higher rates in PEX than in copper. One of the conclusions of the study conducted by Veenendaal and van der Kooj (1999), discussed above, was that though there was greater formation of biofilm in PEX during the 200-day testing period, there was no direct relationship between biofilm formation and growth of *Legionella* and measurements of *Legionella* growth in copper and PEX were not substantially different after 200 days. Van der Kooij et al. (2005) studied biofilm formation and growth of *Legionella* with pipes of copper, stainless steel and PEX. The authors found that *Legionella* concentrations in water and biofilms were at the same levels for all materials after 2 years. Therefore, increased biofilm growth does not correspond to higher amounts of *Legionella* bacteria, and the use of PEX would not lead to increased risk of human contact with pathogenic bacteria. Therefore, this is considered a **less-than-significant** impact.

Mitigation Measure

No mitigation measures are necessary because the impact is less than significant.

IMPACT 4.2-2 **Public Health and Hazards—Increased Risk of Fire Ignition and Fire Spread.** *PEX tubing carrying water within a building is not likely to be flammable. Conformance to CPC requirements and applicable design and installation guidelines, including the use of approved firestop material, would reduce any potential fire hazards–related depressurization of plastic tubing during structural fires. Additionally, plastic tubing is not an efficient heat conductor and structure fires generally do not exceed the temperature necessary to cause plastic tubing to ignite, thus the use of PEX would not increase fire hazards. Therefore, this impact is* ***less than significant****.*

Comments have been made that when filled with water, PEX is not likely to be flammable, but when exposed to heat during a fire, the PEX may rapidly rupture. PEX rupture may drain or depressurize the plumbing system and create openings in wall studs that may encourage the spread of fire (Coalition for Safe Building Materials 2005:44). Concerns exist that the use of PEX tubing poses a significant fire threat because of the highly flammable characteristics of PEX (Coalition for Safe Building Materials 2005:44).

Both copper and plastic tubing are often inserted perpendicularly through 2- x 4-inch wall studs. Heat generated during structural fires may cause PEX to burst or melt. The burst or melted tubing may result in an opening between the tubing and the 2 x 4 (Exhibit 4.2-1). Thus, the wall stud would no longer be sealed. This type of opening could depressurize the space and may encourage the spread of fire.

PEX has characteristics similar to other plastic pipes that have been studied and tested more rigorously than PEX. Fire ignition is the means by which things catch on fire. Plastic pipes and tubing have low thermal conductivity, so fire ignition or a threat of fire spread from high temperatures or heat conduction along plastic pipes that penetrate wood wall studs is highly unlikely (PM Engineer 2003:2–3). Additionally, a database review of fires related to the

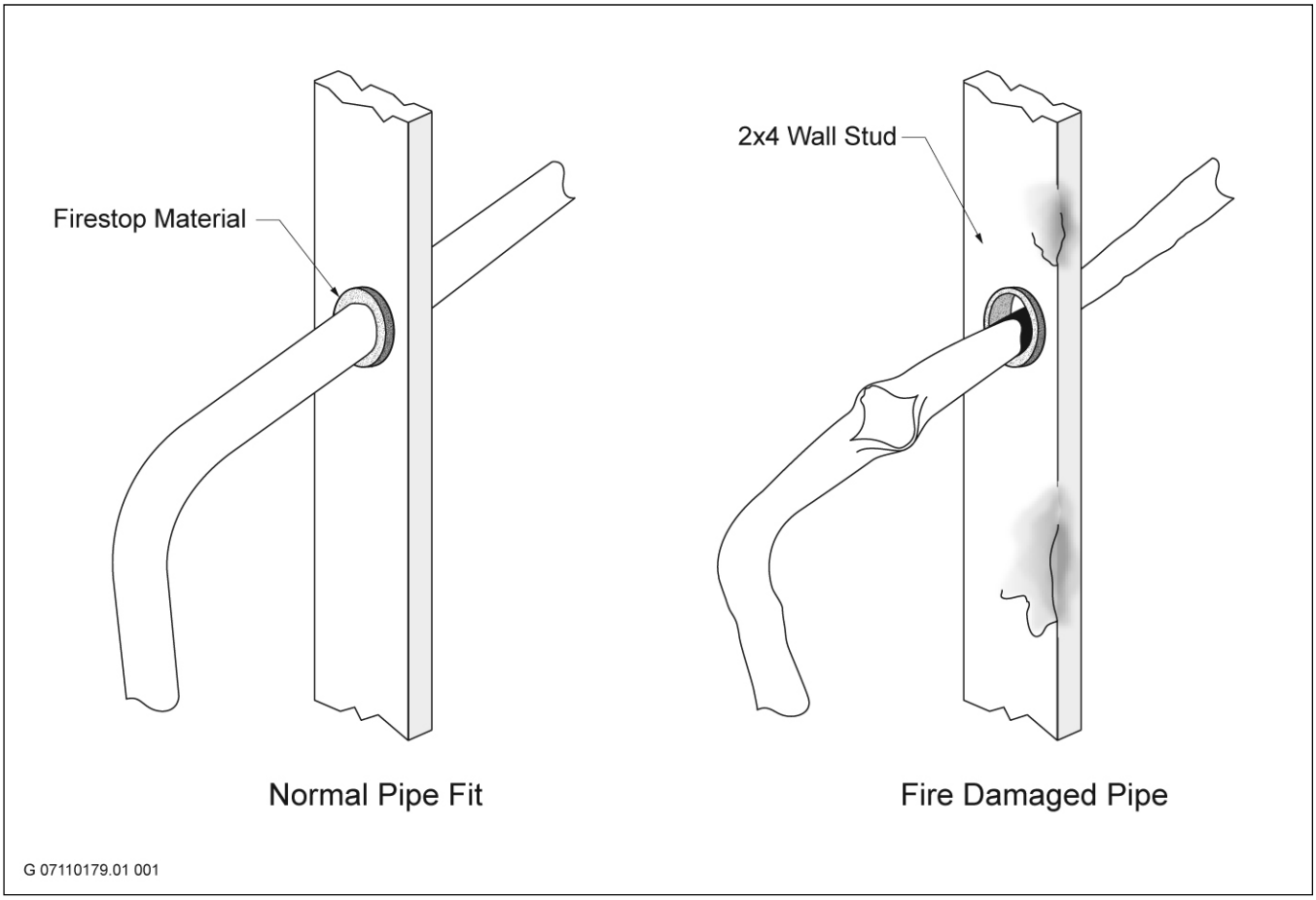
use of plastic pipes during the last 40 to 50 years in the United States concluded that the use of plastic pipe presents no unique fire hazard and does not demonstrate unique issues concerning fire ignition or the spread of fire (Zicherman 2000:6). While temperatures in wall cavities may cause plastic to melt during the early stages of a structural fire, the temperatures are still far too low to cause the plastic to catch on fire (PM Engineer 2003:3). In addition, no studies or evidence demonstrates that depressurized pipes are a substantial fire hazard. Because PEX is not flammable and does not encourage fire spread, its use would not result in increased fire hazard.

CPC Chapter 15, Section 1506.3, specifies that [pipe] "[p]enetrations shall be protected by an approved penetration firestop system installed as tested in accordance with ASTM E 119 or ASTM E 814." ASTM E 119, *Standard Test Methods for Fire Tests of Building Construction and Materials*, provides a relative measure of the fire-test-response of comparable building elements under certain fire exposure conditions (ASTM 2008b). ASTM E 814, *Standard Test Method for Fire Tests of Through-Penetration Fire Stops*, is applicable to through-penetration firestops of various materials and construction (Table 4.2-2). Firestops are intended for use in openings in fire-resistive walls and floors that are evaluated in accordance with ASTM E 119 (ASTM 2008b).

Table 4.2-2
Testing Standards Related to Firestop Materials

Testing Standard	Title	Purpose
ASTM E 814	Standard Test Method for Fire Tests of Through-Penetration Fire Stops	Firestop compatibility
ASTM E 119	Standard Test Methods for Fire Tests of Building Construction and Materials	Firestop compatibility

Source: Data compiled by EDAW in 2008.



Source: Data compiled by EDAW in 2008

Heat Damaged Plastic Pipe **Exhibit 4.2-1**

CPC specifies that plumbing penetrations of floors must have a T rating of at least 1 hour (Section 1505.3), and other penetrations shall have an F rating of at least 1 hour (Section 1505.3). An F rating is based on flame occurrence on the unexposed surface, while the T rating is based on the temperature rise and flame occurrence on the unexposed side of the fire stop. Both of these ASTMs are used to measure and describe the response of materials, products, or assemblies to heat and flame under controlled conditions associated with the T and F ratings (ASTM 2008a).Therefore, PEX products that are certified under these ASTMs are in compliance with CPC Section 1506.3.

Conformance to the applicable design and installation guidelines, such as using the approved firestop material, can prevent any potential for fire hazards related to depressurization of plastic pipes (PM Engineer 2003:4). Eight studies in PM Engineer 2003 discuss fire endurance tests involving cavity wall constructions containing plastic pipes. Each test demonstrated that successful installations can be made using generic firestop materials for smaller diameter pipes and approved penetration firestop systems for larger diameter pipes. These studies cited tests that were conducted at federal and university labs and third-party testing facilities. The use of plastic plumbing does not reduce fire endurance of firestop material provided that the pipe penetrations are properly designed, sized, and sealed (Zicherman 2000:4). The use of approved firestop material would either prevent pipe rupture or actively fill the ruptured pipe space within the wall stud. Therefore the use of plastic pipes, including PEX, is not likely to increase fire ignition and fire spread.

As noted in a letter submitted by the California Department of Forestry, Office of the Fire Marshal (Reinertson, pers. comm., 2006:1), the development of firestop materials, requirements currently in the California Building Standards Code, and 2006 UPC provisions adopted in the 2007 California Building Standards Code (Walls, pers. comm., 2008) all mitigate the fire spread hazard associated with PEX. The letter from the California State Fire Marshal confirms that the adopted Uniform Building Code provisions and other applicable requirements mitigate the possibility of fire spread associated with the use of PEX. The use and proper installation of approved firestop materials would prevent pipe rupture. Therefore, the use of PEX would not result in increased fire hazard.

For discussion of PEX compatibility with certain firestop compounds, please see the discussion below in Impact 4.2-3.

The Plastic Pipe and Fittings Association has tested and compiled information on the firestop capabilities of various plumbing penetrations of walls and other structures (Ackerman, Cen, and Wilging 2004). This document provides diagrams of tested configurations for plumbing penetrations of firestop structures and the T and F ratings for those structures. These tests show possible configurations for floor penetrations using PEX that have both T and F ratings of 2 hours. They also show wall penetrations that have T and F ratings of 1 hour. As demonstrated by the above described configurations, with appropriate fittings and structural penetrations PEX can meet the firestop standards adopted in California. Sample firestop assemblies and system configurations for floors and walls can be found in Appendix D (Ackerman, Cen, and Wilging 2004). Because PEX meets the firestop standards specified in the California Administrative Code, Section 1501.1 et seq., use of PEX would not increase fire hazards or encourage fire spread. Therefore, this impact is considered **less than significant.**

Mitigation Measure

No mitigation measures are necessary because the impact is less than significant.

IMPACT 4.2-3 **Public Health and Hazards—Risk of Premature or Unexpected PEX Failure and Flooding Potentially Increasing the Incidence of Mold.** *Ultraviolet (UV) light, disinfectants such as chlorine, and certain firestop materials can contribute to failure of PEX. However, PEX manufacturers add UV-resistant material into the pipe and include instructions as to how to avoid UV degradation, which decreases the potential for any adverse impact of UV light on PEX. Numerous firestop materials are compatible with PEX and, when appropriately used, firestop materials do not degrade PEX. Finally, there is some evidence that PEX exposed to potentially harsh conditions, such as those found in continuously recirculating hot water systems, may be subject to premature degradation by the oxidants found in common potable water disinfectants and might have a shorter product life than copper, CPVC, or PEX used in traditional domestic applications. However, the possibility that PEX would fail prematurely*

as a result of degradation by disinfectants in continuously recirculating hot water systems is considered to be remote. Continuously recirculating hot water systems are rare, and there is no evidence that PEX has failed prematurely in any continuously recirculating hot water system. Nevertheless, the potential for premature or unexpected PEX failure in continuously recirculating hot water systems and subsequent adverse affects is conservatively considered a ***potentially significant*** *impact.*

Interactions with oxidizers (i.e., UV light, firestop materials) and disinfectants such as chlorine, chloramine, and chlorine dioxide have been reported to deplete stabilizers in PEX (Coalition for Safe Building Materials 2005:33; Vibien et al. n.d., Chung et al. n.d. It has been asserted that these interactions eventually cause polymer chains (combined molecules that contain repeating structural units) in PEX tubing to break down, which may result in brittleness and loss of strength and, it is has been asserted, ultimately premature mechanical failure (Coalition for Safe Building Materials 2005:33). Despite this potential, studies that have addressed chlorine resistance of PEX have concluded that PEX "appears to have good resistance to chlorinated potable water" (Vibien et al. n.d. at p. 4) This conclusion is also supported by the fact that there have been no documented instances of PEX failing as a result of exposure to disinfectants.

The possibility of pipe failure, for any reason, is not limited to PEX. As noted above, pipe failure in California commonly occurs in the most common plumbing material used for conveying potable water, copper tubing. Copper failures are becoming increasingly common and can be attributed to pinhole leaks from nails and degradation from chloramines (See, e.g., Shields, pers. comm., 2008). Ruptures and pinhole leaks can cause serious water damage to homes (Coalition for Safe Building Materials 2005:33; Maryland Department of Housing and Community Development 2004). There is an important distinction between typical occurrences of copper pipe failure and failure of PEX tubing. Copper pipe is subject to accidental perforation during construction and resulting unnoticeable pinholes lead to persistent undetected leaking, which is the type of failure that is known to lead to the formation of mold (Louden and Wick, pers. comm. 2007). In comparison, any PEX failure would result in the immediate and readily apparent release of water from the pipe, which would be expected to result in other noticeable effects (e.g., water damage to ceilings and walls, diminished water pressure) and be repaired prior to the formation of mold. Thus, pinhole leaks of copper present much more tangible risk of toxic mold infestation.

Nonetheless, as with copper pipe, water damage from leaking or ruptured PEX pipes may cause mold to grow, which is often not visible. Mold may be hidden in places such as inside walls, around pipes, and inside ductwork. Other possible locations of hidden mold include the back side of drywall, wallpaper, or paneling; the top side of ceiling tiles; or the underside of carpets and pads. Molds can cause health problems because they produce allergens, irritants, and in some cases, potentially toxic substances (mycotoxins). Inhaling or touching mold or mold spores may cause allergic reactions in sensitive individuals. Allergic responses include symptoms such as sneezing, runny nose, red eyes, and skin rash (dermatitis). Allergic reactions to mold are common and can be immediate or delayed. Molds may also cause asthma attacks in people with asthma who are allergic to mold (EPA 2008).

PEX has been used for many years in many geographic locations. Like many products, issues have arisen that point to problems with, for example, specific lots (batches) of PEX products or particular methods of installation. For example, PEX failures are the subject of a number of lawsuits in Washington State (Coalition for Safe Building Materials 2005:34). The PEX failures in Washington State refer to a specific resin source that failed in several applications, such as distribution, hydronic applications, and where firestop materials were once in contact with the tubing. These failures, however, were attributed to a specific defective lot. All of the failed PEX tubing was produced by a single manufacturer, which is no longer in business (Church, pers. comm., 2007:5). Such failures are not representative of the entire PEX industry. Another current lawsuit concerns a number of failures related to the use of Zurn-manufactured PEX tubing and the brass the fittings manufactured by Zurn for use with Zurn PEX. This lawsuit is ongoing. According to the plaintiffs, the pipe failures appear to be related to either a design or manufacturing defect of the fittings. Therefore, the Zurn suit is not relevant to the general issue of potential PEX failure.

NSF 14 has been modified to include testing of brass fittings containing more than 15% zinc for Dezincification Resistance and Stress Crack Corrosion Resistance to address concerns raised due to changing water quality. BSC has no evidence that brass fittings used with PEX in California are failing, from dezincification or any other reason. The potential for failure of a PEX system from brass fittings is speculative, appears to be based on water quality conditions unique to a few areas in the US which are not limited to brass fittings for PEX, and there is no evidence to suggest any failures that might occur in California would lead to widespread incidences of mold leading to a substantial impact on public health. Moreover, regulatory changes applicable to fittings used with PEX have been adopted to address the potential for failure of brass fittings from dezincification or stress crack corrosion. As noted above, NSF/ANSI 14 was revised in 2009 to add dezincification resistance and stress corrosion resistance requirements for brass fittings. (ANSF/NSF 14-09, Section 5.8 and p. vii.). The standard incorporates a well-recognized and accepted metallurgical test (ISO 6509) that will ensure that brass fittings used with PEX will not experience dezincification and ASTM B858 to ensure protection against stress crack corrosion that could lead to premature failure of the PEX system. All fittings used with PEX tubing will have to meet the performance requirements of NSF 14-2009. For these reasons, the potential impact for failure of a PEX system from a failure of fittings is considered to represent a **less than significant impact**. Although not required to reduce a significant impact, because the most current (2009) version of NSF 14 contains requirements to guard against dezincification of brass fittings that may be used with PEX, it is reasonable to update the California Plumbing Code's list of mandatory standards to reflect the more current performance standard and to require compliance with NSF 14-2009, which will further minimize the potential for a significant impact.

PEX Failure from Ultraviolet Light

UV light may rapidly deplete the stabilizers in PEX, which would dramatically reduce its lifespan (Coalition for Safe Building Materials 2005:36). PEX may be left exposed at construction work sites or laid under slab at the edges of the building where it could be exposed to sunlight during portions of the day, left exposed during pipe installation, slab pour, framing, and sheathing. In tract housing this can add up to a month or more of exposure (Coalition for Safe Building Materials 2005:36). Excessive radiation is known to be detrimental to some plastic pipes. Accordingly, PEX is specially packaged and specific instructions are provided by the manufacturers as to acceptable exposures based on the type, color, and/or composition of the pipe (Church, pers. comm., 2007:3). Although PEX includes additives to prevent UV degradation, PEX should not be stored for extended periods outdoors exposed to the sun. Precautions must be taken after the pipe is removed from the original container. Each PEX manufacturer publishes a maximum recommended UV exposure limit that generally does not exceed a total accumulated time of 60 days, based on the UV resistance of that pipe (NAHB Research Center 2006:10). Most PEX manufacturers add UV-resistant material into the pipe and include instructions to avoid UV degradation. Because of this, and because it is considered reasonable and feasible that persons installing PEX would comply with manufacturers' instructions, substantial incidence of mold resulting from premature failure of PEX from UV degradation is considered an anomalous condition and a **less-than-significant** impact.

PEX Failure from Firestop Materials

Certain firestop materials used to safeguard PEX during fires are thought to accelerate degradation of PEX material, which may lead to pipe rupture (Coalition for Safe Building Materials 2005:35). Specifically, certain intumescent firestop materials may accelerate the loss of stabilizers in PEX, which could lead to pipe failure (Coalition for Safe Building Materials 2005:35). An intumescent is a substance that swells from heat exposure. This fire-resistant material restores the fire-resistance ratings of rated wall and/or floor assemblies by filling any openings, thus impeding the spread of fire through the opening.

Many firestop materials are designed to be compatible with PEX and some are not. Compatible firestops include, but are not limited to, gypsum-based caulking (Coalition for Safe Building Materials 2005:35), Triple S Intumescent Sealant, LCI Intumescent Sealant, and Pensil Silicone Sealant (Specified Technologies, Inc. 2008). Most firestop materials are labeled to indicate whether they are compatible with PEX. Certain solvents are incompatible with PEX tubing and some firestops contain these solvents. Uponor, as well as most (if not all) manufacturers have a list of recommended firestop materials for use with PEX tubing. In all cases, manufacturers

provide listings to ASTM E 814 (standard for penetrations of fire-rated walls) that specify a particular firestop material (Houle, pers. comm., 2008). To comply with the California Building Code requirements, the installation of the PEX tubing through the wall must comply with the listing for the particular assembly that will specify the type of firestop used. All of the firestop manufacturers that Uponor and other manufacturers recommend have the necessary E 814 listings with PEX tubing. (Houle, pers. comm., 2008). Most PEX manufacturer's installation guides also indicate that oil-based firestop materials should not be used and that in the event that the firestop materials are not labeled regarding compatibility with PEX, the PEX should be wrapped with aluminum foil before using the firestop materials to avoid contact of the firestop materials with the PEX. In addition to firestop materials, certain assemblies of materials and fittings are available that create a firestop installation. Because many readily available firestop materials are compatible with PEX, and the information about which materials are appropriate to use with PEX is readily available, the potential impact of substantial incidences of mold caused by premature failure of PEX as a result of use inappropriate firestopping materials is considered **less than significant**.

PEX Failure from Degradation by Disinfectants

Certain disinfectants, including chlorine, chloramine, and chlorine dioxide, commonly used in treating potable water have been reported to degrade PEX in laboratory tests. (Chung et al. n.d.; Vibien et al. n.d.) Although chlorine is the most common disinfectant, some jurisdictions in California are moving from chlorine to chloramine for water supply disinfection (EPA 2007). The primary reason for the trend is that, while both chlorine and chloramine can react with other compounds in water to form disinfection byproducts that are harmful to public health, chloramine forms significantly lower levels of these compounds. Approximately one-third of all public water systems in the United States now use chloramine for disinfection (EPA 2007). There is little evidence that chlorine dioxide is commonly used as a disinfectant in California.

Without attack from chloramines or aggressive water, copper pipes are known to outlast the buildings in which they are installed. However, no sets of full-product-life data are available that show the actual life expectancy of CPVC and PEX; data from available testing methods estimate life expectancy, but are based on extrapolation. CPVC and PEX have simply not been in use in the United States long enough to provide data on performance over time (Thielen, pers. comm., 2008). During preparation of the EIR, dozens of studies, documents, articles and other sources were reviewed and analyzed. This review yielded no documented instances of failure of PEX in actual use by consumers due to exposure to any disinfectant. BSC has no evidence that PEX will not survive for its warranted period. Available evidence suggests that even under conditions where PEX is exposed to chlorine, PEX is markedly durable (Vibien et al. n.d. Specifically, it was determined that even under the most aggressive conditions of continuously recirculating hot chlorinated water, PEX certified to ASTM F876/877 has a predicted test lifetime of 93 years, with a 95 percent lower confidence limit of 52 years. (Id.) Further evidence suggests that the interaction of PEX with chlorine, chloramines and chlorine dioxide is similar Chung et al. n.d..

As noted above, various standards are used for testing the resistance of PEX to distribute hot and cold water. All of the testing methods involve testing water under pressure in a flowing system. This continuous flow ensures that a constant controlled level of disinfectant is present in the water throughout testing. Samples are tested under aggressive (i.e., hot water and high disinfectant content) water quality conditions that are intended to represent worst-case scenarios that might be seen in service life. Elevated temperatures are used to accelerate failures. Expected service life is extrapolated from time to failure under these tests, which take place over a 36- to 62-day period.

These standards specifically address the oxidative stability of PEX in potable chlorinated water applications. (See, e.g., ASTM F876-08 Section 7.11). There is currently no standard or test methodology that tests the oxidative stability of PEX to other common disinfectants, including chloramine or chlorine dioxide. However, a study of the relative impact of all three disinfectants on PEX tubing concluded that "the consistency observed in the failure mechanism for the different oxidants suggests that the methodologies developed for chlorine resistance testing can also be applied to analysis of the impact of chloramines and chlorine dioxide on pipe performance" (Chung et al. n.d). Further, there is evidence that chloramines are less aggressive on PEX than chlorine, with test

results showing a 40% longer lifespan for PEX tested with chloramines compared to testing with free chlorine, as stated in Note 1 of ASTM F2023 (ASTM 2008a). Based on the results of this testing performed by Jana Laboratories, the Plastics Pipe Institute released a statement that that chloramines are less aggressive than free chlorine to PEX pipes and that testing using free chlorine in accordance with ASTM 2023 will conservatively estimate the time-to-failure for PEX pipes when used with the disinfectant chloramines (PPI 2007).

Concerns have been expressed that certification in accordance with the ASTM F2023 test method does not actually ensure the 50-year or 90-year service of PEX products that has been claimed by some manufacturers and third-party testers of PEX because of the extrapolation of data from a short testing period to a long service life period is inherently uncertain (Coalition for Safe Building Materials 2005:33). Additionally, concerns have been raised that exposure to drinking water disinfectants may cause more rapid breakdown of PEX in systems using continuously recirculating hot water and that PEX in such systems may not meet the certified life expectancy of 50 years when certified according to performance standards required by the California Plumbing Code . (Boyher, pers. comm., 2007; Coalition for Safe Building Materials 2008).

ASTM F2023 is a national consensus test method developed as a result of scientific study and with the consensus of experts familiar with technical issues related to plastic materials and product testing. The method details the exposure requirements for PEX tubing, water quality requirements, temperature and pressure requirements and contains detailed information on using the data to determine the extrapolated life expectancy at various operation conditions, including traditional hot water systems and continuous recirculation systems. Testing of PEX tubing is performed under conditions of continuously flowing hot water at 203°, 221°, and 239°F. The test results are then used in a regression analysis to extrapolate to water temperatures of 140°F (hot water) and 73°F (cold water). An equation called Miner's rule is applied to estimate pipe lifetimes based on time to failure under a variety of test conditions assuming the 25% hot water and 75% cold water exposures. While extrapolation is inherently uncertain, it is the best available means of predicting product lifespan. Based on the available evidence, it is reasonable to assume that PEX used in traditional domestic applications (exposure to hot and cold water) that meets the chlorine resistance requirements of ASTM F876 when tested in accordance with ASTM F2023 will not fail prematurely relative to other plumbing products in common use, including copper.

ASTM F876 provides the pass/fail criteria for certifying the oxidative stability of PEX in potable chlorinated water applications when tested in accordance with ASTM F2023. PEX that has been certified to meet the chlorine resistance requirements of ASTM F876 will have a certified minimum time to failure of 50 years. The current California Plumbing Code requires that PEX meet the performance requirements of an older version of ASTM F876 -- ASTM F876-2004a. ASTM F876-2004a was not designed to address PEX lifespan in a 100% continuously recirculating, hot water system. The most current version of the standard, ASTM F876-08, however, addresses 100% hot water for recirculating systems. PEX that meets the chlorine resistance requirements for product life in a continuously recirculating hot water system will be marked as "PEX 5006". (See ASTM F876-08, Section 7.11.3). The digit 5 indicates that the PEX tubing has been tested and meets the requirements for minimum chlorine resistance at end use condition of 100 percent hot water at 140 degrees Fahrenheit. (Section 3.2.1.1(6).)

This section of the EIR analyzes the potential for significant adverse effects to human health if PEX were to result in widespread failures that lead to flooding, which in turn lead to the growth of toxic mold. This impact requires widespread pipe failure as one step in a chain of causation. A single instance of pipe failure, or several, would be insufficient to cause a substantial impact to human health. According to the thresholds of significance applied in this EIR, in order for a significant adverse impact to occur, there must be substantial evidence that PEX will fail prematurely, resulting in flooding that leads to widespread instances of mold infestation associated with significant health risks. Premature pipe failure would require attention and repair in the affected building, which may result in some economic impact, but isolated instances of pipe failure, in and of themselves, are not considered to be a significant environmental impact.

The studies from Jana Laboratories (Vibien, et al. n.d. and Chung, et al, n.d.) cited above define the failure of PEX pipe as the loss of fluid through the wall of the pipe. Images and narrative descriptions in these studies show

that when PEX does fail, it develops longitudinal cracks that pass water. The mode of failure for PEX would thus be immediately noticeable and the residents or occupants of the structure would be able to respond quickly, thus reducing the long-term prevalence of moisture which could potentially lead to toxic mold. The failure mode of PEX thus reduces the likelihood of the relevant impact, which is the possibility of adverse health effects. There are no scientific studies, reports, or other substantial evidence available linking the failure of PEX to mold infestation.

There is no evidence that PEX will fail prematurely in traditional potable water applications. Adequate standards are available to ensure the resistance of PEX to chlorine in both traditional and continuously recirculating hot water systems, and these standards will be effective in assuring resistance in systems where the water is disinfected with chloramine and chlorine dioxide. Independent testing of PEX under highly aggressive conditions (continuously recirculating hot water) resulted in predicted lifespans of 52-93 years, consistent with both manufacturer warranties and the 50-year minimum lifespan provided by ASTM F876-08. (Vibien, et al. n.d.) Because ASTM F876-2004a does not address the possibility of premature PEX failure from disinfectant degradation in continuously recirculating hot water systems, it is reasonable to require that PEX used in such systems meet the chlorine resistance requirements of ASTM F876-08, which is designed to ensure a 50-year lifespan in such systems.

Polybutylene in Chlorinated Water

There are contrasting claims about whether or not polybutylene (PB) and PEX are related and demonstrate similar properties. Both are from the polyolefin family, but PB is derived from butanol and PEX is derived from ethylene. A key concern with PB is that it is vulnerable to degradation from chlorine and to loss of antioxidants, which results in mechanical failure. Some have expressed concern that PEX could be subject to the same kind of failure. It is true that both PB and PEX are members of the polyolefin family, but that does not necessarily mean that PEX automatically behaves similarly to PB (Chaudhuri, pers. comm., 2008).

Lundback et al. (2006) studied PB pipes in chlorinated water and the lifetime was assessed as a function of temperature and chlorine content. The authors found that the lifetime of PEX shortened in chlorinated water substantially, even at a relatively low chlorine content of 0.5 ppm. Further increases in the chlorine content of the water only moderately shortened further the lifetime of PEX. The decrease in the antioxidant concentration was independent of the chlorine concentration in the range of 0.5–1.5 ppm.

No independent peer-reviewed journal articles were located that compare PB and PEX failure under the same conditions; therefore, it is not possible to determine based on literature review whether PEX could fail in a similar manner to PB. Tests are available, however, to determine the product life of PEX given chlorine usage in domestic hot water systems. While it is unknown whether PEX would behave in a similar fashion to PB under similar conditions (though indications from use of PEX so far is that PEX is more resistant to oxidation than PB), the relevant issue is that it is important to test PEX under the chlorine conditions to which it would be used in California to determine its ability to withstand chlorinated water in typical drinking water systems.

High-Density Polyethylene in Chlorinated Water

Almost all PEX is made from high-density polyethylene (HDPE). PEX begins as HDPE but one key difference is that PEX contains cross-linked bonds that create a polymer structure. Hassinen et al. (2004) studied the deterioration of HDPE pipes exposed to chlorinated water at elevated temperatures. The authors found that embedded stabilizers in HDPE were rapidly consumed by the action of chlorinated water. Extensive polymer degradation was confined to the immediate surface of the unprotected inner wall material. This study was conducted on HDPE, not PEX; therefore it is not possible to apply these results directly to PEX. In his analysis report to the California Building Commission (Hoffmann 2005), Hoffman states “Since PEX products will be more stable and resistant to degradation, we can conclude that the development of a similar affected porous surface layer should be substantially less than that observed for HDPE.” However, he does not provide any research or other substantiation for this claim. Therefore, it is uncertain whether PEX could behave in a similar

fashion to HDPE. However, as with the comparison to PB above, the relevant issue is that PEX should be tested under the chlorine conditions to which it would be used in California to determine its ability to withstand chlorinated water in typical drinking water systems.

Conclusion

UV light, certain firestop materials, and water supply disinfectants such as chlorine, chloramine, and chlorine dioxide can contribute to failure of PEX. PEX manufacturers add UV-resistant material into the pipe and include instructions to avoid UV degradation, which decreases the potential for UV light to adversely affect PEX. Numerous firestop materials are compatible with PEX and are made known by the industry, and if these compatible materials are used, firestop materials do not degrade PEX. There is no evidence that conditions believed to have led to failure of brass fittings in a few areas of the U.S. exist in California, and brass fittings used with PEX will have to comply with the newly adopted performance standards designed to prevent failures from dezincification and stress crack corrosion. For these reasons, the risk of premature failure from UV exposure or contact with incompatible firestop materials, or failure of a PEX system due to failure of brass fittings used with PEX, is considered to be less than significant.

Finally, based on the available evidence, it is not anticipated that PEX will fail sooner, or more frequently, than any other plumbing product in use, including copper. Moreover, if failures were to occur, there is no evidence that would support a determination that failures would be widespread, or result in widespread incidences of mold infestation. Adequate standards are available to ensure the resistance of PEX to chlorine in both traditional and continuously recirculating hot water systems, and these standards will be effective in assuring resistance in systems where the water is disinfected with chloramine and chlorine dioxide. Because ASTM F876-2004a does not address the possibility of premature PEX failure from disinfectant degradation in continuously recirculating hot water systems, it is reasonable to require that PEX used in such systems meet the chlorine resistance requirements of ASTM F876-08, which is designed to ensure a 50-year lifespan in such systems. Because PEX tubing used in continuously recirculating hot water systems may potentially have shorter product life as a result of degradation from commonly used disinfectants than copper, CPVC, or PEX in traditional domestic applications, this is considered a **potentially significant impact**. However, certification to the continuous hot water requirements of ASTM F876-08 would ensure that PEX used in continuously recirculating hot water systems has a minimum life of 50 years (and possibly as great at 93 years, based on laboratory tests), which would be sufficient to avoid substantial or widespread premature pipe failure and would thus reduce the risk of any impact from pipe failure to less than significant.

Mitigation Measure 4.2-1: Risk of Premature or Unexpected PEX Failure and Flooding Potentially Increasing the Incidence of Mold.

Mitigation Measure 4.2.1a:

The Building Standards Commission shall amend Table 14-1 of the California Plumbing Code to require compliance with NSF 14-2009, which includes requirements to prevent dezincification and stress crack corrosion of brass fittings used with plastic pipe.

Conclusion: Although not needed to reduce a significant impact, adoption of Mitigation Measure 4.2.1a will further minimize the potential for failure of PEX tubing system by ensuring that brass fittings used in any PEX system meet the most current regulatory standards designed to address dezincification and stress crack corrosion, which are contained in NSF 14-2009.

Mitigation Measure 4.2.1b:

The BSC also shall adopt regulatory language requiring that when installing PEX for any continuously recirculating, hot water system, the PEX tubing must be certified as meeting the chlorine resistance requirements of ASTM F876-08 or an appropriate, equally rigorous standard. Any equally rigorous yet-to-be adopted standard

shall be approved by the Building Standards Commission and shall be one that tests for 100% continuously recirculating hot water and ensures a product lifetime of at least 50 years. The adopted regulatory language shall specify these requirements for all continuously recirculating, hot water systems regardless of the type of disinfection used.

Conclusion: Because the ASTM F876-08 standard assumes 100% hot water to ensure a conservative product lifetime of at least 50 years, adoption of Mitigation Measure 4.2.1b would reduce the risk of premature or unexpected PEX failure in continuously recirculating hot water systems to **less than significant**.

IMPACT 4.2-4 Public Health and Hazards—Increased Safety Hazards for Plumbers. *PEX tubing does not require the use of solvents, glues, or open flames during installation. Also, PEX tubing is lighter than metal pipes. Therefore, there are no health hazards for plumbers and this impact is* ***less than significant****.*

The installation of PEX tubing uses fittings that do not require solvents or glues, which means it does not generate airborne substances in the workplace that would cause harm to plumbers. Additionally, no soldering or welding is required to install PEX tubing, which means there is no risk of burns or fires during installation. Further, PEX tubing weighs less than metal pipes, which reduces potential for health and safety issues related to physical injuries. Because the use of PEX would not result in safety hazards for plumbers, this is considered a **less-than-significant** impact.

Mitigation Measure

No mitigation measures are necessary because the impact is less than significant.

4.2.4 SIGNIFICANT AND UNAVOIDABLE

Because all potentially significant and significant impacts would be reduced to less than significant with the implementation of mitigation, no public health and hazards impacts would be significant and unavoidable.

4.4 WATER QUALITY—REVISED

As described in Chapter 1, Introduction, a lawsuit challenging the adequacy of the EIR upon which the California Building Standards Commission (BSC) based its decision to approve use of PEX pipe for potable water uses in California, was filed in early 2009. As a result, the BSC was directed to remedy specific water quality issues in the EIR, including the following topics as described in the December 4, 2009 ruling of the Alameda County Superior Court: noncancer health risks from leaching of constituents from PEX pipe; short-term genotoxic cancer health risks; and taste and odor impacts. These issues are addressed in the revised analysis provided under Impact 4.4-1 and Impact 4.4-2, as well as additional information in the regulatory setting. Information has also been added to Section 4.4.2, Regulatory Setting and Section 4.4.3, Existing Setting to provide additional clarity about these topics. The validity of the approaches and assumptions used in this analysis, and the determinations about potential health effects from leaching of constituents from PEX pipe into drinking water, were reviewed and confirmed by Jonathan Borak, MD, DABT. Dr. Borak is a clinical professor of epidemiology and public health and associate clinical professor of medicine at Yale University. Dr. Borak's *curriculum vitae* is included in Appendix A.

4.4.1 REGULATORY SETTING

Federal and State of California regulations related to the potential water quality impacts of using PEX pipe are described below. No local water quality plans, policies, regulations, or laws are applicable to the proposed project.

FEDERAL PLANS, POLICIES, REGULATIONS, AND LAWS

Federal Safe Drinking Water Act

Pursuant to the federal Safe Drinking Water Act (42 United States Code Section 300f et seq.), the U.S. Environmental Protection Agency (EPA) establishes national standards for drinking water using a two-step process. First, it establishes what are known as public health goals (PHGs), which are science-based standards at which there is no risk to human health. Second, it considers available technology and cost of treatment to determine the National Primary Drinking Water Regulations that set enforceable regulatory standards called maximum contaminant levels (MCLs). The Safe Drinking Water Act has strict standards for bacteria in drinking water and meeting these standards generally requires disinfection. Pursuant to the Supremacy Clause in the U.S. Constitution (Article VI, Clause 2) states may not adopt regulations that are less stringent than the federal standard. The federal act provides a floor of regulatory standards; it also grants individual states authority to adopt more stringent standards.

Lead and Copper Rule

The Lead and Copper Rule (LCR), Code of Federal Regulations 141.81, was established in 1991. The goal of the LCR is to provide maximum human health protection by reducing lead and copper at consumers' taps. To accomplish this goal, the LCR establishes requirements for community and nontransient/noncommunity water systems. These systems must conduct periodic monitoring and optimize corrosion control. In addition, these systems must perform public education when the level of lead at the tap exceeds the lead action level, treat source water if it is found to contribute significantly to high levels of lead or copper at the tap, and replace lead service lines in the distribution system if the level of lead at the tap continues to exceed the lead action level after optimal corrosion control has been installed. The action levels are 0.015 milligrams per liter (mg/L) for lead and 1.3 mg/L for copper, and the MCL goals, which is similar in concept to a PHG, is 0 mg/L for lead and 1.3 mg/L for copper.

The LCR requires water suppliers to (1) optimize their treatment system to control corrosion in customers' plumbing, (2) determine tap water levels of lead and copper for customers who have lead service lines or lead-based solder in their plumbing system, (3) rule out the source water as a source of significant lead levels, and (4) if lead action levels are exceeded, educate their customers about lead and suggest actions they can take to reduce their exposure to lead through public notices and public education programs. If a water system, after installing and

optimizing corrosion control treatment, continues to fail to meet the lead action level, it must begin replacing the lead service lines under its ownership. Lead service lines are uncommon in California, where the primary sources of lead in drinking water are lead solder and leaching from brass plumbing fixtures.

Disinfection By-Products Rules

EPA drinking water standards require the disinfection of drinking water to kill pathogenic microorganisms that can threaten human health. However, disinfectants, particularly chlorine, react with naturally occurring organic and inorganic matter present in water to form chemicals called disinfection by-products (dbps). EPA has determined that a number of dbps pose a health concern because they have been shown to cause cancer in laboratory animals or affect the liver and the nervous system and cause reproductive or developmental effects in laboratory animals. There are also limited studies that indicate that certain dbps may produce similar effects in people. Based on this information EPA has adopted rules that apply to all community and nontransient noncommunity water systems that add a chemical disinfectant to the water. The rules establish maximum contaminant levels for trihalomethanes (THMs), haloacetic acids (HAAs), bromate, and chlorite, as well as maximum residual disinfectant level goals and enforceable maximum residual disinfectant level standards for three chemical disinfectants: chlorine, chloramines, and chlorine dioxide. Systems that use surface water, or groundwater under the direct influence of surface water, are required to remove increased percentages of organic materials that may react with disinfectants to create dbps.

Agency for Toxic Substances and Disease Registry Minimal Risk Levels

The Agency for Toxic Substances and Disease Registry (ATSDR) is a federal public health agency of the U.S. Department of Health and Human Services. ATSDR developed Minimal Risk Levels (MRLs) in response to the mandate established by the Comprehensive Environmental Response, Compensation, and Liability Act, as amended by the Superfund Amendments and Reauthorization Act, which requires ATSDR and EPA to jointly ascertain significant human exposure levels for hazardous substances and the associated health effects (ATSDR 2009a). An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are intended to serve as screening levels (ATSDR 2009a). MRLs are derived when ATSDR determines that reliable and sufficient data exist to identify the target organ(s) of effect (e.g., kidneys) or the most sensitive health effect(s) for a specific duration for a given route of exposure (e.g., inhalation, oral ingestion) to the substance. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. Oral MRLs are expressed as daily human doses in units of milligrams per kilogram of body mass per day (mg/kg-day).

ATSDR uses the no observed adverse effect level/uncertainty factor (NOAEL/UF) approach to derive MRLs for hazardous substances. MRLs are set below levels that, based on current information, might cause adverse health effects in the people most sensitive to such substance-induced effects. MRLs are derived for acute (1-14 days), intermediate (>14-364 days), and chronic (365 days and longer) exposure durations.

MRLs are generally based on the most sensitive substance-induced end point (i.e., risk type) considered to be of relevance to humans. Most MRLs contain some degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, and nutritionally or immunologically compromised) to effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address these uncertainties consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive than animals to the effects of hazardous substances and that certain persons may be particularly sensitive. Thus the resulting MRL may be as much as a hundredfold below levels shown to be nontoxic in laboratory animals. Exposure to a level above the MRL does not mean that adverse health effects will occur (ATSDR 2009a).

STATE PLANS, POLICIES, REGULATIONS, AND LAWS

California Safe Drinking Water and Toxic Enforcement Act

The California Health and Safety Code prohibits the discharge of chemicals that cause cancer or reproductive toxicity into drinking water (California Health and Safety Code Section 25249.5 et seq.). This code section was originally enacted as a part of the California Safe Drinking Water and Toxic Enforcement Act (popularly known as Proposition 65 or "Prop 65"). Health and Safety Code Section 25249.9 provides an exemption to the discharge prohibition, stating that the prohibition does not apply if (1) the discharge will not cause any significant amount of the discharged or released chemical to enter any source of drinking water and (2) the discharge is in conformity with all applicable laws, regulations, permits, requirements, and orders. The act has been interpreted to prohibit discharge of Proposition 65 chemicals into drinking water from plumbing materials and fixtures through which drinking water passes. The regulations implementing Proposition 65 (California Code of Regulations, Title 22, Division 2, Part 2, Chapter 3. Section 12711, subdivision [a]) state that, with certain exceptions, the levels of exposure deemed to pose no significant risk for drinking water are:

- drinking water MCLs adopted by the California Department of Public Health (DPH), which was previously called the California Department of Health Services (DHS), for chemicals known to the state to cause cancer;
- drinking water action levels (also known as "notification levels") for chemicals known to the state to cause cancer for which MCLs have not been adopted;
- specific numeric levels of concentration for chemicals known to the state to cause cancer that are permitted to be discharged or released into sources of drinking water by a Regional Water Quality Control Board in a water quality control plan or in waste discharge requirements, when such levels are based on considerations of minimizing carcinogenic risks associated with such discharge or release.

Section 12805 establishes similar standards for chemicals that cause reproductive toxicity. Additionally, Section 12705 authorizes the Office of Environmental Health Hazard Assessment (OEHHA) to adopt "No Significant Risk Levels" for carcinogens and "Maximum Allowable Dose Levels" (MADLs) for reproductive toxicants that are intended to provide "safe harbors" for dischargers. MADLs represent the NOAEL.

California Safe Drinking Water Act

The California Safe Drinking Water Act (California Health and Safety Code Section 116270) was passed to ensure that water delivered by public water systems is "pure, wholesome and potable" (California Health and Safety Code Section 116270[e]). The act states that, "It is the policy of the state to reduce to the lowest level feasible all concentrations of toxic chemicals that when present in drinking water may cause cancer, birth defects, and other chronic diseases" (California Health and Safety Code Section 116270[d]). The act provides for the process of adopting drinking water standards and, as described below, the California Administrative Code at Title 22, Division 4, Chapter 15, provides the standards for contaminants. California Health and Safety Code Section 116275 defines primary drinking water standards, or primary MCLs, as the "maximum levels of contaminants that, in the judgment of the department, may have an adverse effect on the health of persons." California Health and Safety Code Section 116365 specifies that the MCLs shall, to the extent technologically and economically feasible, meet the following requirements:

> (1) With respect to acutely toxic substances, avoids any known or anticipated adverse effects on public health with an adequate margin of safety, and
>
> (2) With respect to carcinogens, or any substances that may cause chronic disease, avoids any significant risk to public health.

The drinking water standards are calculated using standard risk assessment methods for cancer and noncancer endpoints.

The act also provides for the establishment of "notification levels" and "response levels" (also known as source removal levels) (California Health and Safety Code Section 116454 et seq.). "Notification level" means the concentration level of a contaminant in drinking water delivered for human consumption that DPH determined may pose a health risk and warrants notification. Notification levels are not drinking water standards but are generally supported by a health risk assessment prepared by OEHHA. Notification levels are nonregulatory, health-based advisory levels established by DPH for contaminants in drinking water for which MCLs have not been established. Notification levels are established as precautionary measures for contaminants that may be considered candidates for establishment of MCLs, but have not yet undergone or completed the regulatory standard-setting process prescribed for the development of MCLs. Chemicals for which notification levels are established may eventually be regulated by MCLs (after a formal regulatory process), depending on the extent of contamination, the levels observed, and the risk to human health. Notification levels may be revised to reflect new risk assessment information.

A "response level" is the concentration of a contaminant in drinking water delivered for human consumption at which DPH recommends that additional steps, beyond notification, be taken to reduce public exposure to the contaminant (California Health and Safety Code Section 116455.) If a chemical concentration exceeds the response level DPH recommends that the drinking water system take the water source out of service (DPH 2007a). Chemicals that pose a cancer risk have a response level that is generally 100 times the notification level.

Title 22 of the California Code of Regulations

NSF International/American National Standards Institute Standard 61—Drinking Water System Components

NSF is a not-for-profit testing organization that has developed product standards and provided third-party conformity assessment services to government, users, and manufactures/providers of products and systems (McLellan, pers. comm., 2008a). NSF has been developing standards for testing and certification of plastics since 1965. NSF is also one of only a handful of organizations certified by ANSI to perform testing and certification to ANSI/NSF Standard 61.

California Code of Regulations Title 22 Section 64591 requires drinking water system components to be tested and certified to NSF International/American National Standards Institute (ANSI) Standard 61— Drinking Water System Components. The 2007 California Plumbing Code Section 604.1 also requires all pipe tube and fittings carrying water used in potable water systems intended to supply drinking water to meet the requirements of NSF/ANSI Standard 61. This standard establishes requirements for the control of potential adverse human health effects from products that contact drinking water (NSF International 2007; McLellan, pers. comm., 2008a) and is the only ANSI standard that evaluates the health effects of chemical extraction from drinking water system components (Bestervelt, pers. comm., 2008).

NSF/ANSI Standard 61 is overseen by the NSF Drinking Water Additives Joint Committee comprised of representation from the regulatory community, the manufacturing industry, and user groups (Bestervelt, pers. comm., 2008). ANSI accredits NSF standards development procedures to ensure a balanced committee of stakeholders develops the standards in an open process. The NSF Council of Public Health Consultants provides technical oversight. The council consists of more than 30 representatives from academia and local, state, and federal regulatory agencies that provide technical advice and oversight of the NSF Standards. The NSF Health Advisory Board is responsible for reviewing and approving all allowable contaminant concentrations that are published in NSF/ANSI Standard. The NSF Health Advisory Board consists of toxicologists from EPA, Health Canada, state and provincial agencies as well as toxicologists from industry and private consulting firms. ANSI has served for nearly 90 years as administrator and coordinator of standardization programs in the United States (www.ansi.org). This private, not-for-profit organization is comprised of more than 1,000 government agencies, professional societies, and corporations. ANSI facilitates the development of American National Standards by accrediting the procedures of organizations that develop standards. Accreditation by ANSI signifies that the procedures used by the standards body meet the ANSI's requirements for openness, balance, consensus, and due

process. ANSI oversees hundreds of organizations that develop standards and over 10,000 American National Standards.

The concentration-based standards for chemical compounds that are used in NSF/ANSI Standard 61 are protective of the three major types of health risk—cancer, the risk of noncancer toxicity from long-term exposure, and the risk of toxicity from acute (short-term) exposure. Consistent with standard toxicological practice, if the toxicological assessment of a particular chemical determines that the level of cancer risk associated with exposure to that chemical is greater than the long-term and acute noncancer risk, then the standard—expressed as a Total Allowable Concentration (TAC)—is set to be protective of cancer risk, and the standard is protective against the other categories of risk. Thus NSF's drinking water standards for TACs always address the type of health risk that is of greatest concern for each particular chemical compound, and the single TAC for a particular chemical is protective of all three categories of risk (McLellan, pers. comm., 2010c).

In order to obtain NSF/ANSI Standard 61 certification, a product must not leach any chemical at levels exceeding the applicable concentration-based standards, as measured according to the test protocol set forth in NSF 61 (NSF International 2007). The protocol measures contaminant concentrations on the 17th day of sample exposure, and after water has been continuously run (or "flushed") through the pipes. These measurements are made on the 17th day in order to more realistically represent the first time consumers would potentially drink water that had passed through the pipe and any contaminants contained therein. Both the California Plumbing Code and widely employed construction practices are designed to ensure that water is run through piping for a substantial period prior to use for drinking water purposes.

The following is typical of residential construction or renovation practices where PEX (or any water piping) is installed. After a building is framed (or "gutted" in the case of a renovation) and the outside sheathing and the roof are in place, water piping (including PEX tubing) is installed in the structure. Once installed, the tubing is capped at the terminal points (at each fixture or other outlet). Then the pipe is hydrostatically pressure tested and flushed and is inspected by the respective building authority pursuant to California Plumbing Code, § 609.4. The plumbing system remains under pressure (with water in the pipes) and is capped while sheet rock is installed, taped and joint compound is applied. A primer coat of paint is applied prior to the installation of cabinets. Once the cabinets are installed, the piping system pressure is temporarily relieved, the caps are removed and stop valves and fixtures are installed. The entire water system then is required to be thoroughly flushed again pursuant to California Plumbing Code, § 609.9. Final inspection is required prior to the system being put into service. During the period between installation of fixtures and occupancy, it is typical for the piping system to begin full service as the construction crew uses water in various finish processes, including painting and site clean-up. The time period between pipe installation and consumer exposure to drinking water typically exceeds 30 days.

Under real world conditions reflecting common construction practices and code requirements, PEX tubing is installed in a home, office building, or hotel long before any person would drink water that has passed through the PEX tubing. Because building codes require that new tubing be flushed prior to use, and because it is known that leached contaminants decline rapidly over time, NSF/ ANSI Standard 61 evaluates whether a product would leach a chemical at a level greater than the applicable drinking water standard after being exposed to water for 17 days NSF International 2007). More details regarding the reasoning used to determine the regimen of water conditions to which products are exposed is outlined in NSF's Exposure Parameters Decision Document (NSF International 1987).

California Drinking Water Standards

Title 22 of the California Code of Regulations also contains California-specific standards for drinking water quality. Using a process similar to that used under the federal Safe Drinking Water Act, California sets its own PHGs and MCLs, which are at least as stringent as the federal standards. Section 116275 of defines primary drinking water standards (i.e., MCLs) as the "maximum levels of contaminants that, in the judgment of the department, may have an adverse effect on the health of persons." California's primary drinking water standard is set through a two-step process: a risk assessment performed by OEHHA to develop a PHG, and a risk management assessment performed by DPH to establish an MCL (DPH 2010).

In the risk assessment portion, OEHHA evaluates the risk to public health posed by the contaminant, including all categories of health risk, and, based on the results of the risk assessment, establishes a PHG. The PHG is the level at which the contaminant will not pose a significant risk of either acute (sudden and severe) or chronic (prolonged or repeated, and cancer or noncancer) effects to human health with an adequate margin of safety; in other words, a PHG is the levels of a contaminant in drinking water that would pose no significant health risk to individuals consuming the water once or on a daily basis over a lifetime (OEHHA 1999b). The exposure assumptions represent the concentration of a contaminant in drinking water that would result in a "de minimis" level of cancer risk if the water were consumed at a specific rate over a 70-year period. Thus, the concentration-based standards are not a ceiling (Borak, pers. comm. 2010a). In other words, exposure at less than the minimum levels (i.e., less than 70 years or less than 3L a day, or to water containing constituents at less than the standard concentration) is insufficient to create a significant risk to public health (Borak, pers. comm. 2010a). In the case of methyl tertiary butyl ether (MTBE), for example, the exposure thresholds set by the State of California of 13 ug/L for cancer risk, and 47 ug/L for noncancer risk, are based on a drinking water rate of 3 liters per day (L/day) over a 70-year lifetime (OEHHA 1999b).

As adopted regulations by DPH, MCLs are intended to be met by all public water systems (DPH 2010). California Code of Regulations Title 22 Section 64445 requires all public water systems to monitor each water source prior to any treatment or at the entry points to its distribution system to test for all chemicals for which an MCL has been established.

DPH also adopts what are known as secondary MCLs, sometimes referred to as secondary standards. Secondary MCLs address taste and odor concerns. For example, the taste and odor standard for methyl tertiary-butyl ether (MTBE) in drinking water, is 5 µg/L, or 5 parts per billion (ppb), below which odor or taste associated with this compound is imperceptible by most members of the public (DPH 2007b).Though secondary MCLs are not enforceable under federal law, they are enforceable in California at the request of an affected community.

California Health and Safety Code, Section 116275(d), describes the purpose of establishing a secondary MCL. The statute states:

> "Secondary drinking water standards may apply to any contaminant in drinking water that may adversely affect the odor or appearance of the water and may cause a substantial number of persons served by the public water system to discontinue its use, or that may otherwise adversely affect the public welfare."

Thus, secondary drinking water standards are aesthetic, and do not pertain to public health risks. In contrast, "primary drinking water standards" are defined as a "maximum levels of contaminants that, in the judgment of the department, may have an adverse effect on the health of persons" (Health and Safety Code, Section 116275[c][1]).

The monitoring requirements set forth by California Code of Regulations Title 22 Section 64444 and Section 64449 indicate how compliance with the primary and secondary MCLs is determined and, in particular, the length of time a primary or secondary MCL is exceeded in order for it to be considered a violation. These two sections require operators of community water systems to monitor their groundwater sources, approved surface water sources, or distribution system entry points representative of the effluent of source treatment. Monitoring for testing against the secondary MCLs is required to occur every three years. Section 64449 further explains that, if a secondary MCL is exceeded, then the community water system shall perform monitoring on a quarterly basis to determine compliance by a running annual average of four quarterly samples and defines a violation of a secondary MCL to occur when the average of four consecutive quarterly samples exceeds the secondary MCL. In other words, a monitoring sample that exceeds a primary MCL or secondary MCL at any single point in time, or during the short term, does not constitute a violation of the respective standard. Violations occur when running or annual averages of monitoring samples exceed the applicable standard.

The California Code of Regulations makes no mention of monitoring water at the tap for determining compliance with the primary and secondary MCLs or the testing of the materials used in piping or components of drinking

water systems (except for lead and copper). While the primary and secondary MCLs are not intended to be used to evaluate plumbing products, they are a relevant reference for evaluating the health (primary MCLs) and aesthetic (secondary MCLs) effects from drinking water.

4.4.2 EXISTING SETTING

As discussed above, in January 2009, the Building Standards Commission certified a Final EIR for this project and regulations removing the prohibition against the use of PEX were adopted. In February 2009, a lawsuit was filed challenging the adequacy of the January 2009 FEIR. The trial court rejected some of the challenges to the 2009 FEIR, and also found that the document did not contain substantial evidence to support certain findings that are further analyzed in this SRDEIR. The trial court's decision is presently on appeal, and as a result, the trial court's judgment is stayed, i.e., the regulations adopted in January 2009 remain in effect. Following the public comment period on this SRDEIR, the Building Standards Commission and the responsible agencies will exercise their discretion to determine the adequacy of this SRDEIR and subsequent actions with respect to the PEX regulations. Although the PEX regulations remain in effect, the following discussion of the existing setting assumes conditions in place prior to the January 2009 approval of the statewide PEX regulations, or any actions by local agencies that may have occurred as a result of that action.

This section contains a brief overview of the current use of piping materials and the effects those materials may have on water quality at the present time. As is described below, every type of piping currently available for use raises certain environmental and public health concerns. Based on this setting, which is the baseline for purposes of environmental impact assessment, this analysis assesses whether the projected increase in the use of PEX that would likely result from approval of the proposed project would result in a significant and adverse impact on the environment or on human health.

Current market share of PEX and other plumbing materials in California establishes the context for the existing environmental setting related to water quality and the baseline against which potential water quality impacts of the proposed project will be compared. As explained in Section 3.4.4, "Current and Projected Uses of PEX," as of 2005 the market share for various plumbing materials in new homes in California was approximately 29% PEX, 13% chlorinated polyvinyl chloride (CPVC), 54% copper, and 4% for all other materials (California Department of Housing and Community Development [HCD] 2006; Ash, pers. comm., 2008). The most current data for PEX (2006) indicates that its share of the market for plumbing materials in new single family homes in California has grown to approximately 37% (Ash, pers. comm., 2008). No data is available on market share for commercial and industrial uses.

PEX

PEX was first developed in Europe and has since come into use around the world for a variety of applications. PEX has a 30-year history of use in the European market. It was first introduced in North America in 1984 where it has been used primarily for radiant floor heating and, more recently, for domestic water distribution systems. It is approved for potable hot and cold water supply systems as well as hydronic heating systems in all model plumbing and mechanical codes across the United States (National Association of Home Builders [NAHB] Research Center 2006); Ash, pers. comm., 2009). PPFA estimates that 132 million feet of PEX were shipped to California in 2005 (PPFA 2007). According to PPFA (Church, pers. comm., 2007), PEX has been used in potable water applications in local jurisdictions throughout California including the Highland area, Santa Clarita, Redding, Chula Vista, and Village of Lakes since the early to mid-1990s.

PEX is currently used in California for radiant heating systems, manufactured homes, certain approved institutional uses, and for hot and cold water distribution, including potable water uses in approximately 230 local jurisdictions, as discussed in Section 3.4.4, "Current and Projected Uses of PEX." Those local jurisdictions make up more than 40% of California cities and more than 50% of California counties. These uses currently account for approximately 37% of the market for plumbing materials in new single-family homes in California.

The various manufacturers of PEX use different, proprietary formulations that may consist of a variety of chemical compounds. A literature search was performed to identify all possible chemical compounds that might be contained in one or more PEX formulations. The results of this search are presented in Table 4.4-1. Table 4.4-1 also lists the NSF drinking water criteria for these compounds and California drinking water standards and Proposition 65 listings, if applicable.

Some concerns that have been raised regarding PEX include its potential to leach some of the chemicals from which it is made into the water passing through it and to be permeated by organic compounds, particularly solvents that may be present in contaminated soils or groundwater.

COPPER

According to the Copper Development Association, Copper has been in use in plumbing for over 2000 years (it has been found in serviceable condition in the ruins of ancient Egypt), though its widespread use in the United States began in the 1920s (Copper Development Association 2008). As recently as 10 years ago, copper accounted for 90% of all plumbing materials in existing homes throughout the United States. In 2004, copper made up 62% of the market for plumbing materials in new homes in California. It likely accounts for a significantly greater percentage in existing homes, though no current data are available for piping in existing homes. Copper is an essential nutrient, but is also toxic at elevated doses, which can harm the environment and human health (Risk Assessment Information System 2005). When it is newly installed before flushing, and again over time, copper corrodes and is released into water that passes through it. The concentration of copper released into the water is highly dependent on the corrosivity of the water flowing through the pipe, the duration of standing water in the pipe, and the age of the pipe (Food and Drug Administration [FDA] 2003).

With the trend toward use of chloramines for disinfection and reverse osmosis for treatment, water in many parts of the state is becoming increasingly corrosive. This has resulted in some water agencies failing to meet the requirements of the copper and lead rule and some wastewater agencies exceeding the total maximum daily load (TMDL) for copper in various water bodies throughout the state. A TMDL is a threshold that in California is established by the regional water quality control boards. Specifically, a TMDL is a calculation of the maximum amount of a pollutant that a water body can receive without impairing the beneficial uses of that particular water body (e.g., drinking water, agricultural uses, swimming) and an allocation of that amount to the pollutant's sources. The issue of corrosion and potential impacts on water quality is discussed in greater depth in Impact 4.4-3 below.

CPVC

For over 20 years California has approved the use of CPVC for street water mains and polyvinyl chloride (PVC) for the service line from the street water main to the house. From 2001 until January 1, 2008, the California Plumbing Code allowed the use of CPVC for residential potable water distribution if specific findings were made and worker safety and flushing requirements were met. (HCD 2006.) Since January 1, 2008, the California Plumbing Code has allowed the statewide use of CPVC for hot and cold water distribution, including potable water uses. Concerns with CPVC include emissions of reactive organic gases and ozone precursors, from the solvents used for installation of CPVC, in volumes that exceed local air district thresholds for reactive organic gases and in areas that are in nonattainment for federal and state ozone regulations.

Hazardous Chemicals Contained in PEX Formulations

The various manufacturers of PEX use different, proprietary formulations that may consist of a variety of chemical compounds. A literature search was performed to identify all possible chemical compounds that might be contained in one or more PEX formulations. The results of this search are presented in Table 4.4-1. The first set of compounds in Table 4.4-1 (compounds in polyethylene [PE], high-density polyethylene [HDPE], and PEX) were identified by Tomboulian et al. (2004) who compiled a list of compounds found by NSF to leach from

Table 4.4-1
Chemicals Possibly Present in PEX Tubing and Comparison between NSF Criteria and California Drinking Water Standards (in mg/L)

Chemical	NSF Values (Standard 61)[1]							California Standards					
	EPA/ Health Canada MCL/MAC	NSF Peer-Reviewed Aqua TAC	NSF Peer-Reviewed STEL	NSF based on EPA guidance Aqua TAC	TOE[7]	NSF International Aqua TAC	TOE[7]	Listed in Prop. 65?[2]	Prop 65 Safe Harbor	PHG[3]	Primary MCL (health-based)[4]	Secondary MCL (taste and odor)[4]	Notification/ Response Levels[5]
	mg/L	mg/L	mg/L	mg/L	mg/L	mg/L	mg/L		mg/L	mg/L	mg/L	mg/L	mg/L
Chemicals in Polyethylene, HDPE or PEX[8]													
acetophenone		0.2	1										
2,4-bis(dimethylethyl)phenol													
Benzene	0.005							x	.0064	0.00015	0.001		
benzothiazole					x								
bis-(dimethylethyl)benzene													
bisphenol A						0.1							
BHT (methyl di(t-butyl)phenol)													
carbon disulfide	0.7							x					.16 / 1.6
cyclohexadienedione													
cyclo-hexanone		30	40										
cyclopentanone					x								
diazadiketo-cyclotetradecane													
dicyclopentylone													
dimethylhexanediol					x								
di-t-butyl oxaspirodecadienedione													
hydroxymethylethylphenyl ethanone													
isobutylene					x								
methanol		20	20										
methyl butenal					x								
methyl di-t-butyl hydroxyphenyl proprionate		0.02	0.1										
methyl (di-t-butylhydroxy-phenyl) propionate													
methylbutenol													
nonylcyclopropane													
Phenolics													
phenylenebis-ethanone													
propenyl-oxymethyl oxirane													
tertiary butyl alcohol (TBA)		9	40										0.012/ 1.2[9]
Tetrahydrofuran						1							
Trichloroethylene	0.005							x		0.0008	0.005		
Polyurethane coatings and liners (h):													
1,4-butanediol													
4,4-methylenedianiline						0.001		x	.0004				
bis(2-ethylhexyl)phthalate		0.0006						x		0.012	0.004		
bisphenol A diglycidyl ether		1	5										
diphenyl(ethyl)phosphine oxide													
di-t-butyl methoxyphenol													
Ethylhexanol						0.05							
tetramethyl peperidinone							x						
Additional Chemicals[10]:													
methyl tertiary butyl ether (MTBE)				0.1[6]						0.013	0.013	0.005	
Phthalates													
carbon black								x					
benzo(a)pyrene	0.0002							x	.00006	0.000004	0.002		
Mercury	0.002							x		0.0012	0.002		
Cadmium	0.005							x	.0041	0.00004	0.005		
PAHs													
Additional Chemicals[11]:													
4-butoxyphenol													
5-methyl-2-hexanone (MIAK)		0.06	0.8										
Additional Chemicals [12]:													
Chloroform	0.08							x	.02				
Toluene	1							x	7	0.15	0.15		

Notes: Shaded chemicals represent those for which NSF values are higher than California drinking water values.
ANS = American National Standard; aqua TAC = total allowable concentration; MAC = maximum acceptable concentration; MCL = maximum contaminant level; mg/L = milligrams per liter; NSF = NSF International, Inc.; PEX = cross-linked polyethylene; PHG = public health goal; STEL = short-term exposure limit; TOE = threshold of evaluation.
[1] NSF and ANSI, 2007: Drinking water systems components Health effects. NSF/ANSI Standard 61 - 2007.
[2] OEHHA, 2007: Chemicals Known to the State to Cause Cancer or Reproductive Toxicity. Safe Drinking Water and Toxic Enforcement Act of 1986. [http://oehha.ca.gov/prop65/prop65_list/Newlist.html]
[3] OEHHA, 2008: Public Health Goals for Water. [http://oehha.ca.gov/water/phg/allphgs.html]
[4] DPH, 2008: Table 64444-A (available at http://www.cdph.ca.gov/certlic/drinkingwater/Documents/MTBE/MTBEregulation.pdf), Table 64431-A (available at http://geosolve-inc.com/Downloads/California_MCLs_in_Drinking_Water.pdf) and Table 64449-A (available at http://www.cdph.ca.gov/certlic/drinkingwater/Documents/Recentlyadoptedregulations/R-21-03-finalregtext.pdf). Title 22 California Code of Regulations California Safe Drinking Water Act & Related Laws and Regulations. [http://www.cdph.ca.gov/certlic/drinkingwater/Pages/Lawbook.aspx].
[5] OEHHA, 1999: Water Notification Levels. [http://www.oehha.ca.gov/water/pals/index.html].
[6] NSF Comment Letter to DGS (Bestervelt, pers. comm., 2008).
[7] Chemicals that did not meet the minimum data requirements to develop chemical specific concentrations were evaluated under the threshold of evaluation (TOE). As defined by Section A.7.1 of NSF Standard 61 (NSF International 2007), a risk assessment is not required for a substance if the normalized concentration is less than or equal to the following concentrations: 3 µg/L (micrograms per liter) (chronic exposure, static normalization conditions), 0.3 µg/L (chronic exposure, flowing normalized conditions), and 10 µg/L (short-term exposure, initial laboratory concentration).
[8] List of chemicals found by NSF to leach from system components (Tomboulian et al., 2004). Some of the chemicals reported by Tomboulian et al. 2004, however, may not be found in PEX, including butyl benzyl phthalate and toluene diamine are not found in PEX tubing (Bestervelt, pers. comm., 2008).
[9] California's notification level for tertiary butyl alcohol is not based on a sufficient human health risk assessment (Bestervelt, pers. comm., 2008). See discussion under Impact 4.4-1, .
[10] Various sources.
[11] Testing on PEX pipes conducted by Skjevrak et al. (2003).
[12] Detected chemicals during NSF testing of Wirsbo Aqua PEX testing, April 2000. Only those with at least one available NSF value or California standard are listed.
Source: Provided by ENSR in 2008.

various water distribution system components. Tomboulian et al. (2004) also list compounds that have leached from polyurethane coatings and liners. These compounds are considered relevant because polyurethane coatings and liners are often used with PEX tubing. In addition to the compounds listed by Tomboulian et al. (2004), additional potentially leachable compounds were compiled from other sources, including Skjevrak et al. (2003).

It has been determined that some of these compounds, including butyl benzyl phthalate and toluene diamine are not found in PEX tubing (Bestervelt, pers. comm., 2008). Therefore, butyl benzyl phthalate and toluene diamine are not considered further in this CEQA analysis.

Carbon black is also identified as a substance potentially present in PEX tubing, and is listed on the Proposition 65 list of "Chemicals Known to the State to Cause Cancer or Reproductive Toxicity." However, carbon black's risks relate to inhalation of airborne, unbound particles of respirable size (CAS No. 1333-86-4). Carbon black is not believed by NSF to be used in PEX tubing (McLellan, pers. comm., 2008e). In addition, reports of its potential use in some brands of PEX would not be a concern because the particles would be bound within the matrix of the pipe, and exposure to airborne particles of carbon black would not occur. Therefore, the Proposition 65 listing for carbon black as airborne unbound particles of respirable size does not apply to PEX tubing (Chaudhuri, pers. comm., 2008). Furthermore, because any carbon black that could potentially be contained in PEX tubing is considered bound, any potential leaching of carbon black from PEX tubing is not a concern under Proposition 65 (Luong, pers. comm., 2008). Therefore, carbon black is not considered further in this CEQA analysis.

Table 4.4-1 also lists the NSF drinking water criteria for these compounds and California drinking water standards and Proposition 65 listings, if applicable. The array of NSF drinking water criteria includes the total allowable concentration (TAC), which is the maximum concentration of a nonregulated contaminant allowed in a public drinking water supply. NSF criteria and/or California standards have not been established for many of the compounds listed in Table 4.4-1.

ODORS

Odors are generally regarded as an annoyance rather than a health hazard. However, manifestations of a person's reaction to foul odors can range from psychological (e.g., irritation, anger, anxiety) to physiological (e.g., circulatory and respiratory effects, nausea, vomiting, headache).

With respect to odors, the human nose is the sole sensing device. The ability to detect odors varies considerably among the population and is quite subjective. Some individuals have the ability to smell very minute quantities of specific substances; others may not have the same sensitivity but may have sensitivities to odors of other substances. In addition, people may have different reactions to the same odor; in fact, an odor that is offensive to one person (e.g., from a fast food restaurant) may be perfectly acceptable to another. Unfamiliar odors are more easily detected than familiar odors and are more likely to cause complaints. This is because of the phenomenon known as odor fatigue, in which a person can become desensitized to almost any odor and recognition occurs only with an alteration in the intensity.

Quality and intensity are two properties present in any odor. The quality of an odor indicates the nature of the smell experience. For instance, if a person describes an odor as flowery or sweet, then the person is describing the quality of the odor. Intensity refers to the strength of the odor. For example, a person may use the word "strong" to describe the intensity of an odor. Odor intensity depends on the odorant concentration in the air. When an odorous sample is progressively diluted, the odorant concentration decreases. As this occurs, the intensity of the odor weakens and eventually becomes so low that detection or recognition of the odor is quite difficult. At some point during dilution, the concentration of the odorant reaches a detection threshold. An odorant concentration below the detection threshold means that the concentration in the air is not detectable by the average human.

A water utility strives to provide drinking water free of objectionable tastes and odors, because users often judge water quality by its aesthetic properties. In addition to background conditions present in source water (such as mineral content), leaching of system materials (such as those used in water distribution systems; here, PEX

tubing) or the permeation of compounds from outside the system (e.g., from soil, water, or vapors) can affect the taste and odor of water.

4.4.3 ENVIRONMENTAL IMPACTS

ANALYSIS METHODOLOGY

The analysis of impacts to water quality is based on the applicable laws and regulations identified in the regulatory setting above, a review of all the possible hazardous chemical compounds contained in PEX, a review of literature about relevant drinking water standards for chemicals known to leach from PEX, available health risk assessments for chemicals known to leach from PEX, the expert opinion of toxicologists familiar with the health effects of contaminants shown to leach from PEX, studies addressing potential permeability and leachability of hazardous chemical compounds from PEX formulations, and surveys of building officials throughout California regarding consumer and professional experience with PEX.

The analysis of chemical compounds that potentially leach from PEX products into drinking water considers the results of both single time point and multiple time point exposure data from tests conducted by NSF in accordance with NSF/ANSI Standard 61—Drinking Water System Components McLellan, pers. comm., 2008a; McLellan, pers. comm., 2008c). First, the analysis identifies those chemical compounds for which California has established health-based drinking water standards (i.e., PHGs or MCLs) that are lower (i.e., more stringent) than the standards necessary to comply with NSF/ANSI Standard 61. Next, the analysis compares the single time point exposure levels NSF has provided for these compounds and, if the single time point exposure levels do not exceed applicable California's drinking water standards, no additional analysis is necessary. If, however, the single time point exposure level for any compound exceeds an applicable California-adopted PHG or MCL, then the multiple point exposure levels are examined and/or standards used by other government agencies are considered.

The primary MCLs, which DPH established to apply to the water supplied to the public by community water systems, are one of many considerations used to assess the potential for significant adverse health effects from each contaminant. Other considerations include the best available scientific information about the magnitude and duration of exposure to chemicals that leach from PEX and input from toxicologists with expertise with the relevant contaminants.

For the analysis of cancer risk specifically, considerations include:

- the maximum total lifetime dose;
- the maximum allowable lifetime dose of MTBE that is protective of an incremental increase in cancer risk of one in one million;
- the extent and duration of any exceedances of the TAC or primary MCL;
- concentration of MTBE; and
- rate of drinking water consumption at that concentration.

The evaluation of taste and odor impacts in drinking water is qualitative in nature but nonetheless takes into account the secondary MCLs established by DPH, including the development, intent and application of secondary MCLs; the extent and duration of potential exceedances; and the extent of any recorded complaints about taste and odor from drinking water in communities that have been using PEX.

If any applicable secondary MCLs could be exceeded, the analysis considers the duration of such exceedances (i.e., short- vs. long-term), the frequency of such occurrences, the likelihood that they would affect a substantial number of people, and the likelihood to result in complaints.

THRESHOLDS OF SIGNIFICANCE

The significance criteria below were developed for use in assessing potential impacts to water quality resulting from implementation of the proposed project. The proposed project would result in a significant effect related to water quality if it would:

- result in a level of a contaminant in drinking water that would cause a substantial adverse effect on human health; or
- would result in a level of a contaminant in drinking water that would exceed a federal or state secondary MCL for taste and odor and cause a substantial number of persons to experience unpleasant taste or odors in drinking water for an extended period of time.

IMPACT ANALYSIS

IMPACT 4.4-1 Water Quality—Human Health Impacts Resulting from Leaching of Chemicals from PEX Tubing. *All PEX tubing sold in California would comply with the health-based standards of NSF/ANSI Standard 61, which are protective of cancer and noncancer (both chronic and acute) risk. Testing for MTBE demonstrates that DPH's primary MCLs would not be exceeded for a length of time or to a degree sufficient to cause a substantial adverse effect on human health. Multiple credible scientific sources cast doubt on the validity of DPH's primary MCL for tertiary butyl alcohol (TBA), and thus, the more robust NSF-established health standard for TBA is used for the purposes of this impact analysis, which shows no significant adverse effects on human health from TBA. Therefore, leaching levels of chemicals from PEX tubing sold in California would not result in significant effects on water quality. This impact would be* ***less than significant****.*

This analysis begins with a discussion of how the health-protective standards in the NSF/ANSI Standard 61 and California drinking water standards apply to PEX, followed by detailed discussion about the potential for PEX to result in increased cancer as well as noncancer toxicity from long-term and short-term exposures to the concentrations of hazardous chemicals known to leach from some PEX formulations into drinking water.

For some compounds that may be present in PEX products, California drinking water criteria are more stringent than those used to certify products using the NSF/ANSI Standard 61. Therefore, it is possible that some compounds could be present in water from NSF-certified PEX pipe that would exceed California drinking water criteria. As discussed above these compounds include benzene, cadmium, carbon disulfide, 1,1-dichloroethane, ethyl benzene, di(2-ethylhexyl) phthalate, benzo(a)pyrene, toluene, TBA, and MTBE. The various manufacturers of PEX use different, proprietary formulations and these formulations may or may not contain one or more of those chemicals for which the California primary or secondary MCL or the notification levels are more stringent than the NSF standards (i.e., those chemicals shaded in Table 4.4-1).

NSF tested new samples of all 271 PEX products that were available between January 1, 2005 and December 31, 2007. All of these tests were performed on samples of new products (i.e., previously unused) and the single time point exposure levels of each sample were measured after subjecting the products to a specific regimen of water conditions. These procedures are referred to as single time point exposure protocols as presented in Section 4.5.6 of NSF/ANSI Standard 61 (McLellan, pers. comm., 2008a). This discussion refers to the extraction levels measured during these tests as "single time point" exposure levels because the chemical concentrations were measured at a single point in time during the same early age of the product sample's in-service life.

The single time point exposure level tests conducted by NSF found that DPH's drinking water standards for benzene, cadmium, carbon disulfide, 1,1-dichloroethane, ethyl benzene, di(2-ethylhexyl) phthalate, benzo(a)pyrene, and toluene were not exceeded in any of the PEX products tested. The single time point exposure levels measured for TBA and MTBE, however, were found to exceed California MCLs or notification levels in

some of the PEX products tested (McLellan, pers. comm., 2008a). Each of these two compounds is discussed in greater detail below.

Tertiary Butyl Alcohol

There is substantial scientific evidence that the California notification level of 12 µg/L for TBA is not appropriate, and that calls into question its applicability to human health risk assessment. This evidence casts doubt on using the notification level as a threshold of significance. The Director of Toxicology at NSF has opined that the notification level is inappropriate as a threshold of significance for several reasons. Foremost, the notification level is not based on a sufficient human health risk assessment (Bestervelt, pers. comm., 2008). An evaluation by the California Office of Environmental Health Hazard Assessment (OEHHA) of risk assessment for TBA indicates that the process for derivation of the 12 µg/L notification level in 1999 was noted as an "interim assessment with preliminary calculations, and by no means represents a full risk assessment" and was "based on limited data" (OEHHA 1999c). The limit-setting process of the TBA risk assessment used methods that have since been determined to not be relevant to human health, a conclusion supported by EPA (EPA 1998 as cited in Bestervelt, pers. comm., 2008). Furthermore, by definition, notification levels are "…nonregulatory, health-based advisory levels…for which maximum contaminant levels have not been established" (California Health and Safety Code Section 116455[c][3]).

NSF conducted a chemical-specific human health risk assessment of TBA that provided a toxicological assessment of TBA in drinking water using risk assessment methodology developed by EPA and identified the TAC for TBA to be 9,000 µg/L, and the short-term exposure limit (STEL) to be 40,000 µg/L, as shown in Table 4.4-1 above (NSF International 2003). NSF/ANSI Standard 61 defines the short-term exposure period as the first 14 days of the in-service life of a product (NSF International 2007). Because NSF's reference criteria for TBA have withstood thorough peer review, they are used in this analysis to determine whether the extraction levels of TBA from PEX piping would result in a level of TBA in drinking water that would cause a substantial impact on human health. The results of NSF's testing indicate that none of the 271 PEX products were found to exceed the TAC of 900 µg/L for TBA (McLellan, pers. comm., 2008a). Therefore, the levels of TBA that leach from PEX products are not considered to cause or contribute to a substantial impact on human health.

Methyl Tertiary-Butyl Ether

NSF/ANSI Standard 61 applies a standard of 100 µg/L (or 100 ppb) as a threshold below which concentrations of MTBE that leach from products that contact drinking water are determined not to result in adverse human health effects (NSF International 2008, while the primary MCL established by DPH for MTBE is 13µg/L (13 ppb) (DPH 2007b).

Both NSF standard and the OEHHA primary MCL for MTBE are developed using standard risk equations that include chemical-specific toxicity values such as cancer slope factors and reference doses which are designed to be protective of sensitive individuals such as children and the elderly. In NSF's risk assessment for MTBE (provided in Appendix B), the extensive literature review identified no data indicating that infants or children are uniquely susceptible to MTBE and, therefore, no additional adjustment factors were applied (McLellan 2009). The main difference between the standard used by NSF and the primary MCL established by DPH for MTBE is that the NSF standard is protective of an incremental increase of cancer of one in one hundred thousand and the primary MCL is protective of an incremental increase of cancer of one in one million. EPA considers a target risk range of one in one million to 100 in one million to be safe and protective of public health (EPA 1991a, as cited in NSF International 2008). MTBE extraction levels collected from both of single time point testing and multiple time point testing, including comparison to the primary MCL of 13µg/L established by DPH, are discussed separately below. The protocol for single time point testing and multiple time point testing are part of NSF/ANSI Standard 61.

Single Time Point Extraction Levels

Table 4.4-2 depicts the single time point exposure levels of MTBE as a percentage of all PEX products tested between January 1, 2005 and December 31, 2007.

Table 4.4-2
Single Time Point Extraction Levels of MTBE as a Percentage of All Products Tested [1]

Compound	Not Detected at 5 µg/L	5 to 13 µg/L	13 to 20 µg/L	Greater than 20 µg/L
methyl tertiary-butyl ether (MTBE)	74.6%	21.4%	4%	0%

Notes: µg/L = micrograms per Liter
[1] All testing was performed between January 1, 2005 and December 31, 2007. Results show a breakdown of PEX product samples according to their single time point extraction levels of MTBE.
Source: Single time point exposure results of NSF/ANSI Standard 61 testing, as presented in Table 2 of McLellan, pers. comm. 2008a. .

As shown in Table 4.4-2, 4% of the tested product samples leached initial concentrations of MTBE that exceed DPH's (health-based) primary MCL of 13µg/L. As described above, all the leached concentrations were measured by NSF on product samples that were new (i.e., previously unused) and, pursuant to the single time point protocol of NSF/ANSI 61, each sample was collected after product samples were subject to a specific regimen of water conditions and at the same early age of the product sample's in-service life (McLellan, pers. comm., 2008a).

Multiple Time Point Extraction Levels

Section 4.5.4.3 of NSF/ANSI Standard 61 specifically states that "when the normalized concentration of a contaminant exceeds, or is expected to exceed, its acceptable level when evaluated as a single time point exposure, determination of the contaminant leaching rate using a multiple time point exposure shall be considered" (NSF International 2007). Because single time point exposure testing showed that some samples of PEX exceed DPH's (health-based) primary MCL of 13µg/L for MTBE, multiple time point testing (also referred to as over-time testing) was conducted to determine the long-term extraction of MTBE (McLellan, pers. comm., 2008d). NSF conducted multiple point time testing of those particular formulations of PEX "with the greatest potential to extract MTBE based on their formulations and their high [single time point] extraction levels of TBA and MTBE" (McLellan, pers. comm., 2008f). Thus, ten samples of PEX from different PEX manufacturers were subject to multiple time point testing; those samples represented all the PEX formulations that could extract MTBE (McLellan, pers. comm., 2008f).

All 10 PEX samples were subjected for 16 days to a regimen of water conditions that mimic the flushing requirements of the California Plumbing Code (discussed in Section 4.4.1, "Regulatory Setting," above) and result in water conditions similar to which first time consumers would be exposed. After the regimen of water conditions, water was tested on 10 separate test days over a 90-day period. The test results are summarized in Table 4.4-3. More details about the testing parameters and results are provided in Appendix E.

As shown in Table 4.4-3, the test results show that the concentrations of MTBE for each PEX sample decline over time, and MTBE extraction levels from all the PEX samples were below 13 µg/L (or 13 ppb) by day 90 (McLellan, pers. comm., 2008d). The specific rate at which MTBE extraction levels diminish with time from each of the PEX samples is also provided by NSF (*See* the plot graphs in Appendix A of McLellan, pers. comm., 2008d, which is provided in Appendix E of this document). These graphs show that the MTBE concentrations were less than 13 µg/L on day one of the tests for six of the 10 samples subjected to multiple time point testing, the MTBE concentrations from two other samples fell below 13 µg/L by the tenth day of testing, and the remaining two samples fall below 13 µg/L by day 90. Therefore, even the formulations of PEX that have the highest initial extraction levels comply with both NSF's standard of 100 µg/L and California's PHG and primary MCL of 13µg/L for MTBE within 90 days of initial use, with the majority complying on day 1.

Table 4.4-3 MTBE Extraction Levels from PEX Piping After 90 Days of Use [1]	
Sample	MTBE Concentration (µg/L [ppb])
1	5.4
2	7.3
3	ND (0.3)
4	ND (0.3)
5	8.8
6	11
7	0.47
8	ND (0.3)
9	ND (0.3)
10	ND (0.3)

Notes: µg/L = micrograms per Liter
ppb = parts per billion
ND = Non-Detectable
[1] Multiple time point testing was performed by NSF on those formulations of PEX most likely to leach high concentrations of MTBE. These 10 samples are representative of the 4% of PEX products that were identified in single time point testing, shown in Table 4.4-2.
Source: Single time point exposure results of NSF/ANSI Standard 61 testing, as presented in Table 1 of (McLellan, pers. comm., 2008d).

HEALTH RISK

The potential for PEX to expose people to significant adverse health risk is analyzed using the information and test results discussed above. Each category of risk is discussed separately below.

Cancer Risk

Both NSF and OEHHA have identified MTBE to be a potential human carcinogen and developed concentration-based standards protective of cancer risk from the oral ingestion of MTBE in drinking water (NSF International 2008; OEHHA 1999). A number of concepts are important to the understanding of how cancer risk is assessed. First, NSF and OEHHA developed their respective standards based on a review of laboratory studies that investigate the dose-response relationship of MTBE. The dose-response relationship (or dose-response model) is a mathematical function that predicts a measure of an effect, commonly referred to as the "response", to a change in dose (EPA 2008). Dose is a function of multiple variables, including the concentration of a substance to which a population is exposed (typically measured in ppm or mg/L for drinking water), the rate of consumption (typically expressed in L/day for drinking water), and the duration of exposure (e.g., the number of days) (EPA 1992). Dose is positively correlated with time, meaning that a longer exposure period results in a higher exposure level for the exposed person or persons. Thus, higher levels of risk are estimated for people if a fixed consumption rate and concentration occur over a longer period of time.

Cancer risk is expressed in terms of the probability of an exposed population experiencing an incremental increase in incidences of cancer. Cancer risk is often expressed as the maximum number of *additional* cancer cases that would occur assuming daily exposure over the 70-year lifetime of one million exposed individuals ("X in a million") (OEHHA 2001; EPA 1997a; McLellan, pers. comm. 2010b). In order to be protective, when the toxicity of any carcinogenic chemical is assessed it is assumed that there is no theoretical level of exposure for such a chemical that does not pose a small but finite increased probability of generating a carcinogenic response (EPA 2010; OEHHA 2001; McLellan, pers. comm. 2010b). Thus, an individual's actual risk of contracting cancer from exposure to a chemical is often less than the theoretical risk. While it would be ideal to completely eliminate all exposure to carcinogens, government agencies recognize that it is usually not possible or feasible to eliminate all traces of a chemical. The goal of most regulatory agencies is to reduce the health risks associated with exposure to hazardous pollutants to a negligibly low level (OEHHA 2001).

As stated in the regulatory setting, each PHG established by DPH, including the PHG/MCL for MTBE, and NSF's TAC, represent the level of a contaminant in drinking water that would pose no significant health risk to individuals consuming water with that concentration of contaminant *on a daily basis over a lifetime* (italics added for emphasis) (OEHHA 1999). Thus, DPH's primary concern is about the cancer risk associated with long-term exposure of people to levels of MTBE that exceed 13 µg/L rather than short-term exposure. (See, e.g., California Code of Regulations, Section 64468.2(l) stating that a "chemical has been shown to cause cancer in laboratory animals such as rats and mice when the animals are exposed at high levels over their lifetimes" and that "chemicals that cause cancer in laboratory animals also may increase the risk of cancer in humans who are exposed over long periods of time.") The relevant consideration in assessing the potential for a chemical to result in an unacceptable risk of cancer is whether people will be exposed to levels of that chemical exceeding the health-protective exposure standard, which could not occur unless a person consumed enough drinking water (i.e., 2 or 3L a day) with contaminant levels exceeding the standard for a period of 70 years. Any exposure less than this level would not result in an unacceptable increase in cancer risk.

Based on the over-time test results (see Table 4.4-3, above), exposure to levels of MTBE that exceed the threshold dose would not occur. MTBE extraction levels in *all samples* were lower than 13 µg/L by day 90; it is evident that no sample would exceed 13 mg/L for a lifetime.

In any case, where the biological response to cancer effects is described in terms of lifetime probabilities, even though exposure may not occur over the entire lifetime, doses are often presented as lifetime average daily doses (LADDs) and typically expressed in mg/day (ppm) or µg/day (ppb) or the total lifetime dose (EPA 1997a; OEHHA 2003). The total lifetime dose refers to the total mass of a chemical to which an individual is exposed over his/her lifetime and it is typically calculated assuming a 70-year lifetime. The lifetime dose is typically expressed in mg/life or µg/life.

For purposes of illustration, the lifetime average daily dose of MTBE determined by DPH to be protective would be the concentration-based standard of 13 µg/L, multiplied by the drinking water rate of 3 L/day, or 39 µg/day. This average dose is protective of an incremental increase in cancer risk of one in one million (10^{-6}). This computation is presented on page F-2 of Appendix F.

Because the concentrations of MTBE that leach from PEX products diminish over time, this analysis examines whether the total lifetime dose of MTBE that leaches from PEX products (a mass quantity) would exceed the maximum allowable lifetime dose that would result in level of increased cancer risk of one in one million (10^{-6}), (also a mass quantity). The maximum allowable lifetime dose associated with the incremental increase in risk of one in one million is the product of the lifetime average daily dose of 39 µg/day and 70 years of exposure for 365 days per year, which is equal to a mass of 996,450 µg over the course of an individual's lifetime. This is the key metric for evaluating the lifetime dose of MTBE leached from PEX pipe. Details of this calculation are included on page F-3 of Appendix F.

Based on the results of the multiple time point testing provided by NSF (McLellan, pers. comm., 2008d), the lifetime dose of MTBE that leaches from PEX was estimated to be 286,751 µg over the course of an individual's lifetime. The calculations used to estimate the lifetime dose of MTBE from PEX are provided on pages F-4 through F-8 of Appendix F. The methods used to estimate the lifetime dose of MTBE from PEX were conservative in a number of ways. First, among the 10 formulations of PEX subjected to multiple time point testing—and these 10 samples are representative of those PEX products most likely to leach higher concentrations of MTBE—the maximum lifetime dose of MTBE from PEX was calculated using the formulation of PEX that leached the highest concentrations of MTBE during the multiple time point testing (i.e., Sample 6, as presented in McLellan, pers. comm., 2008d). Sample 6 leached the highest concentrations of MTBE on both day 1 and day 107 of the multiple time point testing.

Because PEX formulations contain a limited quantity of MTBE it is reasonable to assume that concentrations of MTBE that leach from PEX piping continue to diminish with time beyond the 107-day test period and it is reasonable to use the natural decay function to estimate the rate in which concentrations diminish (Borak, pers. comm. 2010b). Thus, the natural decay function was applied to extrapolate the concentration of MTBE that would

leach from Sample 6 on day 180 using the lowest decay rate calculated among the ten decay rates observed for the 10 tested samples. Further, it was conservatively assumed that the concentration would not diminish beyond the 180th day. Detailed calculations are presented on pages F-4 and F-5 of Appendix F.

Finally, using the very conservative assumptions outlined above, the maximum lifetime dose of MTBE that an individual could consume from water that has been in contact with PEX was estimated to be 286,751 µg, which is less than the total maximum allowable lifetime dose of 996,450 µg that is associated with an incremental increase in cancer risk of one in one million (10^{-6}). In other words, the maximum incremental increase in cancer risk from a lifetime exposure to drinking water from systems that use PEX is 0.29 in one million. This is not a substantial level of cancer risk (Borak, pers. comm. 2010a).

It is theoretically possible that construction workers who install PEX piping or are regularly around PEX pipe installations could drink water that contains concentrations of MTBE that exceed 13 µg/L on a daily basis; however, this is highly unlikely to occur for a number of reasons. First, PEX comprises approximately one third of the market for plumbing materials and only a small percentage of PEX formulations leach initial concentrations of MTBE that exceed 13 µg/L (4% of PEX formulations according to the results of single time point testing presented in Table 4.4-2). Thus, it is unlikely that a worker would be installing only the highest-leaching formulations of PEX on a regular basis. Second, it is reasonable to assume that workers who install PEX are familiar with and understand all applicable CPC requirements, including the flushing requirements for PEX installations. For these reasons, it is reasonable to assume that no worker would consume substantial volumes of water from newly installed PEX of the type leaching the highest levels of MTBE on a daily basis at the exposure levels necessary to produce adverse effects.

In summary, the results of the single time point testing and multiple time point testing of PEX show that the concentrations of leached chemicals from PEX tubing would not exceed any applicable NSF standards or California PHGs/MCL to a degree, or for a period of time, that would cause any significant risk of cancer in persons drinking water that has passed through PEX. Furthermore, detailed calculations, based on multiple conservative assumptions, used to analyze the highest-leaching PEX product indicate that the maximum total lifetime dose of MTBE that an individual could consume by drinking water from systems that use PEX would have an associated incremental increase in cancer risk of less than one in one million (10^{-6}). Thus, while a small percentage of PEX products would leach MTBE at levels that exceed the California MCL within the first 90 days of their in-service life, this level is insignificant in light of the relevant toxicological health risk considerations and would not have the potential to cause substantial adverse effects to human health.

Noncancer Toxicity

As stated in the regulatory setting, the drinking water standards used in NSF/ANSI Standard 61, as well as the PHGs established by California, are protective of all categories of health risk, including noncancer toxicity from long-term exposure. Upon considering all available studies, the adverse effect that occurs at the lowest dose is selected as the critical effect for risk assessment. Because it is impractical to study all possible relationships for all possible health responses to a chemical, toxicity research typically focuses on testing for a limited number of adverse effects that are of greatest risk. The underlying assumption is that if the most critical risk is prevented from occurring, then no other effects of concern will occur (EPA 2010). Thus, no PEX formulation that is certified according to NSF/ANSI Standard 61 would leach concentrations of hazardous chemicals that would subject persons to noncancer chronic toxicity for oral ingestion of drinking water that has come into contact with PEX.

With regard to MTBE, the level of cancer risk from oral ingestion is greater than any other type of risk, including noncancer chronic risk. As a result, both the California PHG/MCL and NSF TAC were set based on the level necessary to protect against cancer risk, which is a lower concentration than the concentrations necessary to be protective of other risks. Thus the adopted levels of 13 µg/L and 100 µg/L, respectively, both are protective of all categories of risk, including cancer and noncancer risk (OEHHA 1999b; NSF International 2008).

This point is demonstrated by the fact that both NSF and OEHHA identified reference concentrations for MTBE that are protective of noncancer toxicity that are greater than the TAC and PHG they respectively established to be protective of cancer risk. A reference concentration is an estimate of a continuous exposure (in this case, via oral ingestion) to the human population that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. The MTBE concentrations that NSF and OEHHA identified as being protective of noncancer toxicity are analyzed further below.

NSF identified a reference concentration of 100 µg/kg-day (and an associated TAC of 700 µg/L) to be protective of noncancer toxicity in its April 2010 *Addendum to Draft Methyl tertiary-Butyl Ether Oral Risk Assessment Document* (*Addendum*) (NSF International 2010), which is provided in Appendix C. The critical effect used by NSF to support this finding was the liver effects associated with oral ingestion of MTBE by rats, an effect identified in a study by Robinson et al. (1990). OEHHA's risk assessment for MTBE, which is included in Appendix D, also considered the study in rats by Robinson et al. (1990) (OEHHA 1999b); however, the reference concentration identified by OEHHA as being protective of noncancer toxicity, 47 µg/L (ppb), is based on effects to the kidneys of male rats, which was another effect identified in Robinson et al. (1990). However, subsequent studies have demonstrated that any adverse kidney effects indicated by the Robinson study were due to a gender- and species-specific effect that is unique to male rats and not applicable to humans. There is no evidence to support a finding that MTBE is likely to result in adverse effects to kidneys in humans (Johnson, Findlay, and Boyne 1992; Klan et al. 1993; Borak, pers. comm. 2010a). Thus, this analysis considers the TAC NSF identified for MTBE as being protective of noncancer toxicity, 700 µg/L, to be more robust and accurate.

Lastly, the concentration of MTBE identified by NSF as bring protective of noncancer toxicity, 700 µg/L, is based on an assumed drinking water consumption rate of 2 L/day for a duration of 70 years. The results of the single time point testing of MTBE, as shown in Table 4.4-2 above, indicate that none of PEX formulations would leach concentrations of MTBE that exceed NSF's reference concentration of 700 µg/L. Therefore, concentrations of MTBE that leach from PEX would not be sufficient to result in noncancer toxicity.

In summary, the results of the single time point testing of PEX show that the concentrations of leached chemicals from PEX tubing would not exceed any applicable NSF standards or the concentrations identified for MTBE by NSF (and OEHHA) as protective of noncancer toxicity. The results of the multiple time point testing show that the concentrations of leached MTBE from PEX would not exceed NSF's TAC (or DPH's less MCL, which is less robust given the subsequent finds from peer review) to a degree, or for a period of time, that would cause any significant level of noncancer chronic risk in persons drinking water that has passed through PEX. While a small percentage of PEX products would leach MTBE at levels that exceed the California MCL for a short-term period, this level of exceedance is insignificant in light of the relevant toxicological health risk considerations and would not constitute a lifetime dose that would have the potential to cause substantial adverse effects to human health.

Toxicity from Short-Term Exposure

For some chemicals, even if the average exposure concentration of a chemical is less than the applicable standards established for the protection of long-term effects (cancer and noncancer), some acute toxic effects could occur from single or limited number of exposures to "peak" concentrations. This is why any short-term exposure level (STEL) established for a chemical is always greater than or equal to the TAC established for a chemical (NSF International 2008). NSF/ANSI Standard 61 defines the short-term exposure period as the first 14 days of the in-service life of a product (NSF International 2007). For MTBE, NSF has not established a STEL; thus, all concentrations that are below the TAC, which is protective of risk from long-term exposure, also are protective of acute risk from short-term exposure (McLellan 2009). In addition to the TAC of 100 µg/L, NSF has also established a NOAEL for MTBE of 300 mg/kg-day, which, by definition, is the level at which there is no observed adverse effect (NSF International 2008).

The primary MCL established by OEHHA is similar in this respect. As stated in the regulatory setting, the PHG is the level at which the contaminant will not pose a significant risk of either acute (sudden and severe) or chronic (prolonged or repeated) effects to human health. Thus, both the OEHHA-established PHG and the drinking water standards used in the NSF/ANSI Standard 61 are protective of all three categories of health risk, including acute

risk from short-term exposure. Therefore, no PEX formulation that is certified according to ANS/ANSI Standard 61 would leach concentrations of hazardous chemicals that would subject a person drinking the water to acute risk.

For MTBE, however, the California PHG of 13 µg/L is more stringent than the NSF standard of 100 µg/L and, as shown in Table 4.4-2 above, testing conducted according to the protocol of NSF/ANSI Standard 61 indicates that concentrations of MTBE greater than 13µg/L can leach from approximately 4% of PEX formulations in the short-term (i.e., within 90 days of installation of new PEX pipe [i.e., the in-service life of the product]). The report prepared by OEHHA that established the PHG for MTBE provides additional insight regarding why the level of 13µg/L level was established (OEHHA 1999). In its report, OEHHA includes the following discussion about the acute health effects from exposure to MTBE:

> "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, and cough) associated with exposure to gasoline containing MTBE have not been confirmed in controlled studies and remain to be fully evaluated."

Based on OEHHA's discussion it can be resolved that acute toxicity is not the critical risk type (or driving factor) used by OEHHA to develop the PHG of 13µg/L; instead cancer risk was considered to be the type of risk of greatest concern and, like all risk standards developed to be protective of cancer risk, this standard is not to be exceeded over the lifetime of an exposed individual rather than any shorter-term period such as the first 14 days of the in-service life of a product, which is the way the NSF/ANSI Standard 61 defines the short-term exposure period of product (NSF International 2007).

Thus, this analysis does not use the PHG of 13µg/L to determine whether short-term exposure to leached concentrations of MTBE from PEX piping would cause a substantial impact on human health. Because OEHHA has not identified a STEL for oral ingestion of MTBE, the assessment of acute toxicity in analysis relies on other, applicable levels, which are discussed below.

Quantitative criteria for evaluating the risk of acute toxicity associated with short-term exposure to MTBE via oral ingestion, such as STELs, have not been established by EPA, DPH, or ARB. EPA's chemical summary for MTBE states that "animal lethality data indicate that MTBE is low in acute toxicity" (EPA 1994). ATSDR, however, has developed minimal risk levels (MRLs) for acute and intermediate exposure to MTBE via oral ingestion. The ATSDR-established MRLs for acute and intermediate exposure to MTBE from oral ingestion are 400 µg/kg-day and 300 µg/kg-day, respectively (ATSDR 2009b). Incorporated into these MRLs is an uncertainty factor of 10 because they are based on animal studies rather than human studies and a second factor of 10 to account for human variability (Chou, pers. comm., 2010). As stated in the regulatory setting above, these and other MRLs developed by ATSDR are intended to serve as screening levels because they are intended to help public health professionals decide where to look more closely (ATSDR 2009a).

As shown in Table 4.4-2, neither MRL established by ATSDR is exceeded for any PEX formulation or product. Applying the assumption that a person consumes drinking water at a rate of 3 L/day, which is the consumption rate OEHHA uses for assessing long-term risk exposure, and the concentration of MTBE in that drinking water is 20 µg/L, which is the upper range of MTBE concentrations measured from PEX formulations (see Table 4.4-2), then the maximum credible exposure of a person drinking water from PEX piping would be 60 µg/day (i.e., 3 L/day times 20 µg/L). This consumption level is well below both of ATSDR's MRLs. Moreover, ATSDR-established MRLs are metrics that are normalized to a person's bodyweight (i.e., per kilogram), and it can be safely assumed that individuals weigh more than 1 kg. For example, based on the ATSDR-established MRL, a 70 kg adult could orally ingest MTBE at a rate up to 28,000 µg/day before experiencing a short-term adverse acute affect and up to 21,000 µg/day before experiencing an intermediate adverse acute affect. Also based on the ATSDR-established MRL, a 10 kg child could orally ingest MTBE at a rate up to 4,000 µg/day before experiencing a short-term adverse acute affect and at a rate up to 3,000 µg/day before experiencing an

intermediate adverse acute affect. This would also be the case if these comparisons were made using the NOAEL of 40,000 ug/kg-day stated in OEHHA's oral risk assessment (*See* OEHHA 1999b), because this value is higher than ATSDR-established MRLs.

In conclusion, PEX tubing that is certified according to NSF/ANSI Standard 61 is compliant with the NSF drinking water standards, which are protective of acute toxicity. Moreover, application of standards with metrics that normalize to a person's bodyweight—including the NOAEL established by OEHHA, the NOAEL established by NSF and the MRLs from ATSDR— shows that neither (heavier) adults nor (lighter) children would consume drinking water at a rate that would exceed the mass of MTBE that their bodies could tolerate without experiencing adverse acute affects. For these reasons, the consumption of drinking water from systems that use PEX tubing would not cause a substantial adverse acute affect on human health.

GENOTOXICITY, MUTAGENICITY, AND OTHER CATEGORIES OF RISK

During the administrative proceedings for the Recirculated DEIR, a commenter asserted that short-term exposure to elevated levels of MTBE in drinking water from PEX pose a health concern because "MTBE is a genotoxic carcinogen" (CSPTC 2008). Genotoxicity or genetic toxicity refers to the degree to which a substance causes damage to or mutation of DNA. Genotoxic substances are known to be potentially mutagenic or carcinogenic, specifically those capable of causing genetic mutation and of contributing to the development of tumors. Contrary to the commenter's assertion, there is no evidence that MTBE is genotoxic in humans.

Where relevant, the drinking water standards incorporated in NSF/ANSI Standard 61 account for potential genotoxic risk (NSF International 2007; NSF International 2008; McLellan, pers. comm., 2008b). With regard to MTBE specifically, when establishing a TAC of 100 ppb NSF's oral risk assessment considered all available studies related to oral ingestion of MTBE, including the chemical's potential to result in genotoxic effects (NSF International 2008, See specifically Section 8.5, Studies of Genotoxicity and Related Endpoints; Section 9.1, Risk Characterization; and Section 9.1.2, Weight of Evidence Evaluation and Cancer Characterization). Despite NSF's statement that MTBE has "some genotoxic potential," the animal studies cited in the risk assessment presented no evidence that would support a finding that exposure to MTBE in drinking water at the levels and for the duration found to be leached by PEX would create any significant risk of genotoxic effects in humans. In a number of instances initial results suggestive of genotoxicity were not confirmed or replicated in subsequent tests, or were attributed to the effects of formaldehyde, or were based on doses substantially higher than any realistic exposure to MTBE in drinking water leached from PEX tubing. Based on these studies of MTBE's genotoxicity, NSF did not identify MTBE as presenting a significant genotoxic risk to human health. This is consistent with the findings of the PHG established by OEHHA, which concluded that "MTBE genotoxicity data is weak" and "there is no clear evidence" of genotoxicity from MTBE (OEHHA 1999b). Therefore, the drinking water standards used in NSF/ANSI Standard 61 and the MCL adopted by DPH, which are protective of both risks from both long-term and acute exposures, are considered to have adequately evaluated the risk of genotoxicity associated with MTBE, and there is no evidence to support a determination that exposure to MTBE in drinking water at the levels and for the duration found to be leached by PEX would create any significant risk of genotoxic effects in humans.

Mutagenicity refers to the capacity of a chemical or physical agent to cause permanent genetic alterations. A mutagen is a substance or agent that induces heritable change in cells or organisms as compared to a carcinogen, which is a substance that induces unregulated growth processes in cells or tissues of multicellular animals, leading to cancer. Some chemicals are both carcinogens and mutagens. EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* addresses a number of issues pertaining to cancer risks associated with early-life exposures and provides specific guidance on potency adjustment only for carcinogens acting through a mutagenic mode of action (EPA 2005). This guidance includes various age-related adjustment factors, for addressing cancer risk to children from early-life exposure to chemicals with a mutagenic mode of action. However, the supplemental guidance states that the adjustment factors are meant to be used only when no chemical-specific data are available to assess directly cancer susceptibility from early-

life exposure to a carcinogen acting through a mutagenic mode of action and, furthermore, MTBE is not one of the many chemicals identified to have a mutagenic mode of action in the supplemental guidance.

In addition, the literature review of laboratory studies regarding the mutagenicity of MTBE in NSF's oral risk assessment did not include conclusive evidence that MTBE has a mutagenic mode of action (NSF International 2008). More generally, NSF's oral risk assessment found that there were no data that indicated infants or children as a uniquely susceptible to MTBE (McLellan 2009). Therefore, the special provisions outlined in EPA's supplemental guidance, including the age-related adjustment factors, were not applied when NSF developed its health protective standard of 100 µg/L. Similarly, the OEHHA's health hazard assessment of MTBE did not find conclusive evidence that MTBE is a mutagen (OEHHA 1999a) and this is why age-related adjustment factors were not applied in DPH's development of the primary MCL of 13 µg/L.

The drinking water standards used in NSF/ANSI Standard 61 and the primary MCL adopted by DPH also account for assays that have been performed for many other types of toxicity, including subchronic toxicity, immunotoxicity, neurotoxicity, developmental toxicity, and reproductive toxicity (NSF International 2007; OEHHA 1999). Similarly, the drinking water standards used in NSF/ANSI Standard 61 and all the California-adopted standards are considered to be protective of risk from these types of toxicities as well.

In summary, the results of the single time point testing and multiple time point testing of PEX show that the concentrations of leached chemicals from PEX tubing would not exceed any applicable NSF standards or DPH's primary MCL to a degree, or for a period of time, that would cause any significant genotoxic, mutagenic, or other type of risk in persons drinking water that has passed through PEX. While a small percentage of PEX products would leach MTBE at levels that exceed the California primary MCL, they would not exceed it for a period of time sufficient to cause substantial adverse effects to human health.

SUMMARY

All formulations of PEX tubing sold in California are required to be certified according to NSF/ANSI Standard 61, which contains requirements that are designed to be protective against significant adverse human health effects— including cancer, chronic, and acute affects, as well as genotoxicity—from products that contact drinking water (NSF International 2007. DPH's primary MCLs for some compounds are more stringent than those used in NSF/ANSI Standard 61; however, single time point testing of PEX shows that leaching levels of all but one of those compounds for which California has a more stringent standard than is used by NSF—benzene, cadmium, carbon disulfide, 1,1-dichloroethane, ethyl benzene, di(2-ethylhexyl) phthalate, benzo(a)pyrene, and toluene—would not exceed DPH's primary MCLs. No PEX products would leach concentrations of TBA that would exceed the more robust, fully protective health standard established by NSF, which is supported by a chemical-specific human health risk assessment.

Furthermore, multiple time point testing of PEX shows that the levels of MTBE that leach from PEX tubing into drinking water either never exceed NSF's TAC of 100 µg/L or DPH's primary MCL of 13 µg/L or, for a small proportion of PEX formulations, diminish to levels below both standards in a sufficiently short time such that no person drinking water from PEX tubing could be exposed to a lifetime dose of MTBE that would result in an substantial increased level of cancer risk of cancer or noncancer toxicity. Because both the NSF-established TACs and California's PHGs (and primary MCLs) for all of these chemical compounds would not be exceeded over the long-term and because both the NSF standards and DPH's primary MCL standards were developed to be protective of both cancer and noncancer risk, chemical concentrations that leach from PEX tubing into drinking water would not expose the population to unacceptable increases in levels of cancer or noncancer toxicity. In addition, because the single time point concentrations of chemicals that leach from PEX tubing into drinking water do not exceed NSF drinking water standards, applicable PHGs established by California, or the MRLs developed by ATSDR, the use of PEX tubing in drinking water systems would not expose the population to levels associated with acute toxicity. Finally, there is no evidence to support a finding that MTBE poses any substantial level of genotoxic or mutagenic risk to humans. For these reasons, the levels of chemical compounds that leach from PEX products are not considered to cause or contribute to a substantial impact on human health (cancer, noncancer, or acute). This impact would be **less than significant**.

IMPACT 4.4-2 Water Quality—Adverse Taste and Odor Impacts. *The proposed project would result in the increased use of PEX tubing in California, a portion of which, upon initial use (i.e., in new pipe), would exceed DPH's secondary MCL for MTBE for taste and odor. However, because: 1) concentrations of these chemicals leaching from plumbing pipes decline rapidly with time (see discussion above and at Appendix E) and would not be anticipated to exceed the standard to an extent or for a duration long enough to cause a substantial number of persons to experience unpleasant taste or odors in their drinking water; and 2) there are no known consumer complaints of taste and odor impacts from PEX tubing despite extensive use for more than a decade in California, this impact is considered* ***less than significant****.*

Some concerns have been raised regarding the potential adverse affect of MTBE or ETBE on the aesthetic quality of water from systems using PEX tubing, particularly the taste and odor of the water from these systems. Although offensive tastes and odors rarely cause any physical harm, they can be unpleasant, leading to distress and citizen complaints to local governments and regulatory agencies. For these reasons, EPA and DPH develop drinking water standards for chemicals that are specifically for the avoidance of unpleasant taste and odor.

NSF/Standard 61 does not include any taste and odor requirements for drinking water system products and materials (NSF International 2007). Taste and odor are psychophysical phenomena (pertaining to the mind and its relation to physical manifestations) and vary from person to person. NSF used to include a taste and odor evaluation as part of NSF/ANSI Standard 61 but, based on previous studies, has determined that any standard would be too subjective and inherently unreliable (McLellan, pers. comm. 2010a). This unreliability is apparent in the many studies NSF reviewed, which is summarized in *Addendum* NSF International 2010). According to the review of taste and odor standards in the addendum, the European Chemicals Bureau determined that individual variability in sensitivity to taste and odor make it difficult to identify odor and taste thresholds for MTBE in water (2002, as cited in NSF 2010). The International Programme On Chemical Safety—a joint program of the World Health Organization, the International Labour Organization, and the United Nations Environment Programme that aims to establish the scientific basis for safe use of chemicals, and to strengthen national capabilities and capacities for chemical safety—reported that the taste threshold for MTBE in water is 134 ppb (1998, as cited in NSF 2010). OEHHA has cited various sources that report odor thresholds for MTBE in water of between 2.5 to 680 ppb (1999b, as cited in NSF 2010), and more recent data by Suffet et al. (2007, as cited in NSF 2010) suggests an odor standard for MTBE in water is of 15 ppb or greater.

There are no regulatory standards for ETBE in drinking water, and there are no federal drinking water standards for MTBE. In its drinking water advisory for MTBE, EPA concludes that maintaining concentrations of MTBE in the range of 20 to 40 µg/L of water or below will likely avert unpleasant taste and odor effects, recognizing that some people may detect the chemical below this level (EPA 1997b). EPA presents these taste and odor values as a range because it recognizes that human responses vary depending upon the sensitivities of the particular individual and the site-specific water quality conditions (EPA 1997b). EPA also explains that the presence or absence of other natural or water treatment chemicals can mask or reveal the taste or odor effects. Thus, variable preexisting water conditions around the country will increase variability in the acceptability of MTBE's presence in drinking water (EPA 1997b).

DPH has established a secondary MCL of 5 µg/L for MTBE, which is part of Chapter 15, Title 22 of the California Code of Regulations. The secondary MCLs established by DPH are also referred to as "consumer acceptance contaminant level ranges" and, unlike primary MCLs, are not developed to be protective of public health. In other words, the secondary MCL of 5 µg/L for MTBE is not a health-based standard; it is an aesthetic one (DPH 1997). In fact, taste and odor characteristics, often referred to as organoleptic properties, cannot be used by EPA for developing primary drinking water standards (EPA 1997b).

Multiple time point extraction testing (described above in Impact 4.4-1) demonstrates that concentrations of MTBE in PEX samples decline steadily with time; MTBE extraction levels from all the PEX samples were below 13 µg/L (or 13 ppb) by day 90, and most were below the secondary MCL of 5 µg/L by day 90. However, because some PEX samples would initially leach concentrations higher than the secondary MCL, this analysis further examines the application, intent, and development of this standard.

The requirements for monitoring and enforcement of secondary MCLs, specified in Chapter 15, Title 22 of the California Code of Regulations, indicate that secondary MCLs are intended to apply to the long-term quality of water delivered by community water systems. Specifically, these regulations state that "each community water system [i.e., all suppliers of domestic water to the public] shall monitor its groundwater sources or distribution system entry points representative of the effluent of a source treatment every three years and its approved surface water sources or distribution system entry points representative of the effluent of source treatment annually" for the secondary MCLs. Thus, the regulation is aimed at water supply sources and does not pertain to how water quality is affected by plumbing pipe or plumbing products.

Moreover, as suggested by the requirement for monitoring only every three years, even where secondary MCLs apply, short-term exceedances of the standards do not necessarily constitute violations. Pursuant to California Code of Regulations Section 64449, if the level of any constituent detected in drinking water supplied by a community water system exceeds its applicable secondary MCL, then the community water system shall initiate quarterly monitoring for that constituent. Under the regulations, a violation of the secondary MCL occurs if the average of four consecutive quarterly samples exceeds the secondary MCL. In other words, an exceedance of a secondary MCL at any single point in time does not constitute a violation of the standard.

This analysis also gives consideration to the methods used by DPH to develop the secondary MCL of 5 µg/L for MTBE, which are published in the *Final Statement of Reasons* for the standard (DPH 1997). Foremost, DPH considered two studies, one in Great Britain and the other by the Orange County Water District, that examine the concentrations of MTBE at which people can detect odor and taste in a laboratory setting. It does not, however, provide evidence that there is any record of citizen complaints or, more importantly, that there is any correlation between relevant MTBE concentrations and complaints.

It is also relevant that the secondary MCL of 5 µg/L represents a level below which most people cannot detect MTBE, based on laboratory testing. Studies show that individuals may be more sensitive to odors when asked to try to detect them in a laboratory setting than in the real world, where perceptions may be affected, and sensitivities muted, by intervening factors. In the drinking water context, such intervening factors could include background water quality, the taste or odor of which can be affected by mineral or disinfectant content, and the fact that consumers in day to day use are not necessarily focused on, or significantly bothered by, minor differences in taste or odor. Similarly, noise impact analyses conducted for CEQA acknowledge that, in a laboratory setting, some individuals can detect a change in noise levels lower than 3 decibels and, however, in real-world settings, most individuals typically cannot detect a change in noise levels less than 3 decibels. Thus, the ability of humans to detect changes in real-world settings is more important than in laboratory settings.

Regulatory provisions for waivers from secondary MCLs are further evidence that water quality that exceeds a standard based on a detection level would not necessarily be deemed unacceptable to consumers. California Code of Regulations Section 64449.2 allows individual communities to apply for a waiver from meeting a secondary MCL if, among other requirements, they conduct a customer survey to confirm that billed customers "prefer to avoid the cost of additional treatment and live with the current water quality situation." DPH's *Final Statement of Reasons* for the standard also acknowledges that individual communities may choose attain this waiver, which further supports the idea that a higher taste and odor standard may be more appropriate for real-world (i.e., non-laboratory) settings. This analysis thus places greater emphasis on the actual use of PEX in California communities rather than studies of human sensitivity in laboratory studies. In this way, this methodology is consistent with regulatory guidance offered by multiple air districts on how airborne odors should be analyzed in CEQA documents, which suggest that such analyses be based on the number and frequency of confirmed and unconfirmed odor complaints and experience with similar odor sources in similar settings (SJVAPCD 2002; SMAQMD 2010; BAAQMD 2009).

Given that local jurisdictions in California have permitted the use of PEX piping in drinking water systems since the early to mid-1990s, some records of taste and odor complaints associated with PEX would likely have been recorded if such complaints existed. Staff at Ascent Environmental conducted a survey of building officials of California jurisdictions that have permitted the use of PEX in their communities. Approximately 50 building officials were contacted by phone or e-mail during March of 2010, and none of the building officials stated that

they had received taste or odor complaints associated with the use of PEX materials in their jurisdictions. These results are corroborated by the oral and written testimony provided to BSC from building officials, plumbers, specialty contractors and mass production homebuilders with substantial experience installing PEX over a decade or more, all of whom stated that they had received no complaints regarding adverse taste or odor in their customers' drinking water from PEX. Finally, PEX has been used in all 49 other states and throughout Europe for several decades, and this use has not resulted in a record of taste and odor complaints. Thus, based on real-world experience, it is not anticipated that the use of PEX in drinking water systems causes, or has the potential to cause, a substantial number of persons to experience unpleasant taste or odors in drinking water.

This analysis also included the examination of taste and odor studies of PEX that were conducted more recently than DPH's development of the secondary MCL for MTBE. One such study was published by Durand and Dietrich in 2007. This study investigated the taste and odor properties of PEX products using the Utility Quick Test, with a particular focus on the levels of 2-Ethoxy-2-methylpropane (ETBE) associated with detectable odors. ETBE has similar properties to MTBE; however, there are no regulatory standards for ETBE in drinking water. The study involved exposing the PEX pipe to water under static conditions (i.e., letting water sit in the tubing) for periods of 3 and 4 days. Panelists on the study were able to smell ETBE at a concentration of 5 µg/L in a laboratory setting; the odor intensity as described by the study participants varied from "weak" to "very weak."

As with the two studies used by DPH to develop the secondary MCL for MTBE, this analysis places less emphasis on the study by Durand and Dietrich (2007) than it does the real-life experiences of communities that have already been using PEX. Moreover, the study is of limited relevance to this analysis, which emphasizes consumer experience under real world conditions, because the Durand and Dietrich study was based on test subjects' reaction to water that had been standing in pipe for up to 3 or 4 days, and there is no evidence that the pipe had been subjected to the flushing requirements that are mandated under the Plumbing Code and part of typical construction practices. (See previous discussion under Impact 4.4-1 regarding the results of the multiple time point testing showing that concentrations of MTBE decline rapidly over time and related discussion of PEX installation and Plumbing Code requirements for flushing of newly installed pipe.) Moreover, the panelists' descriptions of the odor intensity of water that has been standing in new pipe as "weak" to "very weak" do not support a determination that the use of PEX in drinking water systems is likely to cause, a substantial number of persons to experience unpleasant taste or odors in drinking water.

The potential for PEX to result in any adverse effect to taste and odor must be considered relative to existing conditions in California, in which consumers drink water from plumbing systems of a variety of different materials. As noted in Section 4.4.2, PEX has been in use in California since the early to mid-1990's and represents approximately 37% of the market share for existing products. Despite extensive use in a wide range of jurisdiction, there is no record of any consumer complaints of adverse taste or odor of drinking water in California from PEX. Written testimony from building officials, plumbers, contractors, and homebuilders includes references to thousands of PEX systems installed in California since 1996 without a single known taste or odor complaint. (As examples, Griffin Industries, approximately 5,850 systems since 1998 [Nielson, pers. comm., 2008]; Orange Pacific Plumbing, 1,100 systems since 2002 [Hartshorn, pers. comm., 2008]; Pacific Production Plumbing, 35,000 systems since 1993 [Whitt, pers. comm., 2008]; Golden West Plumbing, 1,000 systems since 2001 [Taylor, pers. comm., 2008]; Granite Homes, 1,500 systems since 2000 [Freyermuth, pers. comm., 2008]; Saber Plumbing, 1,250 systems since 2002 [Zlomek, pers. comm., 2008]; Warmington Homes, 600 systems since 2003 [Pulver, pers. comm., 2008]). Oral testimony was received from homebuilders during the EIR process that as of late 2007 more than 100 million feet of Uponor PEX had been installed in Southern California for potable water applications and no calls or complaints of taste and odor had been received (See Banner, oral testimony, 2007). There is no evidence that any person or substantial number of persons has experienced frequent taste and odor impacts attributable to PEX tubing. Based on the substantial amount of PEX that has been installed in California and the lack of consumer complaints it is apparent that any exceedance of secondary drinking water MCLs for MTBE resulting from PEX is not reasonably likely to cause a substantial number of persons served by the public water system to discontinue use of the system or that use of PEX will otherwise adversely affect the public welfare (See Cal Health Safety Code 116275).

The most commonly used material for conveying potable water is copper, which represents approximately 54% of the market share (California Department of Housing and Community Development [HCD] 2006). There is evidence that copper pipe has caused a substantial number of persons in California to experience objectionable tastes and odors in drinking water, which has led to complaints both to building officials and installers. Such complaints are reportedly common with copper and galvanized water delivery systems, which may stem from soldering and sealing compounds (Nielson, pers. comm., 2008). Complaints from users of copper pipe systems report a metallic taste and odor (Shields, pers. comm.., 2008). Based on this evidence it is not reasonable to assume that continued use of PEX would have any greater potential to result in objectionable taste and odors in drinking water than the existing condition, which includes copper pipe and other potable water distribution materials (such as galvanized pipe) documented to cause objectionable taste or odors in drinking water.

As to significance of the potential effect, it is a well-established principle of CEQA that any review of potential significant impacts should focus on the "adverse impacts upon the environment of persons in general." (*Assn. for Protection of Environmental Values in Ukiah v. City of Ukiah* (1991) 2 Cal.App.4th 720, 734.) "The issue is not whether [the project] will adversely affect particular persons but whether [the project] will adversely affect the environment of persons in general. [citation omitted.]" (*Topanga Beach Renters Assn. v. Dept. of General Services* (1976) 58 Cal.App.3d 188, 195.) Thus, where potential impacts may only affect a few people, or in this context, the small number of people in the state population who may be able to detect the taste or odor of MTBE in a small percentage of the PEX products on the market, for a relatively short period of time, both the law and the factual evidence supports the conclusion that the potential for isolated incidences of taste and odor complaints does not constitute a significant impact.

In summary, the use of PEX in drinking water systems would not result in a level of MTBE or ETBE in drinking water that would exceed the state secondary MCL for taste and odor to an extent or for a duration long enough to cause a substantial number of persons to experience unpleasant taste or odors in their drinking water. In addition, because no recorded complaints have been identified about taste and odor associated with PEX in communities where PEX is currently being used, it is not anticipated that the proposed project would cause a substantial number of persons to experience unpleasant taste or odors in drinking water for an extended period of time. This impact would be **less than significant**.

IMPACT 4.4-3 Water Quality—Noncompliance with Drinking Water Standards Resulting from Permeation. *In cases where PEX is placed below the slab (i.e., in bare soil) where contaminated soils are present and permeated by solvents or gasoline, it has the potential to introduce chemicals into drinking water at levels in exceedance of federal and California MCLs, notification and response levels, or the Proposition 65 Safe Harbor levels, as well as to introduce Proposition 65 chemicals for which there are no adopted federal or California standards. Because the project would allow the use of PEX for hot and cold water distribution including potable water uses and the proposed regulations provide no restriction on uses below the slab this project could result in a* potentially significant *impact.*

Summary of Case Reports of Permeation

Lee (1985) discussed several case histories of permeation of plastic pipes by organic compounds in the environment. The East Bay Municipal Utility District in Oakland, California reported four instances of apparent petroleum distillate penetration of polybutylene (PB) water service lines. A case in Maryland was reported in which concentrations of toluene up to 5,500 µg/L were found in a water sample collected from a service line consisting of both PE and PB. The soil surrounding the service line was contaminated with gasoline as a result of a leaking underground storage tank. The Alabama Department of Environmental Management reported permeation of PB service pipes with diesel fuel. In another incident, a private residence in Chattanooga, Tennessee reported that gasoline had leaked from the resident's car in the vicinity of a three-quarter-inch PE service line and permeated the service line. A similar incident occurred in Darien, Connecticut where a resident complaint of gasoline odor in tap water resulted in sample analysis which showed benzene (>100 µg/L) and toluene (>50 µg/L) in the tap water. The odors were absent after flushing and when the homeowners' plumbing was in daily use. Samples collected after the system had not been used for 2 days contained approximately16 µg/L

benzene and a gasoline odor. The resident's 1¼-inch PE service line was replaced with copper after it was determined that an abandoned underground gasoline storage tank on the resident's property had developed a leak and saturated the ground surrounding the line. Although PB, PE, and PEX are all members of the polyolefin family, this does not mean that PEX will automatically behave similarly to PB and PE. However, there is a lack of data regarding how PEX may behave differently from other members of the polyolefin family when it comes to issues of permeability.

Permeation by Various Organic Compounds

Lee (1985) also discussed a research investigation carried out by the American Water Works Service Company to determine the extent and nature of permeation of several different organic compounds through the types of service lines in use in the American Water Works system. Five pipe materials were used—iron, copper, PE, PB, and PVC. The conditions of exposure were designed to simulate worst-case field conditions. One exposure tank involved exposure of the five piping materials to a vapor environment. The second exposure tank involved exposure of the five piping materials to a moist soil environment to which sufficient chemical was added; the pipe was above the saturated soil, but still within the moist capillary zone. Three organic compounds were investigated in each exposure tank—gasoline, trichloroethylene (TCE) and chlordane. The pipes were in contact separately with the three organic compounds for a minimum 10-week exposure period. The pipes were unjointed three-quarter-inch lines filled with tap water. Water samples were analyzed at four intervals during the exposure period. The results were reported as follows:

- Iron and copper pipes were not permeated by any of the organic compounds in either the soil or the vapor environments.
- PE pipe was permeated by TCE within 1 week in both the soil and vapor exposure conditions. Gasoline permeation occurred within 1 day in the vapor and 3 weeks in the soil exposure. Chlordane did not permeate the polyethylene pipe in either the soil or vapor exposure condition.
- Chlordane did not permeate the polybutylene and PVC pipes. Both types of pipes showed permeation of TCE and gasoline in both the soil or vapor exposure conditions.

The study authors concluded that plastic pipe is susceptible to permeation from certain organic compounds, particularly solvents. Based on these results, the authors recommend that limitations are desirable in areas where the potential for soil contamination is high, such as a gasoline storage area.

Theoretical Calculations of Permeation

In his analysis report, Hoffmann (2005) conducted theoretical calculations on the length of time that would be required for an organic compound to permeate through the walls of PEX pipe. He estimated the characteristic time for diffusion of a compound through PEX pipe with a wall thickness of 0.5 centimeter (0.2 inch) and a diffusion coefficient of 1.0 x 10–12 centimeters squared per second to be 8,000 years. The diffusion coefficient used by Hoffmann appears to be representative of termiticides (he lists six representative termiticides—bifenthrin, chlorpyrifos, cypermethrin, fenvalerate, imidachoprid, and permethrin). However, Hoffmann does not comment on the experimental results of Lee (1985) where the author found that PE pipe was permeated by both TCE and gasoline (in both the soil and vapor phase) within several weeks. Lee (1985) found that chlordane did not permeate any of the pipes. Therefore, it is possible that Hoffmann's theoretical calculations apply only to organic compounds that are termiticides or pesticides (such as chlordane). However, his calculations may not apply to solvents, such as gasoline or TCE, which appear to have much faster permeation rates through plastic pipes based on the experimental results reported in Lee (1985).

Permeation by Solvents, Gasoline, Pesticides, and Termiticides

Evidence shows that use of PEX tubing should be restricted under certain soil conditions and, in fact, manufacturers recommend restrictions in certain instances. (Vanguard Piping Systems, Inc. 2000:19.) Manufacture installation handbooks regularly provide warnings such as "must not be installed underground in

areas of known chemical contamination of the soil, such as organic solvents or petroleum distillates, or where there is a high risk of chemical spills." (Id.) A permeation study showed that polyethylene pipe was permeated by both TCE and gasoline (in both the soil and vapor phase) within several weeks. Chlordane was also tested for permeation; however, polyethylene pipe was not permeated by chlordane. The same study also tested iron and copper pipes, which were not permeated by any of the organic compounds in either the soil or the vapor environments. The study authors concluded that plastic pipe is susceptible to permeation by certain organic compounds, particularly solvents. Based on these results, the authors recommend that limitations are desirable in areas where the potential for soil contamination is high, such as a gasoline storage area. Theoretical calculations on permeation of termiticides indicated that these types of organic compounds would not permeate PEX piping (Hoffmann 2005). Therefore, termiticides or pesticides are less likely to permeate PEX piping, and do not represent a concern. However, compounds such as gasoline and chlorinated solvents could present concerns for permeation.

As discussed above, in cases where PEX is placed in contaminated soils and permeated by solvents or gasoline, it has the potential to introduce chemicals into drinking water at levels far in exceedance of federal and state MCLs. Because the project would allow the use of PEX for hot and cold water distribution including potable water uses and the proposed regulations provide no restriction on uses below the slab (i.e. under the house) this project could result in a **potentially significant** impact.

Mitigation Measure 4.4-3: Noncompliance with California and Federal Drinking Water Standards (including Proposition 65) Resulting from Permeation.

- The regulation shall prohibit the installation of PEX for potable water uses below the slab (i.e., in bare soil) unless: PEX is sleeved by a metal or other material that is impermeable to solvents and petroleum products.

Significance after Mitigation: Adoption of Mitigation Measure 4.4-3 would ensure that potential impacts to public health resulting from permeation are reduced to **less than significant**.

4.4.4 Significant and Unavoidable Impacts

Because all potentially significant and significant impacts would be reduced to less than significant with the implementation of mitigation, no water quality impacts would be significant and unavoidable.

8 PREPARERS OF THE ENVIRONMENTAL DOCUMENT

8.1 LEAD AGENCY

California Building Standards Commission

David Walls ..... Executive Director

8.2 EIR CONSULTANTS

PRIME CONSULTANT

Ascent Environmental

Sydney Coatsworth, AICP ..... Project Director/Principal-in-Charge

Austin Kerr ..... Senior Environmental Scientist

Honey Walters ..... Senior Environmental Scientist

Amber Giffin ..... Word Processor/Document Production

SUB CONSULTANTS

Jonathan Borak & Company, Inc.

Jonathan Borak, MD, DABT ..... Principal Epidemiology & Public Health Specialist

Cheryl Fields, MPH ..... Epidemiology & Public Health Specialist

9 REFERENCES

CHAPTER 3, "DESCRIPTION OF THE PROPOSED PROJECT"

Ash, John. Data Research Analyst, National Association of Home Builders [NAHB] Research Center, Marlboro, Maryland. February 29, 2008—e-mail communication with Heather Halsey of EDAW regarding market share for plumbing materials.

California Department of Housing and Community Development. 2006a (September). *Negative Declaration/Initial Study, Multi-Agency Adoption of Regulations Related to the Use of PEX and PEX-AL-PEX for Potable Water*. State Clearinghouse No. 2006092055. Sacramento, CA.

———. 2006b (November). *Recirculated Draft Environmental Impact Report, Adoption of Regulations Permitting Statewide Residential Use of Chlorinated Polyvinyl Chloride (CPVC) Plastic Plumbing Pipe without First Making a Finding of Potential Premature Metallic Pipe Failure Due to Local Water or Soil Conditions*. State Clearinghouse No. 2006012044. Sacramento, CA.

CHAPTER 4.2, "PUBLIC HEALTH AND HAZARDS—REVISED"

Ackerman, E., Y. Cen, R. C. Wilging. 2004. *Firestopping Plastic Pipe in Fire Resistive Construction*. Published by the Plastic Pipe and Fittings Association.

American Society for Testing Materials. 2008a. Document Summary ASTM F2023-05 Standard Test Method for Evaluating the Oxidative Resistance of Crosslinked Polyethylene (PEX) Tubing and Systems to Hot Chlorinated Water. http://www.astm.org/cgi-bin/SoftCart.exe/DATABASE.CART/RELDINE_PAGES/F2023.htm?L+mystore+wogf7995+1203410777. Accessed 2.18.08

———. 2008b. ASTM E119-08a standard Test Methods for Fire Tests of Building Construction and Materials. Available:< http://www.astm.org/cgi-bin/SoftCart.exe/DATABASE.CART/RELDINE_PAGES/R119.htm?U+mystore+vwzi4690>. Accessed March 13, 2008.

Ash, John. Data Research Analyst, National Association of Home Builders [NAHB] Research Center, Marlboro, Maryland. February 29, 2008—e-mail communication with Heather Halsey of EDAW regarding market share for plumbing materials.

Brown, Jeremy. Codes and regulatory manager. NSF International, Ann Arbor, MI. November 6, 2007 – letter to Valerie Namba of the California Department of General Services regarding the notice of preparation EIR for adoption of statewide regulations for use of PEX tubing.

California Department of Health Care Services. 2001 (July). Indoor Air Quality Info Sheet. *Mold in My Home: What Do I Do?* Available:<http://www.dhs.ca.gov/ehlb/IAQ/Mold/mold0107.htm.> Last updated July 2001. Accessed March 11, 2008

California Department of Housing and Community Development. 2006 (November). *Recirculated Draft Environmental Impact Report, Adoption of Regulations Permitting Statewide Residential Use of Chlorinated Polyvinyl Chloride (CPVC) Plastic Plumbing Pipe without First Making a Finding of Potential Premature Metallic Pipe Failure Due to Local Water or Soil Conditions*. State Clearinghouse No. 2006012044. Sacramento, CA.

Chaudhuri, Ishrat. Senior toxicologist. ENSR Corporation, Westford, MA. January 25, 2008—memorandum to Heather Halsey of EDAW concerning biofilm formation in PEX.

Chung, Sarah; Ken Oliphant, Patrick Vibien, and Jingguo Zhang. n.d. *An Examination of the Relative Impact of Common Potable Water Disinfectants (Chlorine, Chloramines, and Chlorine Dioxide) on Plastic Piping System Components*. Jana Laboratories, Inc., Aurora, Ontario. Available: <http://www.janalab.com/pdf/Common%20Potable%20Water%20Disinfectants%206.pdf>.

Church, R. W. Executive Director. Plastic Pipe and Fittings Association, Glen Ellyn, IL. November 30, 2007—letter to Valerie Namba of the California Department of General Services regarding comments on the notice of preparation for an environmental impact report evaluating the proposed adoption of statewide regulations allowing use of PEX piping.

Coalition for Safe Building Materials. 2005 (August 1). *Comments of Coalition for Safe Building Materials (California Pipe Trades Council, California Professional Firefirghters, Consumer Federation of California, Planning and Conservation League, Center for Environmental Health, Sierra Club of California and Communities for a Better Environment) in Opposition to the Proposed Amendment of CPC Sections Sections 604.1, 604.1.1, 604.11, 604.11.1, 604.11.2, 604.13, 604.13.1, and 604.13.2 to Allow the Statewide Approval of PEX and PEX-AL-PEX Drinking Water Pipe, Volume I.* Prepared by Adams Broadwell Joseph & Cardoza, Sacramento, CA; Thomas Reid Associates, Menlo Park, CA; and GT Engineering, Redmond, WA.

Davis, P. J. 2001 (March). *Molds, Toxic Molds, and Indoor Air Quality.* Volume 8, Number 1, ISBN: 1-58703-133-7. California Research Bureau, California State Library, Sacramento, CA.

Department of Biochemistry and Microbiology, University of Forte Hare; Technology Management, CSIR; and Department of Microbiology and Plant Pathology, University of Pretoria. 2000 (January) An Overview of Biofilm Formation in Distribution Systems and Its Impact on the Deterioration of Water Quality. Water Research Commission. ISSN 0378-4738. *Water SA*, 26(1):59-66

DHS. *See* California Department of Health Care Services.

DPH. *See* California Department of Public Health.

Edstrom Industries. 2008. What re Biofilms? Available:http://www.edstrom.com/Resources.cfm?docid=23. Accessed February 27, 2008.

HCD. *See* California Department of Housing and Community Development

Hoffmann , H. R. 2005. Analysis of PEX and drinking water supplies relative to the UPC of California. Report provided to the California Building Standards Commission.

Houle, Rich. Associate produce manager – commercial. Uponor, Apple Valley MN. March 13, 2008 – e-mail to Kelley Taber of Somach, Simmons & Dunn regarding firestop materials and their potential to degrade PEX.

Louden, Dave, Director of Government Affairs, and Bruce Wick, Director of Risk Management, California Professional Association of Specialty Contractors. 2007 (November 27) – letter to Valerie Namba of California General Services regarding Environmental Impact Report on PEX Tubing (including risk of water damage and mold growth from failure of copper piping).

Markku, J. L., I. T. Miettinen, T. Lampola, A. Hirvonen, T. Vartiainen, and P. J. Martikainen. 2005. Pipeline materials modify the effectiveness of disinfectants in drinking water distribution systems. *Water Research* 39: 1962-1971

Maryland Department of Housing and Community Development. 2004 (December). *Pinhole Leaks in Copper Plumbing.* Crownsville, MD. Available:<http://www.wsscwater.com/copperpipe/PinholeLeaksInCopperPlumbing.pdf>

MNB Momba. *See* Department of Biochemistry and Microbiology, University of Fort Hare; Technology Management, CSIR; and Department of Microbiology and Plant Pathology, University of Pretoria.

NAHB Research Center. *See* National Association of Home Builders Research Center.

National Association of Home Builders Research Center, Inc. 2006 (November). Design Guide, Residential PEX Water Supply Plumbing Systems. Upper Marlboro, MD. Prepared for Plastic Pipe Institute, Irving TX; Plastic Pipe and Fittings Association, Glen Ellyn, IL; and Partnership for Advancing Technology in Housing, Washington, DC.NSF International. 2004. Information on plumbing materials standards. Available: <http://www.nsf.org/consumer/plumbing/index.asp?program=Plumbing>. Accessed February 19, 2008.

NSF International.1999 (September). NSF Protocol P 171 Chlorine Resistance of Plastic Piping Materials. NSF International, Engineering and Research Services. Ann Arbor, MI.

———. 2008. Plastic Piping: Frequently Asked Questions.

Plastic Pipe Institute. 2007 (January). *PPI Statement A.* Irving, TX.

PM Engineer. 2003 (October 7). Plastic Pipe and Fire Safety. Available: <http//www.pmengineer.com/CDA/Archives/69afa50448298010VgnVCM1 00000f932a8c0>. Last updated May 1, 2006.

PPI. *See* Plastics Pipe Institute

Reinertson, Kevin. Senior Deputy State Fire Marshal, California Department of Forestry and Fire Protection, Sacramento, CA. September 7, 2006 – letter to Robin Gilb of the California Department of Housing and Community Development regarding fire hazards associated with expanded use of CPVC and PEX.

Shields, Richard, Director of Building and Safety/Public Works, City of Grand Terrace. 2008 (October 22) – letter to Valerie Namba of California General Services regarding comments on the Recirculated Draft Environmental Impact Report on PEX Tubing.

Specified Technologies, Inc. 2008. Firestopping, Products for Life Safety and Code Compliance. Available:http://sti.fmpdata.net/ftp/brochures_catalogs/STI_User_Guide_2007_Edition.pdf>. Accessed March 13, 2008.

Theilen, Mark. Professional plumber. Pacific Plumbing, Penn Valley, CA. March 4, 2008 – e-mail to Jason Barrett of EDAW regarding use of PEX piping.

Theilen, Mark. 2008. Telephone conversation with Jason Barrett of EDAW on March 10, 2008 regarding continuous hot water circulation systems and plumbing material lifespan.

U.S. Environmental Protection Agency. 2007a (June 29). Information about chlormaine in drinking water. Available: <http://www.epa.gov/safewater/disinfection/chloramine/index.html#six>. Last updated June 29, 2007. Accessed March 7, 2008.

———. 2008. A Brief Guide to Mold, Moisture, and Your Home. Available:<http://www.epa.gov/mold/modguide.html>. Last updated May 9, 2007. Accessed February 18, 2008.

Van der Kooij, D., H. r. Veenedaal, and W. J. H. Scheffer. 2005 (April). Biofilm formation and multiplication of Legionella in a model warm water system with pipes of copper, stainless steel and cross-linked polyethylene. Water Research 39:2789-2798.

Veenendaal H. R., and D. van der Kooij. 1999 (June). Biofilm Formation Potential of Pipe Materials in Plumbing Systems, Measurement Results and Elevation. Nieuwegein, Netherhlands.

Vibien, Patrick. Jana Laboratories, Aurora, Ontario, Canada. March 26, 2008 – telephone conversation with Ishrat Chaudhuri of ENSR regarding ASTM F2023 and NSF P171 standards.

Vibien, P., J. Couch, and K. Oliphant, Jana Laboratories Inc., Aurora, Ontario, Canada; and W. Zhou, B. Zhang and A. Chudnovsky, Fracture Mechanics & Materials Durability Laboratory, CME Department, UIC, Chicago, IL, USA. n.d. *Assessing Material Performance in Chlorinated Potable Water Applications.* Available: http//www.janalab.com/pdf/PPXI%20PAPER.PDF

Zicherman, J. B. 2000 (September 5). Plastic Pipe and Fire Safety. The NFPA Fire Journal, Richmond, CA.

CHAPTER 4.4, "WATER QUALITY—REVISED"

Agency for Toxic Substances & Disease Registry. 2009a. *Minimal risk Levels: Narrative*. Availalbe: <http://www.atsdr.cdc.gov/mrls/index.html>. Page last reviewed and updated: September 1, 2009. Accessed April 6, 2010.

Agency for Toxic Substances & Disease Registry. 2009b. *Minimal Risk Levels for Hazardous Substances.* Availalbe: <http://www.atsdr.cdc.gov/mrls/mrls_list.html>. Page last reviewed and updated: September 1, 2009. Accessed April 6, 2010.

Ash, John. Data Research Analyst, National Association of Home Builders [NAHB] Research Center, Marlboro, Maryland. February 29, 2008—e-mail communication with Heather Halsey of EDAW regarding market share for plumbing materials.

ATSDR. *See* Agency for Toxic Substances & Disease Registry.

BAAQMD. *See* Bay Area Air Quality Management District.

Banner, Rick, Keyline Sales. November 14, 2007—oral testimony provided to Valerie Namba of the Department of General Services at public scoping meeting, San Diego, CA.

Bay Area Air Quality Management District. 2009 (November). *California Environmental Quality Act Guidelines Update: Proposed Thresholds of Significance.* San Francisco, CA.

Bestervelt, Lori. Senior Vice President and Chief Technical Officer, NSF International, Ann Arbor, MI. June 23, 2008—Letter to Valerie Namba, Senior Environmental Planner, with the California Department of General Services regarding comments on the DEIR for Adoption of Statewide Regulations Allowing the Use of PEX Tubing.

Borak, Jonathan, MD, DABT, Clinical Professor of Epidemiology & Public Health and Associate Clinical Professor of Medicine at Yale University, New Haven, CT. May 3, 2010a—teleconference with Austin Kerr and Sydney Coatsworth of Ascent Environmental, Sabrina Teller of Remy Thomas Moose and Manley, and Kelly Taber of Somach Simmons and Dunn regarding the methodology for assessing cancer risk associated with leached concentrations of MTBE from PEX piping and the 1990 study by Robinson et al.

Borak, Jonathan, MD, DABT, Clinical Professor of Epidemiology & Public Health and Associate Clinical Professor of Medicine at Yale University, New Haven, CT. May 3, 2010b—telephone conversation with Austin Kerr of Ascent Environmental regarding the natural decay function and rate at which leached concentrations of MTBE from PEX piping diminish over time.

California Department of Housing and Community Development. 2006 (November). *Recirculated Draft Environmental Impact Report, Adoption of Regulations Permitting Statewide Residential Use of Chlorinated Polyvinyl Chloride (CPVC) Plastic Plumbing Pipe without First Making a Finding of Potential Premature Metallic Pipe Failure Due to Local Water or Soil Conditions*. State Clearinghouse No. 2006012044. Sacramento, CA.

California Department of Public Health. 1997. Final Statement of Reasons: Secondary Masimum Contaminatn level for Methyl tert-butyl Ether and Revisions to the Unregulated Chemical Monitoring List. Title 22, California Code of Regulations. Available: <http://www.cdph.ca.gov/certlic/drinkingwater/Documents/MTBE/MTBEsor.pdf >. Accessed April 23, 2010.

——— 2000 (January). *Drinking Water Source Assessment and Protection (DWSAP) Program Document*. Sacramento, CA.

———. 2007a. Drinking Water Notification Levels. Available: <http://cdph.ca.gov/certlic/drinkingwater/pages/notificationlevels.aspx>. Last updated December 14, 2007. Accessed April 14, 2008.

———. 2007b. MTBE: Regulations and Drinking Water Monitoring Results Available: <http://www.cdph.ca.gov/certlic/drinkingwater/Pages/MTBE.aspx>. Accessed February 1, 2008.

———. 2010 (April 14). *Comparison of MCLs and PHGs for Regulated Contaminants in Drinking Water*. Available: <http://www.cdph.ca.gov/certlic/drinkingwater/Pages/MCLsandPHGs.aspx>. Last updated: April 14, 2010.

California State Pipe Trades Council. 2008 (August 14). *PEX Potable Water Pipe: July 10, 2008 Notice of Post-Hearing Modifications to Text of Proposed Building Standards; Opposition toProposed Amendment of CPC Sections 604.1, 604.11, 604.11.1, 604.11.2 and Table 6-4*. A letter authored by Thomas A. Enslow of Adams Broadwell Joseph & Cardozo to Thomas > Morrison, Deputy Executive Director, California Building Standards Commission.

Chaudhuri, Ishrat. Senior Toxicologist, ENSR Corporation, Westford, MA. October 1, 2008—Memorandum to Jason Barrett of EDAW regarding carbon black in PEX tubing and Proposition 65 compliance.

Chou, Selene. 2010. Environmental Health Scientist, Agency for Toxic Substances and Disease Control, Division of Toxicology and Environmental Medicine. Atlanta, GA. April 8, 1010—e-mail response to Austin Kerr of Ascent Environmental, Inc. regarding the uncertainty factors used in deriving the MRLs for MTBE.

Church, R. W. Executive Director. Plastic Pipe and Fittings Association, Glen Ellyn, IL. November 30, 2007—letter to Valerie Namba of the California Department of General Services regarding comments on the notice of preparation for an environmental impact report evaluating the proposed adoption of statewide regulations allowing use of PEX piping.

Copper Development Association. 2008. Copper.org. Available: <http://www.copper.org>. Accessed April 2008.

CSPTC. *See* California State Pipe Trades Council.

DPH. *See* California Department of Public Health.

Durand, M. L., and A. M. Dietrich. 2007. Contributions of silane cross-linked PEX pipe to chemical/solvent odours in drinking water. *Water Science and Technology* 55(5): 153–160.

EPA. *See* U.S. Environmental Protection Agency.

European Chemicals Bureau. 2002. European Union Risk Assessment Report. Tert-Butyl Methyl Ether. CAS No. 1634-04-4. EINECS No. 216-653-1. 3rd Priority List. Volume 19. Institute for Health and Consumer Protection, European Chemicals Bureau, Europena Commission. EUR 20417 EN. September 9—as cited in NSF International 2010.

FDA. *See* U.S. Food and Drug Administration.

Freyermuth, G. Vice President of Purchasing and Product Development. Granite Homes, Irvine, California. June 6, 2008.

Hartshorn, S.R. President. Orange Pacific Plumbing, Inc. May 29, 2008—letter to Valerie Namba of the California Department of General Services regarding comments on the draft environmental impact report evaluating the proposed adoption of statewide regulations allowing use of PEX piping.

HCD. *See* California Department of Housing and Community Development.

Hoffmann, M. R. 2005. *Analysis of PEX and drinking water supplies relative to the UPC of California*. Report provided to the California Building Standards Commission.

International Programme On Chemical Safety. 1998. Environmental Health Criteria 206. Methyl Tertiary-Butyl Ether. United Nations Environment Programme. International Labour Organisation. World Health Organization. Available: <http://www.inchem.org/documents/ehc/ehc/ehc206.htm#PartNumber:1>—as cited in NSF International 2010.

Johnson, W.D., J. Findlay, and R.A. Boyne. 1992. 28-day oral (gavage) toxicity study of MTBE in rats. Prepared for Amoco. Illinois Institute of Technology Research. ITT Research Institute Project No. L08100. Chicago, Illinois, 48 pp. *As cited in* NSF International 2010.

Klan, M.J. W. Johnson, N.S. Hatoum, and J.K. Yermakoff. 1992. 28-day oral (gavage) toxicity study of MTBE in rats [abstract]. Toxicol. 12(1):117. *As cited in* NSF International 2010.

Lee, R. G. 1985 (November 5). *Investigation of plastic pipe permeation by organic chemicals*. Kentucky-Tennessee American Water Works Association Section Meeting.

Luong, Susan. Staff Scientist, California Office of Environmental Health Hazard Assessment, Proposition 65 Section, Sacramento, CA. October 1, 2008—Phone conversation with Nisha Chauhan of EDAW regarding carbon black in PEX tubing and Proposition 65 compliance.

McLellan, Clifton. Director of toxicology services. NSF International, Ann Arbor, MI. March 12, 2008a—letter to Valerie Namba of the California Department of General Services regarding results of PEX testing to support certification to NSF/ANSI Standard 61, with an enclosed t-butonol and methyl-t-butyl ether risk assessment.

McLellan, Clifton. Director of Toxicology Services. NSF International, Ann Arbor, MI. April 15, 2008b—e-mail to Austin Kerr of Ascent Environmental regarding whether the NSF standards address genotoxic, reproductive, and other types of risk.

McLellan, Clifton. Director of Toxicology Services. NSF International, Ann Arbor, MI. August 1, 2008c—Email to Ishrat Chaudhuri of ENSR Corporation regarding the PEX decay/over-time testing being conducted for MTBE and TBA.

McLellan, Clifton. Director of Toxicology Services. NSF International, Ann Arbor, MI. August 6, 2008d—letter to the Plastic Pipe and Fittings Association presenting the results of multiple point tests on cross-linked polyethylene tubing to the multiple time point protocol of NSF/ANSI Standard 61.

McLellan, Clifton. Director of Toxicology Services. NSF International, Ann Arbor, MI. October 5, 2008e—Email to Ishrat Chaudhuri of ENSR Corporation regarding carbon black and PEX tubing.

McLellan, Clifton. Director of Toxicology Services. NSF International, Ann Arbor, MI. December 16, 2008f—e-mail to Dr. Ishrat Chaudhuri regarding the single timepoint and over-time testing performed on PEX products.

McLellan, Clifton. Director of Toxicology Services. NSF International, Ann Arbor, MI. April 29, 2009—letter to Richard Church, Executive Director of Plastic Pipe and Fittings Association regarding results letter written by James J.J. Clark on his Review of Final Environmental Impact Report for the Use of PEX Plastic Piping.

McLellan, Clifton. Director of Toxicology Services. NSF International, Ann Arbor, MI. January 4, 2010a—telephone meeting with Sydney Coatsworth of Ascent Environmental regarding whether NSF/ANSI Standard 61 includes taste and odor criteria.

McLellan, Clifton. Director of Toxicology Services. NSF International, Ann Arbor, MI. March 24, 2010b—e-mail to Austin Kerr of Ascent Environmental, Inc. regarding a reference level for noncancer risk and a short-term exposure level for MTBE in drinking water.

McLellan, Clifton. Director of Toxicology Services. NSF International, Ann Arbor, MI. April 6, 2010c—Email to Austin Kerr of Ascent Environemntal regarding NSF standards and the three categories of health risk.

NAHB Research Center. *See* National Association of Home Builders Research Center.

National Association of Home Builders Research Center, Inc. 2006 (November). Design Guide, Residential PEX Water Supply Plumbing Systems. Upper Marlboro, MD. Prepared for Plastic Pipe Institute, Irving TX; Plastic Pipe and Fittings Association, Glen Ellyn, IL; and Partnership for Advancing Technology in Housing, Washington, DC.NSF International. 2004. Information on plumbing materials standards. Available: <http://www.nsf.org/consumer/plumbing/index.asp?program=Plumbing>. Accessed February 19, 2008.

Nielson, K.A. Operations. Griffin Industries. June 2, 2008—letter to Valerie Namba of the California Department of General Services regarding comments on the draft environmental impact report evaluating the proposed adoption of statewide regulations allowing use of PEX piping.

NSF International. 1987 (January). *Exposure Parameters Decision Document – Indirect Additives Standard*. Ann Arbor, MI.

———. 2000 (April). *NSF testing of Wirsbo Aqua PEX ½ inch*. Laboratory Report. Ann Arbor, MI.

———. 2003. *Oral Risk Assessment Document, t-butanol*, CAS # 75-65-0. Ann Arbor, MI.

———. 2005. *Frequently Asked Questions on Health Effects of PEX Tubing*. Ann Arbor, MI.

———. 2007. *Drinking Water System Components Health Effects*. NSF/ANSI Standard 61. Ann Arbor, MI.

———. 2008 (February). *Methyl Tertiary-Butyl Ether Oral Risk Assessment Document*. CAS # 1634-04-4. Ann Arbor, MI.

———. 2010 (April). *Addendum to Draft Methyl tertiary-Butyl Ether Oral Risk Assessment Document*. CAS # 1634-04-4. Ann Arbor, MI.

OEHHA. *See* Office of Environmental Health Hazard Assessment.

Office of Environmental Health Hazard Assessment. 1999a (March). Adoption of a Public Health Goal for MTBE in Drinking Water. Available: <http://oehha.ca.gov/water/phg/399MTBEa.html>. Accessed March 30, 2010.

———. 1999b (March). *Public Health Goal for Methyl Tertiary Butyl Ether (MTBE) in Drinking Water*. Prepared by OEHHA, Pesticide and Environmental Toxicology Section, Anna M. Fan, Chief; and Deputy Director for Scientific Affairs, George V. Alexeeff. Available: <http://oehha.ca.gov/water/phg/pdf/mtbe_f.pdf>. Accessed April 6, 2010.

———. 1999c (June 2). *Expedited Evaluation of Risk Assessment for Tertiary Butyl Alcohol in Drinking Water*. Prepared OEHHA Staff. Sacramento, CA.

———. 2001. *A Guide to Health Risk Assessment.* Available: <http://www.oehha.org/pdf/HRSguide2001.pdf>. Accessed: April 1, 2010.

———. 2003 (August). *Air Toxics Hot Spots Program Risk Assessment Guidelines: The Air Toxics Hot Spots Program Guidance Manual for Preparation of Health Risk Assessments.* Oakland, CA. Available: <http://www.oehha.org/air/hot_spots/pdf/HRAguidefinal.pdf>. Accessed: April 1, 2010.

Plastic Pipe and Fittings Association. 2007 (October 18). Estimate of PEX tubing used in the State of California in 2005.Glen Ellyn, IL.

PPFA. *See* Plastic Pipe and Fittings Association.

Pulver, M. Purchasing Manager. Warmington Homes California. June 6, 2008—letter to Valerie Namba of the California Department of General Services regarding comments on the draft environmental impact report evaluating the proposed adoption of statewide regulations allowing use of PEX piping.

Risk Assessment Information System. 2005 (August 17). Toxicity profile for copper. Available: <http://rais.ornl.gov/tox/profiles/copper_c.shtml>. Last updated August 17, 2005. Accessed March 7, 2008.

Robinson M, Bruner RH, Olson GR. 1990. Fourteen- and ninety-day oral toxicity studies of methyl tertiary-butyl ether (MTBE) in Sprague-Dawley rats. *J. Am. Coll. Toxicol*. 9(5): 525-540.

Sacramento Metropolitan Air Quality Management District. 2010. *CEQA Guide to Air Quality Assessment*. Sacramento, CA. Available: <http://www.airquality.org/ceqa/ceqaguideupdate.shtml>.

San Joaquin Valley Air Pollution Control District. 2002 (January 10). *Guide for Assessing and Mitigating Air Quality Impacts.* Fresno, CA. Available: <http://www.valleyair.org/transportation/CEQA%20Rules/GAMAQI%20Jan%202002%20Rev.pdf>.

Shields, Richard, Director of Building and Safety/Public Works, City of Grand Terrace. 2008 (October 22) – letter to Valerie Namba of California General Services regarding comments on the Recirculated Draft Environmental Impact Report on PEX Tubing.

SJVAPCD. *See* San Joaquin Valley Air Pollution Control District.

Skjevrak, I., A. Due, K. O. Gjerstad, and H. Herikstad. 2003. Volatile organic components migrating from plastic pipes (HDPE, PEX and PVC) into drinking water. *Water Research* 37: 1912–1920.

SMAQMD. *See* Sacramento Metropolitan Air Quality Management District.

Suffet, I.H. 2007. A re-evaluation of the taste and odour of methyl tertiary butyl ether (MTBE) in drinking water. *Water Sci Technol.* 55(5):265-73—as cited in NSF International 2010.

Taylor, W. General Manager. Golden West Plumbing, Inc. June 6, 2008—letter to Valerie Namba of the California Department of General Services regarding comments on the draft environmental impact report evaluating the proposed adoption of statewide regulations allowing use of PEX piping.

Tomboulian, P., L. Schweitzer, K. Mullin, J. Wilson, and D. Khiari. 2004. Materials used in drinking water distribution systems: contribution to taste and odor. *Water Science and Technology* 49(9):219–226.

U.S. Environmental Protection Agency (EPA). 1992 (May 29). *Guidelines for Exposure Assessment.* EPA/600/Z-92/ 001. Published on May 29, 1992, Federal Register 57(104):22888-22938.

———. Office of Pollution Prevention and Toxics. 1994 (August). EPA 749-F-94-017a. Available: <http://www.epa.gov/chemfact/s_mtbe.txt>. Accessed April 7, 2010.

———. 2007 (June 29). Information about chlormaine in drinking water. Available: <http://www.epa.gov/safewater/disinfection/chloramine/index.html#six>. Last updated June 29, 2007. Accessed March 7, 2008.

———. 1997a (August). *Exposure Factors Handbook*. National Center for Environmental Assessment. Available: <http://www.epa.gov/ncea/pdfs/efh/efh-complete.pdf>. Accessed: April 15, 2010.

———. 1997b (December). *Fact Sheet–Drinking Water Advisory: Consumer Acceptability Advice and Health Effects Analysis on Methyl Tertiary-Butyl Ether (MtBE)*. EPA-822-F-97-009. Office of Water, Washington, D.C. Available: <http://www.epa.gov/waterscience/criteria/drinking/mtbefact.pdf>. Accessed: April 23, 2010.

———. 1998. *Assessment of Thyroid Follicular Cell Tumors*. U.S. Environmental Protection Agency, Washington, DC, EPA/630/R-97/002, 1998. Available: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=13102 >. Last Updated January 3 2006. Accessed March 25, 2010. as cited in Bestervelt, pers. comm., 2008

———. 2005 (March). *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens.* EPA/630/R-03/003F. Risk Assessment Forum, Washington, D.C. Available: <http://www.epa.gov/ttn/atw/childrens_supplement_final.pdf >. Accessed: April 14, 2010.

———. 2008 (September 30). Benchmark Dose Software, Appendix C: Glossary of Terms. Available: <http://www.epa.gov/ncea/bmds/bmds_training/appendices/glossary.htm#bmdl>. Accessed May 4, 2010. Last updated September 30, 2008.

———. 2010. *Human Health Risk Assessment: Step 2 - Dose-Response Assessment*. Available: <http://www.epa.gov/risk/dose-response.htm>. Accessed March 31, 2010.

U.S. Food and Drug Administration. 2003 (November). Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products. U.S. Department of Health and Human Services. Office of Training and Communication, Division of Drug Information, Rockville, MD.

Vanguard Piping Systems, Inc. 2000. *Installation Guidelines for the Vanguard Vanex®PLUS+ PEX Plumbing System with CRIMPSERT™ Insert Fittings*. McPherson, KS.

Whitt, T. Chief Executive Officer. Pacific Production Plumbing. June 3, 2008—letter to Valerie Namba of the California Department of General Services regarding comments on the draft environmental impact report evaluating the proposed adoption of statewide regulations allowing use of PEX piping.

Zlomek, J. Chief Operating Officer. Saber Plumbing Company, Inc. June 6, 2008—letter to Valerie Namba of the California Department of General Services regarding comments on the draft environmental impact report evaluating the proposed adoption of statewide regulations allowing use of PEX piping.

CHAPTER 5, "CUMULATIVE IMPACTS"

Bestervelt, Lori. Senior Vice President and Chief Technical Officer, NSF International, Ann Arbor, MI. June 23, 2008—Letter to Valerie Namba, Senior Environmental Planner, with the California Department of General Services regarding comments on the DEIR for Adoption of Statewide Regulations Allowing the Use of PEX Tubing.

California Department of Housing and Community Development. 2006 (November). *Recirculated Draft Environmental Impact Report, Adoption of Regulations Permitting Statewide Residential Use of Chlorinated Polyvinyl Chloride (CPVC) Plastic Plumbing Pipe without First Making a Finding of Potential Premature Metallic Pipe Failure Due to Local Water or Soil Conditions*. State Clearinghouse No. 2006012044. Sacramento, CA.

California Department of Public Health. 2006 (November). MTBE: Regulations and Drinking Water Monitoring Results. Available: <http://www.cdph.ca.gov/certlic/drinkingwater/Pages/MTBE.aspx>. Last updated November 29, 2006. Accessed April 28, 2008.

DPH. *See* California Department of Public Health.

EPA. *See* U.S. Environmental Protection Agency.

HCD. *See* California Department of Housing and Community Development.

Office of Environmental Health Hazard Assessment. 1999 (June 2). *Expedited Evaluation of Risk Assessment for Tertiary Butyl Alcohol in Drinking Water*. Prepared OEHHA Staff. Sacramento, CA.

Plastic Pipe and Fittings Association. 2007 (October 18). Estimate of PEX tubing used in the State of California in 2005.Glen Ellyn, IL.

PPFA. *See* Plastic Pipe and Fittings Association.

Taber, Kelley. Somach Simmons & Dunn (on behalf of the Plastic Pipe and Fittings Association), Sacramento, CA. June 23, 2008—Letter to Valerie Namba, Senior Environmental Planner with the California Department of General Services regarding the Draft EIR on the Adoption of Statewide Regulations Allowing the Use of PEX Tubing.

U.S. Environmental Protection Agency. 2007 (April). *Executive Summary in Inventory of U.S. Greenhouse Gas Emissions and Sinks: 1990–2005*. Washington, D.C.

Appendix A

Curriculum Vitae of Dr. Jonathan Borak

BORAK, Jonathan Benjamin

BUSINESS ADDRESS:

Office: Jonathan Borak & Company
234 Church Street, New Haven, Connecticut, 06510
(203) 777-6611 Fax: (203) 777-1411
Email: jborak@jborak.com
Website: http://www.jborak.com

Hospital: Occupational and Environmental Medicine Program
Yale School of Medicine
135 College Street, New Haven, Connecticut 06510
Telephone: (203) 785-5885

CURRENT APPOINTMENTS:

Clinical Professor of Epidemiology and Public Health, Yale University
Clinical Professor of Medicine, Yale University
Adjunct Associate Professor of Medicine, John Hopkins University
Member, Yale Program in Occupational and Environmental Medicine
President, Jonathan Borak & Company

EDUCATION:

1968	BA (Cum Laude)	Amherst College
1972	MD	New York University
1974-76	Graduate Studies in Economics	McGill University

PROFESSIONAL TRAINING:

1972-73	Internship, Department of Medicine, Royal Victoria Hospital, Montreal, Quebec
1973-74	Junior Assistant Resident, Department of Medicine, Royal Victoria Hospital, Montreal, Quebec
1974-75	Clinical and Research Fellow, Department of Medicine, Royal Victoria Hospital, Montreal, Quebec
1975-76	Senior Assistant Resident, Department of Medicine, Royal Victoria Hospital, Montreal, Quebec
1976-77	Resident, Department of Medicine, Royal Victoria Hospital, Montreal, Quebec
1977-78	Clinical Fellow, Section of Gastroenterology, Yale-New Haven Hospital, New Haven, Connecticut

COMPETITIVE FELLOWSHIPS and AWARDS:

1974-76	Clinical Scholar, Robert Wood Johnson Foundation.
1977-78	Research Fellowship, Conseil de la Recherche en Sante du Quebec
1994	President's Award, American College of Occupational and Environmental Medicine

1996	Meritorious Service Award, American College of Occupational and Environmental Medicine
2002	President's Award, American College of Occupational and Environmental Medicine
2003	Adolph G. Kammer Merit in Authorship Award, American College of Occupational and Environmental Medicine
2004	Robert A. Kehoe Award of Merit Recognition, American College of Occupational and Environmental Medicine
2005	George H. Gerchman Memorial Prize, American College of Occupational and Environmental Medicine
2008	President's Award, American College of Occupational and Environmental Medicine

PROFESSIONAL CERTIFICATION:

Fellow, American College of Physicians
Fellow, American College of Occupational and Environmental Medicine
Fellow, Royal College of Physicians of Canada
Diplomate, American Board of Internal Medicine
Diplomate, American Board of Preventive Medicine
Diplomate, American Board of Toxicology
Diplomate, National Board of Medical Examiners
Licentiate, Medical Council of Canada

PROFESSIONAL EXPERIENCE:

CLINICAL and TEACHING ACTIVITIES

2008-Current	Clinical Professor of Medicine, Yale University
2007-Current	Clinical Professor of Epidemiology & Public Health, Yale University
2003-Current	Adjunct Associate Professor of Medicine, Johns Hopkins University
2000-Current	Director, Yale University Interdisciplinary Risk Assessment Forum
1999-2007	Associate Clinical Professor of Epidemiology & Public Health, Yale University
1993-2008	Associate Clinical Professor of Medicine, Yale University.
1983-1993	Assistant Clinical Professor of Medicine, Yale University.
1981-1983	Clinical Instructor of Internal Medicine, Yale University.
1988-2001	Courtesy Attending Physician, Department of Emergency Medicine, Hospital of St. Raphael, New Haven, Connecticut.
1988-1998	Consulting Physician (Internal Medicine, Emergency Medicine, Toxicology), Hospital of St. Raphael, New Haven, Connecticut.
1980-1988	Director, Section of Emergency Medicine, Hospital of St. Raphael, New Haven, Connecticut.
1979-1988	Associate Attending Physician, Department of Ambulatory Services, Hospital of St. Raphael, New Haven, Connecticut.

1986 Visiting Professor, St. George's University School of Medicine, Kingstown Medical College, St. Vincent, W.I.

1978-80 Attending Physician, Department of Ambulatory Services, Mercy Hospital, Springfield, Massachusetts.

1978-79 Attending Physician, Emergency Physicians Incorporated, Chicopee, Massachusetts.

YALE UNIVERSITY TEACHING ACTIVITIES

Courses Taught: 1997-Current

1998-Current EHS 511b. Applied Risk Assessment: Course Director
Graduate-level course listed in the School of Medicine, Department of Epidemiology and Public Health. This course is also listed as a graduate-level course in the School of Forestry and Environmental Studies (F&ES 96005b).

2000-Current EHS 580a. Special Topics in Society and Risk Assessment: Course Director
Graduate-level course listed in the School of Medicine, Department of Epidemiology and Public Health.

2002-Current EHS 503a. Introduction to Toxicology: Course Director
Graduate-level course listed in the School of Medicine, Department of Epidemiology and Public Health. This course is also listed as a graduate-level course in the School of Forestry and Environmental Studies (F&ES 96005a).

2005-Current EHS 508a Assessing Exposures to Environmental Stressors: Lecturer
Graduate-level course listed in the School of Medicine, Department of Epidemiology and Public Health.

2005-Current EPH 500 Introduction to Epidemiology and Public Health: Lecturer
Graduate-level (second-year required) course in the School of Medicine.

2001-Current EHS 551a and b. Seminar in Environmental Health: Lecturer
Graduate-level course listed in the School of Medicine, Department of Epidemiology and Public Health.

1997-Current EHS 575b/INT 151b. Introduction to Occupational and Environmental Medicine: Lecturer Graduate-level course listed in the School of Medicine, Department of Epidemiology and Public Health and the Department of Internal Medicine.

2005-Current interdisciplinary Center for Bioethics Summer Internship Program: Lecturer
International program for undergraduate and graduate students, supported by the Donaghue Medical Research Foundation

2008-Current FES 96017. Fundamental of Environmental Health: Lecturer
Graduate-level course listed in the School of Forestry and Environmental Studies.

2006-Current Faculty Advisor, Yale Center for Environmental Law & Policy
The Center is a joint initiative between the Yale School of Forestry & Environmental Studies and the Yale Law School.

2002-2007 EHS 510b. Fundamentals of Environmental Health & Risk Assessment: Lecturer
Graduate-level course listed in the School of Medicine, Department of Epidemiology and Public Health.

1999-2002 EHS 509a. Environmental Toxicology: Lecturer
Graduate-level course listed in the School of Medicine, Department of Epidemiology and Public Health, and cross-listed in the School of Forestry and Environmental Studies.

Thesis and Dissertation Committees

2008 Primary Advisor: Catherine Salipante-Zaidel: "Markov Chain Analysis of the Use of Beryllium Lymphocyte Proliferation Tests for Screening of Asymptomatic Individuals". Masters Thesis for MEE, Yale School of Forestry and Environmental Studies

2005 Primary Advisor: H. Dean Hosgood: "Silica and Lung Cancer: Industrial Hygiene Methods and Mathematical Modeling Revisited". Masters Thesis for MPH in Environmental Health Sciences, Yale School of Medicine

2002 Primary Advisor: Susan Chemerynski: "Methodological Uncertainties in the Exposure Assessment of Diesel Particulate Matter: Implications for Risk Assessment". Masters Thesis for MPH in Environmental Health Sciences, Yale School of Medicine

2002 Committee Member: Montira Pongisiri: "Institutional Capacity to Assess and Manage Risk-Tradeoffs: The DDT/Malaria Dilemma". Dissertation for PhD in Environmental Policy, Yale School of Forestry and Environmental Studies

2003 Committee Member: Carlos Gonzalez: "The Beef Hormone Ban in the European Union and the Role of the WTO in Resolving Scientific Barriers to Trade". Dissertation for PhD in Environmental Policy, Yale School of Forestry and Environmental Studies

ORGANIZATIONAL ACTIVITIES

United States Environmental Protection Agency

1996-2006 National Advisory Committee to Develop Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL)

National Research Council (National Academy of Sciences)

2001-2005 Subcommittee on Toxicologic Assessment of Low-Level Exposures to Chemical Warfare Agents

American College of Occupational and Environmental Medicine

1999-2002 Board of Directors
1999-2002 Board Finance Committee
1993-Current Council on Scientific Affairs (Chair 1999-Current)
2008-Current Council on Public Affairs
2003-2004 Planning Committee, 2005 American Occupational Health Conference
1997-2002 Council on Conferences (Associate Chair 1998-2002)
1993-1999 Course Director, Core Curriculum in Environmental Medicine.
1992-Current Committee on Environmental Medicine (Chair 1993-96)
1993-2000 Committee on Medical Surveillance (Chair 1998-2000)
1996-1998 Seminar Chair, 1998 American Occupational Health Conference
1992-1993 Scientific Chair, 1993 State-of-the-Arts Conference
1997-2002 Committee on Conferences (Associate Chair 1997-2002)
1995-2006 Committee on Government Affairs

1992-1997 Committee for Liaison with Government Agencies
1995-1997 Committee on Distance Learning (Associate Chair 1996-1997)
1993-1996 Occupational Medicine Self-Assessment Program
1993-1997 House of Delegates

National Institute of Environmental Health Sciences
2009-current Review Panel – RFA ES-09-001 – Partnership for Environmental Public Health

International Dose-Response Society (previously the International Hormesis Society)
2005-Current Executive Committee

Cyanide Poisoning Treatment Coalition
2006-2009 Board of Directors

American Industrial Hygiene Association
1990-2000 Committee on Emergency Response Planning

Connecticut State Medical Society
1994-1996 Section of Preventive Medicine (Chairman 1994-96)
1983-1994 Committee on Emergency Medical Services (Chairman 1985-1988)
1987-1992 Committee on Organ and Tissue Transfer

Occupational and Environmental Medical Association of Connecticut
1992-1998 Board of Directors
1994-1995 President
1993-1994 President-Elect
1992-1993 Secretary-Treasurer

American College of Emergency Physicians
1992-1994 Liaison to ATSDR Case Studies in Environmental Medicine
1991-1994 Section of Disaster Medicine (Chair, Hazardous Materials Subsection 1991-1994)
1988-1990 National Councilor (Alternate)
1987-1988 National Committee on Chapter Grants
1984-1986 National Committee on Bio-Ethics

Connecticut Poison Control Center
1993-1999 Medical Advisory Committee

American College of Surgeons
1984-1988 Associate Member, Connecticut Committee on Trauma

American Heart Association
1981-2000 Instructor, Advanced and Basic Cardiac Life Support
1985-1987 National Faculty for Advanced Cardiac Life Support
1980-1984 State Chairman, Advanced Cardiac Life Support
1980-1984 State Emergency Cardiac Care Task Force

Connecticut College of Emergency Physicians
1986-1987 President
1980-1990 Board of Directors

Connecticut Red Cross
1987-1992 Medical Advisory Committee on Blood Programs

Connecticut Dept of Health Services, Office of Emergency Medical Services
1985-1988 Helicopter Over-site Committee (Chairman, Patient Care Review)
1987-1988 Trauma Network Committee

Emergency Medical Systems Council of South Central Connecticut
1980-1988 Medical Advisory Committee (Chairman 1987-1988)

New Haven County Medical Association
1984 Committee on Consumer Protection

Town of North Haven, Connecticut
1987-1995 Local Emergency Planning Committee (Chairman 1988-1990)

Town of Branford, Connecticut
1982-84 Ambulance Commissioner

Shirley Frank Foundation, New Haven, Connecticut
1983-1989 Board of Directors
1983-1989 Chairman, Medical Treatment/Quality Assurance Committee
1985-1989 Executive Committee

Alcohol Services Organization of South Central Connecticut
1981-1984 Board of Directors

Columbus House Shelter, New Haven, Connecticut
1981-83 Founding Member, Board of Directors

World Figure Skating Championships
1980-81 Medical Director

Canadian Association of Interns and Residents
1973-75 Board of Directors

Federation des Medicins Residents du Quebec
1973-75 Treasurer

Canadian National Committee on Physician Manpower
1973-74 Committee Member

PROFESSIONAL LICENSURE:

State of Connecticut #19428
State of New York #117-092

PROFESSIONAL ORGANIZATIONS and SOCIETIES:

American College of Physicians
American College of Emergency Physicians
American College of Occupational and Environmental Medicine
American College of Preventive Medicine
Royal College of Physicians of Canada
Society for Toxicology
Society for Risk Analysis
Society of Occupational Medicine (London)
American Industrial Hygiene Association
Association of Occupational and Environmental Clinics

Medichem
International Hormesis Society
Ramazzini Society
Connecticut State Medical Society
Occupational and Environmental Medical Association of Connecticut
New Haven County Medical Society
New Haven Medical Association

PUBLICATIONS and EDITORIAL ACTIVITIES:

Editorial Activities

2004-Current Editorial Board, Journal of Occupational and Environmental Medicine

2003-Current Editorial Board, Journal of Occupational and Environmental Hygiene

2007-Current International Advisory Board, Occupational Medicine

1999-2004 Editorial Board, American Industrial Hygiene Association Journal

1997-2004 Associate Editor, OEM: Occupational and Environmental Medicine Report

1992-Current Editorial Reviewer: American Journal of Industrial Medicine; American Journal of Critical Care and Respiratory Medicine; Annals of Occupational Hygiene; Annals of Emergency Medicine; Critical Reviews in Toxicology; Dose Response; Human and Ecological Risk Assessment; Inhalation Toxicology; Journal of the Air & Waste Management Association; Nonlinearity in Biology, Toxicology and Medicine; Psychological Reports; Regulatory Toxicology and Pharmacology; Toxicology and Applied Pharmacology; Toxicology & Industrial Health

1991-2004 Editorial Board, OEM: Occupational and Environmental Medicine Report

1988-Current Peer Reviewer, Case Studies in Environmental Medicine, US Agency for Toxic Substances and Disease Registry, Atlanta, Georgia

2006-Current Peer Reviewer, Medical Management Guidelines for Acute Chemical Exposures, US Agency for Toxic Substances and Disease Registry, Atlanta, Georgia

1991-92 Peer Reviewer, Toxicology Profiles, US Agency for Toxic Substances and Disease Registry, Atlanta, Georgia

1979-81 Consulting Editor, Update Publications, Ltd., London

Books and Monographs

Borak J, Callan M, Abbott W: Hazardous Materials Exposure: Emergency Response and Patient Care. Englewood Cliffs, NJ: Prentice Hall, 1991.

Borak J, Callan M, Abbott W: Hazardous Materials Exposure: Emergency Response and Patient Care - Instructor's Manual. Englewood Cliffs: Prentice Hall, 1991.

Levy B,. McCunney RM, Adamowski SE, Borak J, Halperin W, McDiarmid MA, Orris P: Occupational Medicine Self-Assessment Program (3rd Ed). Arlington Heights: American College of Occupational and Environmental Medicine, 1993.

Medical Management Guidelines for Acute Chemical Exposures. (Principal Authors: Borak J, Olsen K, Sublet V). Atlanta: Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services, 1994.

Borak J (ed): Core Curriculum in Environmental Medicine. Arlington Heights, IL: American College of Occupational and Environmental Medicine, 1994.

Russi M, Borak J: The OSHA Asbestos Standard: A Medical Compliance System. New Haven, CT: AEGIS Healthcare Systems, 1995.

Borak J (Guest Editor): Amler R, Amler S, Balk SJ, McLellan RM (Guest Contributors): Pediatric Environmental Health (ATSDR-HE-CS-2002-0002). Case Studies in Environmental Medicine, US Agency for Toxic Substances and Disease Registry, Atlanta, 2002.

Ducatman AM, Borak J, Kaye W, Peipens L (Guest Contributors): Investigating Disease Clusters (ATSDR-HE-CS-2002-0006). Case Studies in Environmental Medicine. Atlanta: Agency for Toxic Substances and Disease Registry, 2002.

McCunney RJ, Rountree P, Barbanel C, Borak J, Bunn W, Levin J, Harber P (ed): A Practical Approach to Occupational and Environmental Medicine (3rd Edition). Philadelphia, Lippincott Williams & Wilkins, 2003.

Book Chapters and Technical Reports

Borak J: Training and Education of Workers and Managers. In: Levy B (ed): Air Pollution in Central and Eastern Europe. Boston: Management Sciences for Health, 1991.

Borak J, Callan M, Abbott W: Protection of the Health Care System. In: Tokle G (ed): Hazardous Materials Response Handbook (Second Edition). Quincy, MA: National Fire Protection Association, 1993.

Borak J: Anion and Osmolar Gaps. In: Viccellio P (ed): Handbook of Medical Toxicology (1st edition). Boston: Little, Brown, 1993.

Borak J: Worksite and Environmental Emergencies: Planning Requirements. In: McCunney RJ (ed): A Practical Approach to Occupational and Environmental Medicine. Boston: Little, Brown, 1994.

Borak J: Les nouvelles normes de qualité de l'air aux Etats-Unis: bases épidémiologiques et bénéfices attendus. In: Pollution Atmospherique Urbaine et Santé Humaine. Paris: la Société de Pneumologie de Langue Française, 1997.

Borak J: Anion and Osmolar Gaps. In: Viccellio P (ed): Handbook of Medical Toxicology (2nd edition). Boston: Lippincott-Raven, 1998.

McKay CA, Borak J: Chlorine. In: Haddad LM, Winchester JF, Shannon M (ed): Clinical Management of Poisoning and Drug Overdose (3rd edition). Philadelphia: Saunders, 1998.

Borak J: Four Organic Pollutants in the Quinnipiac River: Effects on Human Health. In: Tyrrell ML (ed): Quinnipiac River Point Source Pollution: Is it Still a Problem? New Haven: Center for Coastal and Watershed Systems, Yale School of Forestry and Environmental Studies, 2000.

Russi M, Borak J: Chemical Hazards in Health Care Workers. In: Orford R (ed): Clinics in Occupational and Environmental Medicine: Occupational Health in the Healthcare Industry. Philadelphia: W.A. Saunders, 2001; 1(2):369-395.

Borak J: Surveillance and Monitoring for Occupational Carcinogens. In: Whysner J, Shields PG (eds): Clinics in Occupational and Environmental Medicine: Cancer in the Workplace: Agents, Mechanisms, Detection, Diagnosis, Management and Prevention: Philadelphia:
W.A. Saunders, 2002; 2(4): 737-752.

Borak J: Medical Aspects of Environmental Emergencies. In: McCunney RJ, Rountree P, Barbanel C, Borak J, Bunn W, Levin J, Harber P (eds): A Practical Approach to Occupational and Environmental Medicine (3rd Edition). Philadelphia: Lippincott Williams & Wilkins, 2003; 768-773.

Borak J, Heywood JB, Parsley W, Pickett T, Widmer W: FY 2003 Two Hundred Bus Procurement: Expert Panel Report to Massachusetts Bay Transportation Authority. 10/14/2002

Borak J, Pleus R: Toxicology. In: McCunney RJ, Rountree P, Barbanel C, Borak J, Bunn W, Levin J, Harber P (eds): A Practical Approach to Occupational and Environmental Medicine (3rd Edition). Philadelphia: Lippincott Williams & Wilkins, 2003; 554-570.

Moore JS, Rose S, Borak J: Ergonomics. In: McCunney RJ, Rountree P, Barbanel C, Borak J, Bunn W, Levin J, Harber P (eds): A Practical Approach to Occupational and Environmental Medicine (3rd Edition). Philadelphia: Lippincott Williams & Wilkins, 2003; 607-623.

Borak J, Fields C, Sirianni G: The Toxicology of Complex Mixtures. In: Lutrell WE, Jederberg WM, Still KE, Robert K (ed): Toxicology Principles for the Industrial Hygienist. Fairfax: American Industrial Hygiene Association, 2008; 273-282.

Fields C, Borak J: Iodine Deficiency in Vegetarian and Vegan Diets: Evidence-Based Review of the World's Literature on Iodine Content in Vegetarian Diets. In: Preedy VR, Burrow GN, Watson RR (ed): Comprehensive Handbook on Iodine. Oxford: Academic Press, 2009; 521- 531.

Borak J: Cyanide Treatment in Fire Victims. In: American Academy of Orthopedic Surgeons: Assessment and Treatment of Trauma. Sudbury, MA: Jones & Bartlett, 2010; 196-197.

Borak J, Sirianni G: Clinical Practice of Biological Monitoring: Trichloroethylene. In: Hoffman H, Phillips S (eds): Clinical Practice of Biological Monitoring. Beverly, MA: OEM Press, 2009 (in press).

Journal Articles

Borak J: Clinical decisions analysis [letter]. Journal of the American Medical Association, 1977; 237:641.

Borak J: *Hypertension: A Policy Perspective* by MC Weinstein and W Stason [book review]. Annals of Internal Medicine, 1977; 87:135.

Borak J: Data requirements for clinical decisions on renovascular hypertension. Clinical and Investigative Medicine, 1979; 2:105.

Meyer C, McBride WJ, Goldblatt RS, Borak J, Marignani P, Contino C, McCallum R: Flexible fiberoptic sigmoidoscopy in asymptomatic and symptomatic patients: a comparative study. Gastrointestinal Endoscopy, 1979; 25:43.

Borak J, Vasey F, Lauter S, Dorval G, Osterland CK: Immunofluorescence assay for antinuclear factor: a nonspecific test in hospitalized patients. Canadian Medical Association Journal, 1979; 121:1372.

Abstracted in: Twenty-Fifth Rheumatism Review. Atlanta: Arthritis Foundation, 1981.

Borak J, Vasey F, Lauter S, Dorval G, Osterland CK: Immunofluorescence assay for antinuclear factor: the meaning of specificity [letter]. Canadian Medical Association Journal, 1980; 123:474.

Meyer C, McBride WJ, Goldblatt RS, Borak J, Marignani P, Black HR, McCallum RW: Clinical experience with flexible sigmoidoscopy in asymptomatic and symptomatic patients. Yale Journal of Biology and Medicine, 1980; 53:345.

Borak J, Veilleux S: Does statistical training improve physician logic? Clinical Research, 1981; 29:316A.

Borak J, Veilleux S: Prophylactic lidocaine: Uncertain benefits in emergency settings. Annals of Emergency Medicine, 1982; 11:493.

Borak J, Veilleux S: Errors of intuitive logic among physicians. Social Science and Medicine, 1982; 16:1939.

Bell C, Borak J, Loeffler JR: Pneumothorax in drug abusers: A complication of internal jugular venous injections. Annals of Emergency Medicine, 1983; 12:167.

Borak J, Veilleux S: Informed consent in emergency settings. Annals of Emergency Medicine, 1984; 13:731.

Reprinted in Connecticut Medicine, 1984; 48:235.

Granata AV, Halickman JF, Borak J: Utility of military anti-shock trousers (MAST) in anaphylactic shock. Journal of Emergency Medicine, 1985; 2:349.

Starr LM, Borak J, Waymaster S: Responding to industrial accidents requires development of disaster plan. Occupational Health and Safety, 1985; 55:19.

Borak J: A Primer on EMS for Connecticut physicians. Connecticut Medicine, 1985; 49:657.

Starr LM, Bush DF, Borak J, Waymaster S, Somerfield M: Emergency teams and industry have different perceptions of each other. Occupational Health and Safety, 1986; 55(June):20.

Borak J, Bush DF, Starr L, Waymaster S: The hazards of ignorance: the EMS/Industry interface. Journal of Emergency Medical Services, 1986; 11(September):6.

Starr LM, Bush DF, Borak J, Waymaster S: Workplace medical emergencies. The Health Psychologist, 1986; 8(2):2.

Borak J, Starr LM: On emergency medical preparedness for industrial accidents. ECO, 1987; (March):3.

Starr LM, Leach T, Borak J: Occupational emergencies and EMS. Journal Emergency Care and Transport, 1988; 17:46.

Herbener D, Borak J: Cutaneous larva migrans in Northern climates. American Journal of Emergency Medicine, 1988; 6:462.

Borak J: The Superfund Amendments and Reauthorization Act of 1986: Implications for prehospital services. Emergency Care Quarterly, 1990; 6(3):29.

Borak J: HazMat training. Journal of Emergency Care and Transport, 1991; 20(4):44.

Borak J: Predicting HazMat effects through exposure routes and injury mechanisms. Rescue, 1991; 4(3):62.

Borak J: Phosgene toxicity: Review and update. Occupational and Environmental Medicine Report, 1991; 5:19.

Borak J: Welding-related illness: New thoughts on an old malady. Occupational and Environmental Medicine Report, 1991; 5:89.

Borak J, Sidell FC: Agents of chemical warfare. I. Sulfur mustard. Annals of Emergency Medicine, 1992; 21:303.

Sidell FC, Borak J: Agents of chemical warfare. II. Nerve agents. Annals of Emergency Medicine, 1992; 21:865.

Borak J: Acute acrylonitrile toxicity: Reconsideration of mechanisms and antidotes. Occupational and Environmental Medicine Report, 1992; 6:19.

Borak J: Cadmium nephropathy: Review and update. Occupational and Environmental Medicine Report, 1992; 10:75.

Borak J: Toxicology of glycol ethers: a quick review. Occupational and Environmental Medicine Report, 1993; 7:43.

Borak J, Jaffe D: Aluminum and Alzheimer's disease. Occupational and Environmental Medicine Report, 1994; 8:3.

Borak J: Environmental Surveillance: understanding of exposure limits needed for proper job application. Occupational Health and Safety , 1994; 63(5):30.

Borak J, Russi M, Jaffe D: Criteria for significant threshold shift in occupational hearing programs: a re-evaluation. Occupational and Environmental Medicine Report, 1994; 8:49.

Borak J: Environmental Surveillance: ACGIH's Threshold Limit Values. Occupational Health and Safety, 1994; 63 (8):26.

Borak J: Environmental Surveillance: OSHA's outdated Air Contaminants system. Occupational Health and Safety , 1994; 63(12):41.

Russi M, Borak J: Special Report: Medical surveillance under the new Asbestos Standards. Occupational and Environmental Medicine Report, 1995; 9:6.

Borak J: Workplace monitoring and environmental surveillance: What's the difference? Occupational Health and Safety, 1995; 649:(4):30.

Borak J: Pharmacologic mechanism of antidotes in cyanide and nitrile poisoning (letter). Journal of Occupational and Environmental Medicine, 1995; 37:793.

Flaten TP, Pollack ES, Hill G, Borak J, Bonham GH: Aluminum and Alzheimer’s disease: concluding remarks. EnvironMetrics 1995; 6:319.

Borak J: *Dioxins and Health*, edited by A Schecter [book review]. Journal of Occupational and Environmental Medicine 1995:38:305.

Borak J, Israel L: Does *in utero* exposure to PCBs cause developmental toxicity? Occupational and Environmental Report, 1997; 11:13.

Borak J, Wise JP: DNA-Protein crosslinks as biomarkers of formaldehyde exposure. International Journal of Occupational and Environmental Health, 1997; 3:307.

Borak J: Chromium valence and chromium species: A carcinogenicity dilemma (editorial). Occupational and Environmental Medicine Report, 1997; 11:93.

Borak J, Pastides H, Van Ert M, Russi M, Herzstein J: Exposure to MTBE and acute human health effects: a critical literature review. Human and Ecological Risk Assessment, 1998; 4:177.

Borak J, Wise JP: Does aluminum exposure of pregnant animals lead to accumulation in mothers or their offspring? Teratology 1998; 57:127.

Borak J, Silverstein BD: Emergency response plans: the benefits of integration. Occupational Hazards, 1999: 61(9): 44.

Borak J, Cohen HJ, Hethmon TA: Copper exposure and metal fume fever: Lack of evidence for a causal relationship. American Industrial Hygiene Association Journal 2000: 61:832.

Borak J, Russi M, Puglisi JP: Meta-analyses [letter]. Environmental Health Perspectives, 2000: 108:A542.

Borak J, Diller WF: Phosgene exposure: Mechanisms of injury and treatment strategies. Journal of Occupational and Environmental Medicine, 2001; 43:110.

Borak J: Why diesel and why now? [editorial]. Occupational and Environmental Report, 2001; 15:65.

Borak J, Sirianni G, Cohen H, Chemerynski S, Jongeneelen F: Biological vs. ambient exposure monitoring of creosote facility workers. Journal of Occupational and Environmental Medicine, 2002; 44:310.

Reprinted in: Journal of the Institution for Social and Policy Studies. 2003; 4:7.

Recipient of the 2003 **Adolph G. Kammer Merit in Authorship Award** of the American College of Occupational and Environmental Medicine

Cohen HJ, Borak J, Hall T, Sirianni G, Chemerynski S: Exposure of miners to diesel particulate matter in underground non-metal mines. American Industrial Hygiene Association Journal, 2002; 63:651.

Cohen, HJ, Sirianni G, Chemerynski S, Wheeler R, Borak J: Observations on the suitability of the Aethalometer for vehicular and workplace monitoring. Journal of the Air & Waste Management Association, 2002; 52:1258.

Borak J, Sirianni G, Cohen HJ, Chemerynski S, Wheeler R: Comparison of NIOSH 5040 method vs. Aethalometer to monitor diesel particulate in school buses and work sites. American Industrial Hygiene Association Journal, 2003; 64:260.

Sirianni G, Chemerynski S, Cohen HJ, Wheeler R, Borak J: Sources of Interferences in field studies of diesel exhaust emission. Applied Occupational and Environmental Hygiene, 2003; 18:591.

Fiellin M, Chemerynski S, Borak J: Editorial: Race, ethnicity and the SEER Database. Medical and Pediatric Oncology, 2003; 40:413.

Borak J, Fiellin M, Chemerynski S: Who is Hispanic? Implications for epidemiological research in the United States. Epidemiology, 2004; 15:240-244.

Borak J: Adequacy of iodine nutrition in the United States. Connecticut Medicine, 2005; 69:73-77.

Borak J, Slade MD, Russi M: Risks of brain tumors in rubber workers: a meta-analysis. Journal of Occupational and Environmental Medicine 2005; 47:294-298.

Fields C, Dourson M, Borak J: Iodine-Deficient Vegetarians: A hypothetical perchlorate-susceptible population? Regulatory Toxicology and Pharmacology, 2005; 42:37-46.

Borak J: Soy protein and hypothyroidism. Journal of Pediatric Endocrinology and Metabolism, 2005; 18:621.

Fields C, Borak J: *Toxicology of the Kidney* by JB Tarloff and LH Lash [book review]. Journal of Occupational and Environmental Medicine 2005; 47:1317-1318.

Borak J: The Beryllium Occupational Exposure Limit: Historical perspectives and current inadequacy. Journal of Occupational and Environmental Medicine 2006; 48:109-116.

Borak J, Sirianni G: Hormesis: Implications for cancer risk assessment. Dose Response 2006; 3:443-451.

Borak J, Woolf SH, Fields CA: Use of BeLPT for screening of asymptomatic individuals: An evidence-based assessment. Journal of Occupational and Environmental Medicine 2006; 48:937-948.

Borak J: The Beryllium Occupational Exposure Limit: Historical perspectives and current Inadequacy: Author's Response [letter]. Journal of Occupational and Environmental Medicine 2006; 48:998-1001.

Borak J, Hosgood HD: Seafood Arsenic: Implications for human risk assessment. Regulatory Toxicology and Pharmacology 2007; 47:204-212.

Borak J, Woolf SH, Fields CA: Use of BeLPT for screening of asymptomatic individuals: Author's Response [letter]. Journal of Occupational and Environmental Medicine 2007; 49:358-9.

Borak J, Sirianni G: Studies of Self-pollution in Diesel School Buses: Methodological Issues. Journal of Occupational and Environmental Hygiene 2007; 4:660-668.

Sirianni G, Hosgood HD, Slade MD, Borak J: Particle size distribution and particle size-related silica content in granite quarry dust. Journal of Occupational and Environmental Hygiene 2008; 5:279-285.

Russi MB, Borak JB, Cullen MR: An examination of cancer Epidemiology studies among populations living close to toxic waste sites. Environmental Health 2008; 7:32.

Slade MD, Borak J: *Statistical Evidence in Medical Trials: What do the data really tell us?* By SD Simon [book review]. Journal of Occupational and Environmental Medicine 2008; 50:602.

Borak J: *Nanotoxicology: Characterization, Dosing and Health Effects.* By NA Monteiro-Riviere and CL Tran [book review]. Journal of Occupational and Environmental Medicine 2009; 51:620.

Borak J: Five classic articles in Public Health. Yale Journal of Biology and Medicine 2010; (in press).

Sirianni G, Borak J: How clean is "Clean"? Regulations and standards for workplace clothing and personal protective equipment. Journal of Occupational and Environmental Medicine 2010 (in press).

Committee and Group Publications

Bioethics Committee, American College of Emergency Physicians: Medical, moral, legal, and ethical aspects of resuscitation for patients who have minimal ability to function or ultimately survive. Annals of Emergency Medicine, 1985; 14:919.

American Hospitals in Transition: Business Implications and Strategic Considerations for Medical Suppliers. New York: Channing, Weinberg & Co., 1984.

Committee on Organ and Tissue Transfers, Connecticut State Medical Society. HIV testing of transfusion recipients. Connecticut Medicine, 1990; 54:217.

Badon SJ, Cable RG and Committee on Organ and Tissue Transfers, Connecticut State Medical Society. Yersinia enterocolitica contamination of blood. Connecticut Medicine, 1992; 56:287.

Emergency Response Planning Committee, American Industrial Hygiene Association: The AIHA 1996 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook. Fairfax: AIHA, 1996.

World Health Organization. Environmental Health Criteria 194: Aluminium. Geneva: World Health Organization, International Program on Chemical Safety, 1997.

Environmental Medicine Committee, American College of Occupational and Environmental Medicine: Multiple Chemical Sensitivities: Idiopathic Environmental Intolerance. Journal of Occupational and Environmental Medicine 41:940, 1999.

National Advisory Committee to Develop Acute Exposure Guideline Levels for Hazardous Substances: Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume #1. Washington, DC: National Academy Press, 2000.

National Advisory Committee to Develop Acute Exposure Guideline Levels for Hazardous Substances: Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press, 2001.

National Advisory Committee to Develop Acute Exposure Guideline Levels for Hazardous Substances: Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 2. Washington, DC: National Academy Press, 2002.

National Advisory Committee to Develop Acute Exposure Guideline Levels for Hazardous Substances: Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 3. Washington, DC: National Academy Press, 2003.

National Advisory Committee to Develop Acute Exposure Guideline Levels for Hazardous Substances: Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 4. Washington, DC: National Academy Press, 2004.

National Research Council Subcommittee on Toxicologic Assessment of Low-Level Exposures to Chemical Warfare Agents: Review of the Department of Defense Research Program on Low-Level Exposures to Chemical Warfare Agents. Washington, DC: National Academy Press, 2005.

National Advisory Committee to Develop Acute Exposure Guideline Levels for Hazardous Substances: Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 5. Washington, DC: National Academy Press, 2006.

Calabrese EJ, Bachmann KJ, Bailer AJ, Bolger PM, **Borak J**, et al.: Biological Stress Response Terminology: Integrating the Concepts of Adaptive Response and Preconditioning Stress within a Hormetic Dose-Response Framework. Toxicology and Applied Pharmacology 2007; 222:122-128.

Internet Resources

Borak J: International Cyanide Antidote Database. Cyanide Poisoning Treatment Coalition. Available at: http://www.cyanidepoisoning.org/pages/ICAD.asp

Sirianni G, Borak J: How clean is “Clean”? Regulations and standards for workplace clothing and personal protective equipment: On-Line Supplemental Guide. Journal of Occupational and Environmental Medicine. Available at: http://links.lww.com/JOM/A28

PRESENTATIONS:

Borak J: "Medical decision making: The case of renovascular hypertension". Annual Meeting, Robert Wood Johnson Clinical Scholar Program; Asheville, N.C., 1976.

Borak J: "An evaluation of the adequacy of methods used in clinical investigations of renovascular hypertension". American Federation for Clinical Research, Sydenham Society; Atlantic City, 1976.

Meyer C, McBride WJ, Goldblatt RS, Borak J, Marignani P, Contino C, McCallum R: "Flexible fiberoptic sigmoidoscopy in asymptomatic and symptomatic patients". American Society of Gastrointestinal Endoscopy; New Orleans, 1979.

Borak J, Veilleux S: "Errors of intuitive logic among physicians". Annual Meeting, Robert Wood Johnson Clinical Scholar Program; Scottsdale, 1981.

Borak J: "The epidemiology of cardiac arrest". Annual Scientific Session, Connecticut State Medical Society; New Haven, 1985.

Borak J: "Emergency medicine: What is it and where is it going?". Tenth Annual Symposium, The Wilkerson Group; New York, 1985.

Bush DF, Starr LM, Borak J, Waymaster S: "Communication about medical emergencies: The different perceptions of plant safety directors and EMTs". International Communication Association; Evanston, 1985.

Borak J: "Communication -- The key to the comprehensive emergency response system". International Communication Association; Chicago, 1986.

Bush DF, Starr LM, Borak J, Rachlis V: "The role of the primary care physician in preparation for industrial disasters". International Communication Association; Oxford, England, 1986.

Borak J: "Acute medical aspects of SARA Title III". Summer National Meeting, American Institute of Chemical Engineers; Denver, 1988.

Starr LM, Rachlis V, Borak J: "How to structure the communication process of primary care physicians when discussing occupational health hazards". International Conference on Doctor-Patient Communication; London, Ontario, 1986.

Borak J: "SARA Title III for physicians: Navigating the muddy water of community Right-to-Know". Postgraduate Seminar, American Occupational Health Conference, American College of Occupational Medicine; Boston, 1989.

Borak J: "EMS and hazardous materials". SARA Title III: Progress and Prospects, Department of Environmental Protection, State of Connecticut; Cromwell, 1989.

Borak J: "The implications of SARA Title III for EMS services". SARA Title III State Planning Conference, Department of State Police, State of Michigan; Lansing, MI, 1989.

Borak J, Flynn D: "The management of hazardous materials accidents in the emergency department". Scientific Assembly, Emergency Nurses Association; Washington, D.C., 1989.

Borak J, Leonard RB: "Hazardous materials: Approach and management". Scientific Assembly, American College of Emergency Physicians; Washington, D.C., 1989.

Borak J: "A Guide to SARA Title III for physicians: Disaster planning and community Right-to-Know". Disaster '90: The International Disaster Management Conference; Orlando, 1990.

Borak J: "Emergency medical response to industrial accidents: The U.S. perspective". Medische Rampenplanning en de Gentse Industrie, (Medical Disaster Planning in the Ghent Industries), Rijksuniversiteit; Ghent, Belgium, 1990.

Borak J: "Acute toxic inhalation injuries". Annual Meeting, Connecticut Lung Association; New Haven, 1990.

Borak J: "Environmental toxins: The emergency medicine response". National Medical Association; Las Vegas, 1990.

Borak J: "Disasters and trauma: Managing the aftermath". National Society for Patient Representation, American Hospital Association; Washington, D.C., 1990.

Borak J: "HazMat and the EMS responders". Connecticut HazMat Week, Commission on Fire Prevention and Control; New Haven, 1990.

Borak J: "Medical monitoring". Connecticut HazMat Week, Connecticut Commission on Fire Prevention and Control; New Haven, 1990.

Borak J, Callan M: "Mitigation and response to chemical warfare and terrorism". Disaster '91: The International Disaster Management Conference; Orlando, 1991.

Borak J: "The contaminated victim". SARA Title III Workshops, State Emergency Response Commission, State of Connecticut; Cromwell, CT, 1991.

Connor S, Borak J: "Hazard emergencies: Recognition and management for nurses". (Full-Day Course), American Occupational Health Conference, American Association of Occupational Health Nurses; San Francisco, 1991.

Borak J, Callan M, Abbott W: "Hazardous materials emergency response for EMS personnel". (24-hour OSHA certification program). Emergency Response Conference; Rosemont, 1991.

Borak J: "What physicians need to know about environmental regulations". Environmental Medicine Seminar, New Hampshire Medical Society; Portsmouth, NH, 1991.

Borak J: "Toxic reproductive hazards". Annual Meeting, Philadelphia Occupational Health Nurses Association; West Point, PA, 1991.

Borak J, White S: "Hazardous materials update". Annual Educational Conference, National Association of Emergency Medical Technicians; Kansas City, 1991.

Borak J, Bouvier KJ: "HazMat: The essentials of training EMS". Annual Educational Conference, National Association of Emergency Medical Technicians; Kansas City, 1991.

Borak J: "Training and education of workers and managers". Air Pollution in Central and Eastern Europe: Health and Public Policy; Frydek-Mistek, Czechoslovakia, 1991.

Borak J: "EMS first responders at Hazmats incidents". Connecticut Hazardous Materials Week, Connecticut Commission on Fire Prevention and Control; New Haven, 1991.

Borak J: "The pathophysiology of inhalation injury". Recognition and Treatment of Toxic Inhalation Emergencies; Norwalk Hospital, Norwalk, CT, 1991.

Borak J, Moss M: "HazMat exposure: Health effects and medical monitoring". Connecticut Hazardous Materials Week, Connecticut Commission on Fire Prevention and Control; New Haven, 1991.

Borak J: "Hazmats recognition and identification". Pre-Conference Workshop, EMS Today Conference; Albuquerque, 1992.

Borak J: "Health effects of Hazmats exposure". Pre-Conference Workshop, EMS Today Conference; Albuquerque, 1992.

Borak J: "Personal protection from Hazmats exposure". Pre-Conference Workshop, EMS Today Conference; Albuquerque, 1992.

Borak J: "Hazmats incident procedures". Pre-Conference Workshop, EMS Today Conference; Albuquerque, 1992.

Pendergrass JA, Forster F, Borak J, Vance L: "What you need to know to talk to an Industrial Hygienist". Postgraduate Seminar, American Occupational Health Conference, American College of Occupational and Environmental Medicine; Washington, 1992.

Klein HM, Borak J: "Resource allocation for environmental health training". Fifth National Environmental Health Conference; Centers for Disease Control; Atlanta, 1992.

Borak J, Falk H, Elliott D, Goldstein BD, Melius J, Cullen MR, Rusch G: "The what, why and how of environmental emergencies: A guide for occupational physicians". American Occupational Health Conference, American College of Occupational and Environmental Medicine; Washington, 1992.

Borak J: "The emergency planning elements of EPA and OSHA regulations". American Occupational Health Conference, American College of Occupational and Environmental Medicine; Washington, 1992.

Borak J: "Environmental regulations: What the occupational health professional should know. Annual Conference, New England Occupational Medicine Association; Boston, 1992.

Borak J, Polsky SS: "Medical control of hazardous materials incidents". Clinical Forum: Current Concepts, Emerging Trends; American College of Emergency Physicians; Kansas City, 1993.

Borak J: "Hazardous materials injury: Prehospital and hospital care". Clinical Forum: Current Concepts, Emerging Trends; American College of Emergency Physicians; Kansas City, 1993.

Borak J: "Hazardous materials incidents: Hospital based decontamination procedures". Clinical Forum: Current Concepts, Emerging Trends; American College of Emergency Physicians; Kansas City, 1993.

Borak J: "Medical emergencies in the workplace". Harvard School of Public Health Education Resource Center, Boston, 1993.

Borak J: "Toxicology of hazardous materials". Medical Grand Rounds, Department of Emergency Medicine, Rhode Island Hospital, Providence, 1993.

Borak J: "Hazardous materials emergencies". 3rd Annual Occupational Health Nursing Institute, Environmental and Occupational Health Sciences Institute, University of Medicine and Dentistry of New Jersey, 1993.

Olson, KR, Borak J, George E, Lum M, Tominack R: "Clinical Management of Hazardous Materials Emergencies: Mini-Symposium for Poison Center Professionals". International Congress of Clinical Toxicology, New York, 1993.

Borak J: "Basics of HazMat Toxicology". Annual Meeting, International Congress of Clinical Toxicology, New York, 1993.

Borak J: "ED Management of HazMat incidents". Scientific Assembly, Emergency Nurses Association, Seattle, 1993.

Borak J: "Hazmats: Emergency response and patient care". Scientific Assembly, American College of Emergency Physicians, Chicago, 1993.

McLellan RM, Borak J: "Treatment, Prevention and Control of Environmental Exposures". State-of-the-Art Conference, American College of Occupational and Environmental Medicine, Dallas, 1993.

McCunney RJ, Borak J: "Occupational Medicine Self-Assessment Program III". State-of-the-Art Conference, American College of Occupational and Environmental Medicine, Dallas, 1993.

McLellan RK, Borak J: "Sources of Environmental Exposure". State-of-the-Art Conference, American College of Occupational and Environmental Medicine, Dallas, 1993.

Borak J: "Environmental Disaster Issues". State-of-the-Art Conference, American College of Occupational and Environmental Medicine, Dallas, 1993.

Borak J, Mitchell FL, Sublet VH: "Environmental Medicine Case Studies". State-of-the-Art Conference, American College of Occupational and Environmental Medicine, Dallas, 1993.

Borak J: "Occupational Health Hazards of Hospital Workers". Grand Rounds in Internal Medicine, Thomas Jefferson Medical College, Philadelphia, 1993.

Borak J: "Environmental Disaster Issues". State-of-the-Art Conference, American College of Occupational and Environmental Medicine, Dallas, 1993.

Borak J: "Prepare for Industrial Emergencies and Disasters". American Occupational Health Conference, American College of Occupational and Environmental Medicine, Chicago, 1994.

Borak J: "Monitoring Exposure to Heavy Metals". Medical Surveillance in the Workplace. American Occupational Health Conference, American College of Occupational and Environmental Medicine, Chicago, 1994.

Borak J: "Hazardous Materials Emergencies". Grand Rounds in Emergency Medicine, Hartford Hospital, Hartford, 1994.

Borak J: "Health Effects of Hazardous Materials" . Post Graduate Seminar. State-of-the-Art Conference, American College of Occupational and Environmental Medicine, Denver, 1994.

Borak J, Mitchell FL, Lewis-Younger C, Middleton D, Lum MR: "Cases in Environmental Medicine : The Physician's Perspective". American Occupational Health Conference, American College of Occupational and Environmental Medicine, Chicago, 1994.

Borak J: "Incident Procedures for Hazardous Materials Emergencies" . Post Graduate Seminar. State-of-the-Art Conference, American College of Occupational and Environmental Medicine, Denver, 1994.

Borak J: "Emergency Planning for Governmental Agencies and Contractors". New Environmental Issues & Liabilities of Governmental Agencies & Contractors, Federal Publications, Washington, DC and San Diego, 1995.

Borak J, McCunney RJ, Dunn W, Dhara R: "Emergency Response Planning for Toxic Air Releases". American Occupational Health Conference, American College of Occupational and Environmental Medicine, Las Vegas, 1995.

Levy B, McCunney RJ, Borak J, Orris P: "Occupational Medicine Self-Assessment Program". American Occupational Health Conference, American College of Occupational and Environmental Medicine, Las Vegas, 1995.

Pope A, Kipen HM, Lum M, Borak J, Roberts M: "Integrating Environmental Health into Medical School Curricula". American Occupational Health Conference, American College of Occupational and Environmental Medicine, Las Vegas, 1995.

Borak J: "Controversies in Environmental Medicine: Reformulated Gasoline, Methyl tert-Butyl Ether and Human Health". New England College of Occupational and Environmental Medicine, Boston, 1995.

Borak J: "Toxic Terrorism and Inhaled Poisons". Third Annual Advances in Toxicology, University of Connecticut School of Medicine, Farmington, 1995.

Borak J: “Inhalation Toxicology of Hazardous Materials”. Grand Rounds in Emergency Medicine, Rhode Island Hospital, Providence, 1996.

Borak J: "Health Effects of Acute Hazardous Materials Exposure". Post Graduate Seminar. American Occupational Health Conference. American College of Occupational and Environmental Medicine, San Antonio, 1996.

McCunney RJ, Borak J, Orris P: "Occupational Medicine Self-Assessment Program". Post Graduate Seminar. American Occupational Health Conference. American College of Occupational and Environmental Medicine, San Antonio, 1996.

Kess SL, Hryhorczuk DO, Falk H, Mitchell FL, Hall AH, Borak J: “Career Opportunities in Environmental Medicine”. American Occupational Health Conference, San Antonio, 1996.

Borak J: “Les Novelles Normes de Qualité de L’air Aux États-Unis: Bases Épidémiologiques et Bénifices Attendus”. Pollution Atmospherique Urbaine et Santé Humaine. Faculté de Médecine Xavier Bichat, Paris, 1997.

Borak J, Goldstein BM, Kavlock R, Lipshultz LI, Wolff MS: “Endocrine Disrupter Chemicals, Environmental Exposures and Human Health". American Occupational Health Conference. American College of Occupational and Environmental Medicine, Orlando, 1997.

Borak J: “Determination of Work-relatedness of Disease - Evidence of Disease: What Is Necessary?" American Occupational Health Conference. American College of Occupational and Environmental Medicine, Orlando, 1997.

Borak J: “Fluoride and Drinking Water: Historical Perspective and Current Toxicology". American Occupational Health Conference. American College of Occupational and Environmental Medicine, Orlando, 1997.

Borak J: "Health Effects of Acute Hazardous Materials Exposure". Post Graduate Seminar. State of the Art Conference. American College of Occupational and Environmental Medicine, Nashville, 1997.

Borak J: “Risk Assessment: Survival Guide for Physicians”. State of the Art Conference. American College of Occupational and Environmental Medicine, Phoenix, 1998.

Borak J: "Pollutants in the Quinnipiac River: Effects on Human Health". Point Source Pollution Conference. Yale School of Forestry and Environmental Studies, New Haven, 1999.

Borak J, Upfal M: "Occupational Health Services Course for General Practitioners: Clinical Occupational Health: Train-the-Trainer". (3-day educational program for Slovak physicians, sponsored by Harvard Institute for International Development and US Agency for Industrial Development). Bratislava, Slovakia, 1999.

Borak J: Plausible Conservatism and Maximal Use of Scientific Information: A Risk Assessment Paradigm. Yale University Interdisciplinary Bioethics Conference, New Haven, CT, 2000

Borak J: Toxicology, Risk Assessment, and the "New, New" Science. Annual Meeting, Kentucky Medical Association, Louisville, KY, 2000.

Bunn, W, Borak J, Cohen JT, Mauderly J, Modarres M: Health Effects of Diesel and Other Combustion Technologies. Society of Automotive Engineers, International Truck & Bus Meeting. Chicago, 2001

Chemerynski S, Borak J: Diesel Exhaust: A Risk Assessment Conundrum. Yale University Interdisciplinary Risk Assessment Forum, New Haven, CT, 2000

Borak J, Brandt-Rauf, P, Cooper W, Diaz J, McLellan R, Pendergast J: Environmental Medicine Series: Water, Water Everywhere – But is it Safe to Drink? Millennium Series, American Occupational Health Conference, Chicago, 2002.

Sirianni G, Cohen H, Borak J, Chemerynski S, Wheeler R, Gunter B, Jongeneelen F: Assessment of Creosote Exposure among Wood Preservation Workers: A Pilot Study. American Industrial Hygiene Conference and Exposition, San Diego, 2002.

Chemerynski S, Borak J, Sirianni G, Cohen H: Pseudo Hormesis: An Explanation in Search of a Manifestation. Non-Linear Dose-Response Relationships in Biology, Toxicology and Medicine, International Conference, Amherst, MA, 2002.

Chemerynski S, Borak J, Sirianni G, Cohen H: Uncertainties Surrounding the Risk Assessment of Diesel Particulate Matter. Annual Meeting, American Public Health Association, Philadelphia, 2002.

Sirianni G, Chemerynski S, Cohen H, Borak J, Jongeneelen F: Assessment of Creosote Exposure in Wood Preservation Workers at Two Locations. American Public Health Association, Philadelphia, 2002.

Borak J: The Toxicology of Chemical Warfare Agents. Yale University Interdisciplinary Risk Assessment Forum, New Haven, CT, 2000.

Borak J, Warnock DW, Woodward S, Hardin B, Redd SC, McLellan RM: Overview of the Issues of Indoor Mold. American Occupational Health Conference, American College of Occupational and Environmental Medicine, Atlanta, 2003.

Borak J, Dalton P, Kipen HM, Morata TC, Rabinowitz PM: Adverse Effects of Toxic Exposures on Sensory Perception. American Occupational Health Conference, American College of Occupational and Environmental Medicine, Atlanta, 2003.

Borak J: Evidence, Risk Assessment and Causality: State of the Art Conference. American College of Occupational and Environmental Medicine, Toronto, 2003.

Borak J, Brandt-Rauf P, Maier L, Talaska G: Molecular Epidemiology: Studying the Interactions of Exposures, Genetics and Health. American Occupational Health Conference, American College of Occupational and Environmental Medicine, Kansas City, 2004.

Borak J: Implications of Hormesis for Risk Assessment. 3rd International Conference on Non-linear Dose-response Relationships in Biology, Toxicology and Medicine, University of Massachusetts, Amherst, 2004.

Borak J: What is a 'Susceptible Sub-Population'? Yale University Interdisciplinary Risk Assessment Forum, New Haven, CT, 2004.

Borak J: Uncertainty, Variability and Susceptible Sub-Populations. Occupational Medicine Colloquium, University of Connecticut Health Center, Farmington, 2005.

Borak J: An Introduction to Risk Assessment as an Issue of Ethics. Summer Ethics Program, Yale Center for Bioethics, Institute for Social and Policy Studies, New Haven, 2005.

Borak J: Scientific Risk Assessment and the Future of Occupational and Environmental Medicine. George H. Gehrman Memorial Lecture. State of the Art Conference. American College of Occupational and Environmental Medicine, Chicago, 2005

Hosgood D, Borak J, Slade M: Silica and Lung Cancer: a Monte Carlo Analysis. Annual Meeting, American Public Health Association, Philadelphia, 2005.

Borak J, Sirianni G: Methodological Limitations in Studies Evaluating Diesel Emissions inside School Bus Cabins. Annual Conference, Air & Waste Management Association, New Orleans, 2006.

Borak J: The Origins of Scientific Risk Assessment in Occupational and Environmental Health Policy. Annual Student Day Lecture, Institute of Environmental and Human Health Texas Tech University, Lubbock, TX 2006.

Borak J: Does Silica Cause Lung Cancer (in the Absence of Silicosis)? Occupational Medicine Colloquium, University of Connecticut Health Center, Farmington, 2006.

Hosgood HD, Sirianni G, Slade MD, Borak J: Combining Historical and Contemporary Exposure Data to Evaluate Silica-Related Lung Cancer. Annual Conference, Air & Waste Management Association, Pittsburgh, 2007

Borak J: Origins of Risk Assessment in Occupational Health Policy. Connecticut Chapter, American Industrial Hygiene Association, Hamden, 2007

Borak J, Hoffmann G, McCord J: Plenary Session: Dose-Response 2008. Annual Meeting of the International Dose-Response Society, Amherst, 2008.

McAdoo B, Borak J: Global Environmental Disasters. The Foreign Affairs Symposium at Hopkins: Global Leadership for the 21st Century. Johns Hopkins University, Baltimore, 2009.

Borak J: The Ethics of Risk Assessment. Bio-Ethics Society at Yale. New Haven, 2009.

Borak J: "Risk Assessment: A Practical Introduction for Physicians". (Half-day continuing education program).

Post Graduate Seminar. State of the Art Conference. American College of Occupational and Environmental Medicine, San Antonio, 1999.

Post Graduate Seminar. State of the Art Conference. American College of Occupational and Environmental Medicine, Nashville, 2000.

Borak J, Becker C, Ducatman AM, Kipen HM, McKinnon HW, McLellan RM, Mitchell FL, Russi M: "Core Curriculum in Environmental Medicine". (Continuing Education Program, accredited for 14 CME credits by American College of Occupational and Environmental Medicine and included as a component of the "Essentials of Occupational and Environmental Medicine").

State-of-the-Art Conference, American College of Occupational and Environmental Medicine, Dallas, 1993

American Occupational Health Conference, American College of Occupational and Environmental Medicine, Chicago, 1994

American Occupational Health Conference, American College of Occupational and Environmental Medicine, Las Vegas, 1995

American Occupational Health Conference, American College of Occupational and Environmental Medicine, San Antonio, 1996

American Occupational Health Conference, American College of Occupational and Environmental Medicine, Orlando, 1997

American Occupational Health Conference, American College of Occupational and Environmental Medicine, Boston, 1998

Borak J: "Hazardous Materials Training for Hospital Emergency Personnel" (16-Hour Continuing Education Program).

Occupational Safety & Health Spring Academy, Concord, NH. (Sponsored by Harvard School of Public Health), 1992.

Exeter, NH (Sponsored by Exeter Hospital), 1992.

Bentley College, Waltham, MA. (Sponsored by Harvard School of Public Health), 1992

Pittsburgh, PA (Sponsored by Allegheny County Health Department), 1994.

Bombay, India (Sponsored by US Agency for Industrial Development, World Environment Center and the National Safety Council of India), 1996

Vadadora, India (Sponsored by US Agency for Industrial Development and World Environment Center and the National Safety Council of India), 1996

Cochin, India (Sponsored by US Agency for Industrial Development, World Environment Center and the National Safety Council of India), 1996

Borak J: "An Introduction to Industrial Hazards for Physicians". (Continuing Education Program, accredited for 7 Category CME credits by American College of Emergency Physicians, 1988-92).

Wallingford, CT (Sponsored by Connecticut ACEP), 1988.

Bristol, PA (Sponsored by Rohm and Haas Company), 1988.

Pasadena Medical Center, Pasadena, TX (Sponsored by ARCO Chemical) 1988.

Newtown Square, PA (Sponsored by ARCO Chemical Company), 1989.

Hospital of St. Raphael, New Haven (Sponsored by Connecticut ACEP), 1989.

Rhode Island Hospital, Providence (Sponsored by Rhode Island ACEP), 1990.

Pre-Conference Seminar, Disaster '91: The International Disaster Management Conference; Orlando, 1991.

Seattle (Sponsored by Washington ACEP), 1991

Concord, MA (Sponsored by Emerson Hospital), 1991.

Concord, NH (Sponsored by Harvard School of Public Health), 1992.

Boston, MA, (Sponsored by Conference of Boston Teaching Hospitals), 1992

Pittsburgh, PA (Sponsored by Allegheny County Health Department), 1994.

Map Ta Phut, Thailand (Sponsored by US Agency for Industrial Development and World Environment Center), 1995

Bangpoo, Thailand (Sponsored by US Agency for Industrial Development and World Environment Center), 1995

Serang, Indonesia (Sponsored by US Agency for Industrial Development and World Environment Center), 1995

Boston, MA (Sponsored by Metropolitan Boston EMS Council), 1996.

Appendix B

MTBE Oral Risk Assessment—NSF International

METHYL TERTIARY-BUTYL ETHER

CAS # 1634-04-4

ORAL RISK ASSESSMENT DOCUMENT

NSF International
Ann Arbor, MI
February 2008

© 2008 NSF International

TABLE OF CONTENTS

1.0 INTRODUCTION 3
2.0 PHYSICAL AND CHEMICAL PROPERTIES 5
2.1 Organoleptic Properties 6
3.0 PRODUCTION AND USE 6
3.1 Production 6
3.2 Use 6
4.0 ANALYTICAL METHODS 7
4.1 Analysis in Water 7
4.2 Analysis in Biological Matrices 7
5.0 SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE 7
5.1 Sources of Human Exposure 7
5.2 Sources of Environmental Exposure 8
6.0 COMPARATIVE KINETICS AND METABOLISM IN HUMANS AND LABORATORY ANIMALS 8
6.1 Absorption 10
6.2 Distribution 11
6.3 Metabolism 12
6.3.1 Humans 12
6.3.2 Laboratory Animals 12
6.4 Elimination/Excretion 14
6.5 Physiologically-based pharmacokinetic models 14
7.0 EFFECTS ON HUMANS 15
7.1 Case Reports 15
7.2 Epidemiological Studies 15
8.0 EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS 15
8.1 Limited-Exposure Effects 16
8.1.1 Irritation and Sensitization Studies 16
8.1.2 Ocular Exposure Studies 16
8.2 Single-Exposure Studies 16
8.3 Short-Term Exposure Studies 17
8.3.1 Three-Day Gavage Study In Female B6C3F$_1$ Mice 17
8.3.2 Fourteen-Day Gavage Study In Male And Female Sprague-Dawley Rats 17
8.3.3 Fourteen-Day Gavage Studies In Male Sprague-Dawley Rats 18

8.3.4 Fifteen-Day Gavage Study In Male Sprague-Dawley Rats *19*
8.3.5 Three-Week Gavage Study In CD-1 Mice *19*
8.4 Long-Term and Chronic Exposure Studies 19
8.4.1 Subchronic Studies *20*
8.4.2 Chronic Studies *24*
8.5 Studies of Genotoxicity and Related End-Points 25
8.5.1 Mutagenicity Assays *26*
8.5.2 Assays of Chromosomal Damage *26*
8.5.3 Other Assays of Genetic Damage *27*
8.6 Reproductive and Developmental Toxicity Studies 28
8.6.1 Reproduction Studies *29*
8.6.2 Developmental Toxicity Studies *33*
8.7 Studies of Immunological and Neurological Effects 34
8.7.1 Immunological Effects *34*
8.7.2 Neurological Effects *35*
9.0 RISK CHARACTERIZATION 35
9.1 Hazard Identification 35
9.1.1 Evaluation of Major Non-Cancer Effects and Mode of Action *35*
9.1.2 Weight-of-Evidence Evaluation and Cancer Characterization *39*
9.1.3 Mode of Action (Carcinogenic Effects) *40*
9.1.4 Selection of Key Study and Critical Effect *42*
9.1.5 Identification of Susceptible Populations *43*
9.2 Dose-Response Assessment 43
9.2.1 Dose-response assessment based on tumor data in male rats *44*
9.2.2 Dose-response assessment based on tumor data in female rats *45*
9.2.3 Oral Slope Factor Calculation *46*
9.3 Exposure Assessment 48
9.4 TAC Derivation 48
9.5 STEL Derivation 48
10.0 RISK MANAGEMENT 49
10.1 SPAC Derivation 49
11.0 RISK COMPARISONS AND CONCLUSIONS 49
12.0 REFERENCES 60
13.0 APPENDIX A 69
13.1 Benchmark Dose for Leydig Cell Tumors after Gavage Exposure 69
13.2 Benchmark Dose for Lymphomas/Leukemias after Gavage Exposure 71

13.3 Benchmark Dose for Leydig Cell Tumors after Inhalation Exposure.....73
13.4 Benchmark Dose for Renal Tumors after Inhalation Exposure.....76
13.5 Benchmark Dose for Renal Tumors after Inhalation Exposure (omit highest dose)..78
14.0 PEER REVIEW HISTORY.....80

AUTHORS, PEER REVIEWERS, AND ACKNOWLEDGEMENTS

Author:
NSF Toxicology Services
1.800.NSF.MARK
NSF International
789 Dixboro Road
Ann Arbor, MI 48105

Disclaimer:
The responsibility for the content of this document remains solely with NSF International, and the author noted above should be contacted with comments or for clarification. Mention of trade names, proprietary products, or specific equipment does not constitute an endorsement by NSF International, nor does it imply that other products may not be equally suitable.

Internal NSF Peer Reviewers:
Clif McLellan, M.S.
Gwen Ball, Ph.D.
Carolyn Gittilland, M.S.

EXECUTIVE SUMMARY

METHYL t-BUTYL ETHER – Oral Risk Assessment CAS # 1634-04-4			
PARAMETER	LEVEL	UNITS	DERIVED
$BMDL_{10}$ (10% Benchmark Dose Level)	32	mg/kg-day	From a chronic gavage study in rats
10^{-5} Cancer Risk Level	0.003	mg/kg-day	From a chronic gavage study in rats
Oral RfD (oral reference dose)	Not determined	mg/kg-day	Not applicable
TAC (total allowable concentration)	0.1	mg/L	For an adult drinking 2L water/day
SPAC (single product allowable concentration)	0.01	mg/L	For an adult drinking 2L water/day
STEL (short term exposure level)	Not Determined	mg/L	Not applicable
KEY STUDY	Belpoggi, F., M. Soffritti, and C. Maltoni. 1995. Methyl-tertiary-butyl ether (MTBE) - a gasoline additive - causes testicular and lympho-haematopoietic cancers in rats. Toxicol. Ind. Health. 11(2):119-149.		
CRITICAL EFFECT(S)	Leydig (testicular interstitial) cell tumors in male rats and hemolymphoreticular leukemias/lymphomas (combined) in female rats		
UNCERTAINTY FACTORS	There were no uncertainty factors applied, since a cancer risk assessment assuming a linear mode of action was performed.		
TOXICITY SUMMARY	Increased liver weights, aspartate aminotransferase, blood urea nitrogen, cholesterol, and centrilobular hypertrophy were observed in rats administered methyl t-butyl ether via gavage for 28 days or more. Short-term and subchronic gavage exposures were associated with increased mean absolute and relative kidney weights in male rats and hyaline droplet formation in the renal proximal tubules. The increases in liver weight, liver-related clinical measurements, and centrilobular hypertrophy were likely due to an adaptive mechanism by the liver to metabolize methyl t-butyl ether, based on CYP450 induction data and the lack of reported non-neoplastic effects after chronic gavage exposures. However, the chronic non-neoplastic data were not available for review. Chronic gavage exposure was associated with an increase in Leydig cell tumors in male rats and leukemias/lymphomas (combined) in female rats. No standardized two-generation reproduction or developmental studies via the oral route were identified. Attempts to characterize the mode of action for the Leydig cell tumors in non-standardized reproduction studies revealed that single gavage doses at approximately 500 mg/kg-day resulted in reduced circulating testosterone immediately following dosing. At gavage doses of 1,200 mg/kg-day for 14 days, decreased circulating testosterone and luteinizing hormone, increased estradiol, and decreased testicular microsomal aromatase activity were observed in male rats. *In vivo* metabolism data indicate that oral exposure to methyl t-butyl ether for up to 28 days induces various CYP450 isozymes. Methyl t-butyl ether is oxidatively demethylated to t-butanol. In rodents, the biotransformation of t-butanol has been shown to yield 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid. No evidence of hepatic peroxisome proliferation was observed. All investigations on nephrotoxicity were consistent with α-2μ-globulin nephropathy, which was not considered relevant to humans. The weight of genotoxicity evidence suggests that methyl t-butyl ether has some genotoxic potential and there were insufficient data to support a non-genotoxic mode of action. Thus, a 10^{-5} cancer risk level for methyl t-butyl ether was extrapolated from the chronic gavage $BMDL_{10}$ which was essentially the same, whether based on the Leydig cell tumors in male rats (32 mg/kg-day) or on lymphatic tumors in female rats (36 mg/kg-day).		
CONCLUSIONS	There are no chronic data in humans, but there is "*suggestive evidence of carcinogenic potential*" after gavage exposure to methyl t-butyl ether in rats. The drinking water action levels developed in this risk assessment are protective of public health, since they were calculated based on the tumor incidences observed in a chronic gavage study. Although the study was flawed, it was considered adequate for the purposes of risk assessment and more appropriate than using a chronic inhalation study with inhalation to oral route extrapolation to estimate a lifetime cancer risk from oral exposure to methyl t-butyl ether.		

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated contaminant **methyl t-butyl ether** in drinking water as an extractant from one or more drinking water system components evaluated under NSF/ANSI 61 (2007) or as a contaminant in a drinking water treatment chemical evaluated under NSF/ANSI 60 (2007). Both non-cancer and cancer endpoints have been considered, and risk assessment methodology developed by the U.S. Environmental Protection Agency (U.S. EPA) has been used.

Non-cancer endpoints are evaluated using the reference dose (RfD) approach (Barnes and Dourson, 1988; Dourson, 1994; U.S. EPA, 1993; U.S. EPA, 2002), which assumes that the threshold for these endpoints will not be exceeded if appropriate uncertainty factors (Dourson et al., 1996; U.S. EPA, 2002) are applied to the highest dose showing no significant effects. This highest dose is derived from human exposure data when available, but more often is derived from studies in laboratory animals. Either the no-observed-adverse-effect level (NOAEL) taken directly from the dose-response data or the calculated lower 95% confidence limit on the dose resulting in an estimated 10% increase in response (the LED_{10} or $BMDL_{10}$ from benchmark dose programs) can be used (U.S. EPA, 2007a). The lowest-observed-adverse-effect level (LOAEL) can also be used, with an additional uncertainty factor, although the benchmark dose approach is preferred in this case. The RfD is expressed in mg/kg-day. It is defined by the U.S. EPA as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (Barnes and Dourson, 1988; U.S. EPA, 1993; U.S. EPA, 2005a).

NSF uses the RfD to derive three product evaluation criteria for non-cancer endpoints. The total allowable concentration (TAC), generally used to evaluate the results of extraction testing normalized to static at-the-tap conditions, is defined as the RfD multiplied by the 70 kg weight of an average adult assumed to drink two liters of water per day. A relative source contribution (RSC), to ensure that the RfD is not exceeded when food and other non-water sources of exposure to the chemical are considered, is also applied in calculating the TAC. The relative source contribution should be data derived, if possible. Alternately, a 20% default contribution for water can be used (U.S. EPA, 1991a). The TAC calculation is then as follows:

$$\text{TAC (mg/L)} = \frac{[\text{RfD (mg/kg-day)} \times 70\text{ kg}] - [\text{total contribution of other sources (mg/day)}]}{2\text{ L/day}}$$

or

$$\text{TAC (mg/L)} = \frac{\text{RfD (mg/kg-day)} \times 70\text{ kg}}{2\text{ L/day}} \times 0.2\text{ (RSC)}$$

The single product allowable concentration (SPAC), used for water treatment chemicals and for water contact materials normalized to flowing at-the-tap conditions, is the TAC divided by the estimated total number of sources of the substance in the drinking water treatment and

distribution system. In the absence of source data, a default multiple source factor of 10 is used. The multiple source factor accounts for the possibility that more than one product in the water and/or its distribution system could contribute the contaminant in question.

Finally, a short-term-exposure level (STEL), at a higher level than the TAC, may be calculated for contaminants such as solvents expected to extract at higher levels from new product, but also expected to decay rapidly over time. The STEL is calculated from the NOAEL or the LED_{10} of an animal study of 14- to 90-days duration, with uncertainty factors appropriate to the duration of the study. The contaminant level must decay to a level at or below the TAC under static conditions, or to a level at or below the SPAC under flowing conditions within 90 days, based on the contaminant decay curve generated from over-time laboratory extraction data.

Endpoints related to cancer are evaluated using modeling to fit a curve to the appropriate dose-response data (U.S. EPA, 1996a, U.S. EPA, 1999; U.S. EPA, 2003b). If there is sufficient evidence to use a non-linear model, the LED_{10} or $BMDL_{10}$, divided by the anticipated exposure, is calculated to give a margin of exposure. If there is insufficient evidence to document non-linearity, a linear model drawing a straight line from the LED_{10} or $BMDL_{10}$ to zero is used as a default. If a linear model (generally reflecting a genotoxic carcinogen) is used, a target risk range of 10^{-6} to 10^{-4} is considered by the U.S. EPA to be safe and protective of public health (U.S. EPA, 1991a). For the purposes of NSF/ANSI 60 (2005) and 61 (2007), the TAC is set at the 10^{-5} risk level, and the SPAC is set at the 10^{-6} risk level. Use of a higher risk level is not ruled out, but would generally require documentation of a benefit to counteract the additional risk.

The RfD, TAC, SPAC, and STEL values derived in this document are based on available health effects data and are intended for use in determining compliance of products with the requirements of NSF/ANSI 60 (2005) and 61 (2007). Application of these values to other exposure scenarios should be done with care and with a full understanding of the values derivation and the comparative magnitude and duration of the exposures. These values do not have the rigor of regulatory values, as data gaps are generally filled by industry or government studies prior to regulation. Data gaps introduce uncertainty into an evaluation and require the use of additional uncertainty factors to protect public health.

The general guidelines for this risk assessment include those from the National Research Council (NRC, 1983) and from the Presidential/Congressional Commission on Risk Assessment and Risk Management (1997a; 1997b). Other guidelines used in the development of this assessment may include the following: Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), draft revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), draft final Guidelines For Carcinogen Risk Assessment (U.S. EPA, 2003b), Guidelines for Carcinogen Risk Assessment (2005b), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991b), Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996b), Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1998), A Review of the Reference Dose and Reference Concentration Process (U.S. EPA, 2002), Recommendations for and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988), and Health Effects Testing Guidelines (U.S. EPA, 2007b).

The literature search strategy employed for this compound was based on the Chemical Abstract Service Registry Number (CASRN) and at least one common name. As a minimum, the following data banks were searched:

- ChemID Plus
- Registry of Toxic Effects of Chemical Substances (RTECS)
- Hazardous Substances Data Bank (HSDB)
- GENE-TOX
- Environmental Mutagen Information Center (EMIC)
- Developmental and Reproductive Toxicology (DART)
- TOXLINE – Core and Special
- TRI (Toxics Release Inventory)
- Chemical Carcinogenesis Research Information System (CCRIS)
- Medline (via PubMed)
- Integrated Risk Information System (IRIS)
- Syracuse Research Corporation Online Toxic Substance Control Act Database (TSCATS)
- Current Contents (as requested)

The literature search for this chemical was conducted on September 29, 2003 and updated on January 23, 2008. This document includes all relevant information retrieved as a result of those searches.

2.0 PHYSICAL AND CHEMICAL PROPERTIES

Methyl t-butyl ether is an aliphatic dialkyl ether with synonyms of 2-methoxy-2-methylpropane; 2-methyl-2-methoxypropane; ether, tert-butyl methyl; MTBE; methyl 1,1-dimethylethyl ether; methyl tert-butyl ether; methyl tertiary-butyl ether; propane, 2-methoxy-2-methyl-; t-butyl methyl ether; tert-butyl methyl ether (ChemIDPlus, 2003). It has trade names of 3 D Concord, Driveron, HSDB 5487, and UN 2398 (IPCS, 1998). It has the following structure, and physical and chemical properties listed in Table 1:

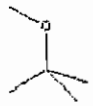


Table 1. The physical and chemical properties of methyl t-butyl ether

Property	Data	Reference
Empirical Formula	$C_5H_{12}O$	OEHHA, 1999
CAS#	1634-04-4	OEHHA, 1999
Molecular Weight	88.15	OEHHA, 1999
Physical State and Color	colorless liquid at room temperature	IPCS, 1998
Melting Point	-109°C	OEHHA, 1999
Boiling Point	55.2°C	IPCS, 1998
Density	0.7404 at 20°C	IPCS, 1998
Vapor Pressure	33,500 Pa at 25°C	IPCS, 1998
Water Solubility	51 g/L at 25°C	OEHHA, 1999
Dissociation Constant (pK_a)	Not reported	
n-Octanol/Water Partition Coefficient (log K_{ow})	0.94-1.3[a] 1.43 (estimated)[b]	[a] IPCS, 1998 [b] http://esc.syrres.com
Henry's Law Constant (air/water partition)	5.87×10^{-4} atm-m^3/mole at 25°C	OEHHA, 1999

2.1 Organoleptic Properties

Methyl t-butyl ether has a terpene-like odor (IPCS, 1998). Individual variability in sensitivity to taste and odor make it difficult to identify odor and taste thresholds for methyl t-butyl ether in water (ECB, 2002). IPCS (1998) has reported that the taste threshold for methyl t-butyl ether in water is 134 ppb. OEHHA (1999) has cited various sources that report odor thresholds for methyl t-butyl ether in water of between 2.5 to 680 ppb. The U.S. EPA (1997) recommended a drinking water level of 20-40 ppb for methyl t-butyl ether, based on averting taste and odor. More recent data by Suffet et al. (2007) suggests that the odor threshold for methyl t-butyl ether in water is ≥ 15 ppb.

3.0 PRODUCTION AND USE

3.1 Production

Industrially, methyl t-butyl ether is derived from the catalytic reaction of methanol and isobutylene over an acidic ion-exchange resin catalyst such as sulfonated styrene cross-linked with divinyl benzene in the liquid phase at 38-93°C and 100-200 psi (IPCS, 1998). It can also be prepared from methanol, t-butanol, and diazomethane.

Methyl t-butyl ether is among the 50 highest production volume chemicals (IPCS, 1998). In 1999, total worldwide annual production of methyl t-butyl ether was about 21 million tons or 46.3 billion pounds (ECB, 2002). Methyl t-butyl ether is a high production volume chemical in the United States (U.S. EPA, 2007c) and European Union (2004).

3.2 Use

It is anticipated that the use of methyl t-butyl ether will continue to increase (IPCS, 1998). North America is the largest consumer of methyl t-butyl ether, accounting for about two-thirds of the

world's annual use (IPCS, 1998). In 1996, the US was the world's largest consumer of methyl t-butyl ether with a usage of 10.6 million tons (12.2 billion pounds) per year.

The major use of methyl t-butyl ether is as an oxygenated additive in gasoline, in which it is blended at 2 to 11.5% by volume (ECB, 2002). IPCS (1998) reports that methyl t-butyl ether has been added to gasoline in concentrations up to 17% by volume. Only a minor amount is used for other purposes, such as solvent instead of diethyl ether or diisopropyl ether in both the chemical and pharmaceutical industry and laboratories (ECB, 2002). Approximately 25% of gasoline in the USA is blended with methyl t-butyl ether (IPCS, 1998). Methyl t-butyl ether is almost exclusively used to provide both octane enhancement and an increase in the oxygen content of gasoline. No approved uses for methyl t-butyl ether as a direct or indirect food additive were identified under Title 21 of the U.S. Code of Federal Regulations (U.S. FDA, 2007).

4.0 ANALYTICAL METHODS

4.1 Analysis in Water

Sorption/desorption, including purge and trap systems, and headspace procedures have been used to prepare water for analysis of methyl t-butyl ether (IPCS, 1998). The analytical methods for methyl t-butyl ether in water have been reviewed by IPCS (1998). These methods include the static headspace procedure using gas chromatography with photoionization detection (GC-PID) with a detection limit of 10.8 $\mu g/m^3$ and the purge and trap procedure using gas chromatography-mass spectrometry with detection limits ranging from 0.06 to 5 µg/L. NSF International uses U.S. EPA (1995) method 502.2 employing gas chromatography for volatile compounds to detect methyl t-butyl ether as an extractant from drinking water system components tested to NSF/ANSI Standard 61 (2007). The reporting limit is 0.5 µg/L.

4.2 Analysis in Biological Matrices

Methyl t-butyl ether is analyzed in biological matrices generally by gas chromatography, using a range of capillary columns and detector systems suited to the specific matrix (IPCS, 1998).

5.0 SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

5.1 Sources of Human Exposure

Methyl t-butyl ether does not occur naturally in the environment (IPCS, 1998). Groundwater may become contaminated with methyl t-butyl ether through leaking underground storage tanks or spillage from overfilling of the storage tanks (ECB, 2002). In the USA, methyl t-butyl ether has been detected in storm water, surface water, including streams, rivers, and reservoirs, groundwater, and drinking water (IPCS, 1998). Methyl t-butyl ether is infrequently detected in public drinking-water systems from groundwater. In all but three out of 51 systems in which it was reported, the concentration was ≤20 µg/L. There are inadequate data to characterize the concentration of methyl t-butyl ether in public drinking-water systems from surface water. Methyl t-butyl ether has been found at high levels (i.e. ≥1,000 µg/L) in a few private wells used for drinking water (IPCS, 1998). Methyl t-butyl ether has been detected as an extractant from

drinking water system components tested to NSF/ANSI 61 (2007) at normalized concentrations up to 0.2 mg/L.

Workers with potential exposure to methyl t-butyl ether include those involved in the production, distribution, and use of methyl t-butyl ether and methyl t-butyl ether-containing gasoline, including service station attendants and mechanics (IPCS, 1998). The sources of industrial occupational exposure to methyl t-butyl ether have been reviewed by ECB (2002) and include individuals involved in the production, formulation, transportation, or distribution of methyl t-butyl ether. These exposures include personnel employed at service stations, those involved in maintenance operations and automotive repairs, and individuals in the chemical or pharmaceutical industries in which methyl t-butyl ether is used as a solvent. Exposure of the public to methyl t-butyl ether can be principally by inhalation of fumes while refueling motor vehicles and drinking contaminated water (McGregor, 2006). Maximum internal doses resulting from such exposures are unlikely to exceed 0.05 mg/kg-day and will normally be very much lower.

5.2 Sources of Environmental Exposure

Methyl t-butyl ether may enter the environment during all phases of the petroleum fuel cycle (IPCS, 1998). Sources include auto emissions, evaporative losses from gasoline stations and vehicles, storage tank releases, pipeline leaks, other accidental spills, and refinery stack releases. Annual estimates of methyl t-butyl ether mass releases to the environment from all potential sources have not been reported in the scientific literature. However, releases from storage tanks, vehicular emissions, and evaporative losses from gasoline stations and vehicles are perceived to be important sources.

Concentrations of methyl t-butyl ether detected in storm water ranged from 0.2 to 8.7 µg/L with a median of less than 1.0 µg/L. For streams, rivers, and reservoirs, the range of detection was from 0.2 to 30 µg/L, and the range of medians for several studies was 0.24 to 7.75 µg/L. Methyl t-butyl ether has generally not been detected in deeper groundwater or in shallow groundwater in agricultural areas. When detected, the concentration is less than 2.0 µg/L. Methyl t-butyl ether is more frequently found in shallow groundwater (top 5-10 feet of these aquifers) in urban areas. In this setting, the concentrations range from less than 0.2 µg/L to 23 mg/L, with a median value below 0.2 µg/L (IPCS, 1998).

6.0 COMPARATIVE KINETICS AND METABOLISM IN HUMANS AND LABORATORY ANIMALS

Numerous studies investigating the kinetics and metabolism of methyl t-butyl ether in humans and laboratory animals are available. These data have been reviewed by several regulatory organizations, including European Chemicals Bureau (ECB, 2002), Office of Environmental Health Hazard Assessment of the California EPA (OEHHA, 1999), the International Programme on Chemical Safety of the World Health Organization (IPCS, 1998), the European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC, 1997), the Agency for Toxic Substances and Disease Registry (ATSDR, 1996), and Health Canada (1992). Several review articles on these data are also available in the scientific literature.

Methyl t-butyl ether was absorbed into the blood of human volunteers who rapidly drank 2.8 mg methyl t-butyl ether in 250 mL Gatorade (Prah et al., 2004). Mean blood levels of methyl t-butyl ether peaked at 0.17 µmol/L between 15 and 30 minutes following administration and declined to at or below the detection limit (0.05 µmol/L) at the 24-hour sampling period. In human volunteers who rapidly drank 6.7 µl methyl t-butyl ether in "about 5 mg" of lemon-lime solution, peak blood levels of methyl t-butyl ether ranged from 5 to 15 ng/ml (0.06-0.17 µmol/l) (ECB, 2002).

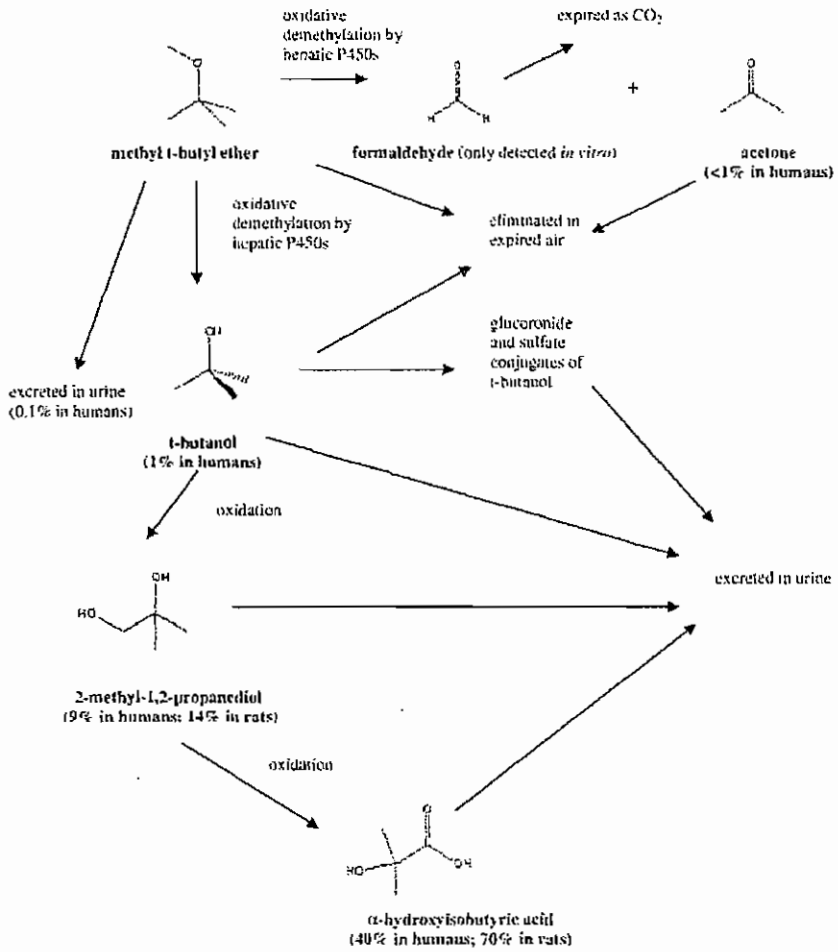
In rodents, methyl t-butyl ether is well absorbed and distributed following oral administration (IPCS, 1998). Rapid and complete absorption across the gastrointestinal tract was observed in rats administered methyl t-butyl ether via gavage at 40 mg/kg (ECB, 2002). At 400 mg/kg oral exposure in rats, the percentage of total absorbed dose eliminated in expired air increased with a corresponding decrease in the percentage eliminated in urine, indicating a saturation of metabolism (IPCS, 1998).

In vivo studies on the metabolism of methyl t-butyl ether in humans and rats indicate qualitatively similar overall metabolism (ECB, 2002). Methyl t-butyl ether is oxidatively demethylated by microsomal enzymes to t-butanol and formaldehyde, but the latter has only been shown *in vitro*. In rodents, the biotransformation of t-butanol has been shown to yield 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid (Figure 1).

The cytochrome P450-mediated biotransformation of methyl t-butyl ether has been explored in several *in vitro* studies with liver microsomes from humans, rats, and mice (ECB, 2002). Metabolism of methyl t-butyl ether by rat liver microsomes produced equivalent amounts of formaldehyde and t-butanol, and data strongly suggest that when expressed, CYP2B1 is the major enzyme involved in methyl t-butyl ether demethylation and that CYP2E1 may have a minor role.

Since these kinetic and metabolism data for methyl t-butyl ether in humans and laboratory animals have been reviewed previously, the current review focuses on only the new oral data since these reviews. Recent data confirm that methyl t-butyl ether is rapidly absorbed following oral administration. Approximately 30% of administered dose in humans was cleared by exhalation as unchanged methyl t-butyl ether and as t-butanol within 10-20 min. Less than 0.1% of the administered dose was recovered in expired air as acetone. Approximately 50% of the administered dose in humans was eliminated in the urine as unchanged methyl t-butyl ether (~0.1%), t-butanol (~1%), 2-methyl-1,2-propanediol (~9%), and 2-hydroxyisobutyrate (~40%).

Figure 1. Proposed metabolic scheme of methyl t-butyl ether



6.1 Absorption

Previous data in humans or laboratory animals demonstrate that methyl t-butyl ether is rapidly absorbed following oral administration. Recent data by Prah et al. (2004), Amberg et al. (2001), and Dekant et al. (2001) confirm this observation. Methyl t-butyl ether was rapidly absorbed

from the gastrointestinal tract and a significant part of the administered dose was transferred into blood of human volunteers ingesting methyl t-butyl ether in water or Gatorade. No other recent data regarding the absorption of methyl t-butyl ether following oral exposure in humans or laboratory animals were identified.

6.2 Distribution

Recent data regarding the distribution of methyl t-butyl ether after oral exposure were limited to the measurement of methyl t-butyl ether and one of its metabolites, t-butanol, in blood after oral ingestion in human volunteers.

Fourteen healthy male volunteers ingested 2.8 mg methyl t-butyl ether (unspecified purity) in 250 mL Gatorade (Prah et al., 2004). Gatorade was used as the vehicle to mask the unpleasant taste of methyl t-butyl ether. Blood samples were collected after 0, 5, 15, 30, 45, 60, 75, 90, 105, 120, 180, 240, 360, and 1,440 minutes. Mean levels of methyl t-butyl ether and t-butanol in the blood were determined using gas chromatography/mass spectrometry. The plasma half-life of methyl t-butyl ether was determined. The area under the plasma concentration versus time curve was estimated for methyl t-butyl ether alone and for methyl t-butyl ether plus t-butanol.

Mean blood levels of methyl t-butyl ether peaked at 0.17 µmol/L between 15 and 30 minutes following administration and declined to at or below the detection limit (0.05 µmol/L) at the 24-hour sampling period. Blood levels of t-butanol peaked at 0.23 µmol/L at the 45-minute sampling period and did not return to pre-exposure levels by the 24-hour sampling period. Elimination of methyl t-butyl ether from the blood was best characterized by a three-compartment model. The mean half-life for methyl t-butyl ether elimination from the blood in the first, second, and third phases was 14.9, 102.0, and 417.3 minutes, respectively. The mean area under the plasma concentration versus time curve was estimated to be 1,682 µmol/hr/L for methyl t-butyl ether alone, 20,025 µmol/hr/L for t-butanol, and 10,854 µmol/hr/L for methyl t-butyl ether and t-butanol combined. The mean area under the curve ratio of t-butanol to methyl t-butyl ether was 13.1 in the blood. Since this study also included the dermal and inhalation routes of exposure, the study authors suggested that these pharmacokinetic estimates were useful in constructing a physiologically-based pharmacokinetic model for methyl t-butyl ether in humans across different routes of administration.

Three human volunteers per sex and dose ingested 0, 5, or 15 mg ^{13}C-methyl t-butyl ether in 100 mL water (Amberg et al., 2001; Dekant et al., 2001). Blood samples were collected at 60-minute intervals for the first four hours and at 120-minute intervals thereafter until 12 hours. A final blood sample was collected 24 hours after administration.

At 5 mg, the maximum concentration in the blood averaged 0.10 µM, and these concentrations were obtained with the first blood samples, which were taken after one hour. Elimination of methyl t-butyl ether from the blood occurred in three phases, and the mean half-life of each phase was 0.8, 1.8, and 8.1 hours. Mean blood concentrations of t-butanol were 1.82 uM. The mean terminal half-life of t-butanol clearance from the blood was 8.1 hours. Levels of methyl t-butyl ether and t-butanol in blood declined to at or near the limit of detection at the 12- and 24-hour sampling times, respectively.

At 15 mg, the maximum concentration in the blood, which was reached after one hour, averaged 0.69 μM. Elimination of methyl t-butyl ether from the blood occurred in three phases, and the mean half-life of each phase was 0.7, 1.2, and 3.7 hours. Mean blood concentrations of t-butanol were 0.45 uM. The mean terminal half-life of t-butanol clearance from the blood was 8.5 hours.

6.3 Metabolism

6.3.1 Humans

The metabolism of methyl t-butyl ether was studied in three human volunteers per sex and dose after ingestion of 0, 5, or 15 mg ^{13}C-methyl t-butyl ether in 100 mL water (Amberg et al., 2001; Dekant et al., 2001). Mass spectrometry was used to identify urinary metabolites in urine samples collected at 6-hour intervals for 96 hours. At 5 and 15 mg, 46% and 49%, respectively, of the administered dose was eliminated in the urine as unchanged methyl t-butyl ether, t-butanol, 2-methyl-1,2-propanediol, and 2-hydroxyisobutyrate. At 5 mg, unchanged methyl t-butyl ether, t-butanol, 2-methyl-1,2-propanediol, and 2-hydroxyisobutyrate comprised 0.01, 1, 9, and 36% of the administered dose, respectively. At 15 mg, unchanged methyl t-butyl ether, t-butanol, 2-methyl-1,2-propanediol, and 2-hydroxyisobutyrate comprised 0.1, 1, 8, and 40% of the administered dose, respectively. Hepatic first-pass metabolism was not observed. The authors concluded that the metabolic pathway for methyl t-butyl ether after oral exposure was identical to concurrently conducted inhalation exposure studies.

The metabolism of methyl t-butyl ether was studied in a panel of 12 human liver microsomes isolated from nine male and two female donors (Le Gal et al., 2001). The human liver microsomes metabolized methyl t-butyl ether into t-butanol and formaldehyde. The mean Michaelis-Menten constant (Km), which describes the catalytic power of an enzyme or rate of a reaction catalyzed by an enzyme, was determined. The mean apparent Km(1) was determined to be 0.25 mM, which was considered low by the study authors, and the mean apparent Km(2) was 2.9 mM, which was considered high. The study authors concluded that kinetic data, along with the results from correlation studies and chemical inhibition studies, support the assertion that the major enzyme involved in methyl t-butyl ether metabolism is CYP2A6, with a minor contribution of CYP3A4 at low substrate concentration.

6.3.2 Laboratory Animals

Williams and Borghoff (2000) investigated the hypothesis that methyl t-butyl ether-induced decrease in serum testosterone levels in male rats may be due in part to the ability of methyl t-butyl ether to induce the metabolism of endogenous testosterone and, hence, enhance its clearance. Fifteen male Sprague-Dawley rats per dose were administered 0 or 1,500 mg/kg-day methyl t-butyl ether (> 99.9% purity in corn oil) via gavage for 15 days. In a second experiment, fifteen male Sprague-Dawley rats per dose were administered 0, 250, 500, 1,000, or 1,500 mg/kg-day methyl t-butyl ether (> 99.9% purity in corn oil) via gavage for 28 days. At study termination, the rats were sacrificed, body and liver weights were determined, and hepatic microsomes were isolated for measurement of CYP450 activity. Testosterone hydroxylase activities of hepatic microsomes, which were used as markers for CYP450 enzyme activities, were also assessed. These enzymes included 2-α-, 2-β-, 6-β-, 7-α-, 16-α-, and 17-β-

hydroxytestosterone. The activities of p-nitrophenol and UDP-glucuronosyltransferase were also assessed to evaluate the mechanism of centrilobular hypertrophy observed in rodents after repeated methyl t-butyl ether exposures. The formation of formaldehyde, a metabolite of methyl t-butyl ether, was also measured.

After 15 days, total hepatic microsomal cytochrome CYP450 was increased 1.3-fold in rats treated with 1,500 mg/kg-day methyl t-butyl ether. CYP1A1/2, CYP2A1, CYP2E1, and CYP2B1/2 activities were increased 1.5-, 2.4-, 2.3-, and 6.5-fold, respectively, at 1,500 mg/kg-day after 15 days. 7-α-hydroxytestosterone was statistically increased by 2.4-fold compared to controls.

After 28 days, total hepatic microsomal cytochrome CYP450 was not statistically different compared to control. At 1,000 mg/kg-day after 28 days, a statistical increase in mean relative liver weight (10-14%, not further specified) and a 2.0-fold increase in CYP2B1/2 were observed compared to controls.

After 28 days at 1,500 mg/kg-day, a statistical increase in mean relative liver weight (10-14%, not further specified) was observed. CYP 2B1/2, CYP2E1, CYP3A1/2, and UDP-glucuronosyltransferase activities were statistically increased by 2.9-, 2.0-, 2.1-, and 1.7-fold respectively, compared to controls. 6-β-hydroxytestosterone was statistically increased by 2.1-fold compared to controls. UDP-glucuronosyltransferase was statistically increased compared to controls. Formaldehyde production was statistically increased compared to controls at 1,500 mg/kg-day after 28 days. Methyl t-butyl ether also induced its own metabolism 2.1-fold at 1,500 mg/kg-day after 28 days, and the authors noted that this effect was consistent with the induction of CYP2E1 and CYP2B1. It should be noted that mean body weight was reduced by 12% compared to controls at 1,500 mg/kg-day after 28 days.

The study authors concluded that methyl t-butyl ether induced mild increases in testosterone hydroxylase enzymes. Further, the increase in UDP-glucuronosyltransferase was consistent with the centrilobular hypertrophy observed in rodents after repeated methyl t-butyl ether exposures. The decrease in serum testosterone observed following methyl t-butyl ether administration may be the result of enhanced testosterone metabolism and subsequent clearance. However, the authors stated that the most pronounced effects were observed at the high dose of 1,500 mg/kg-day, at which clinical signs of toxicity and reduced body weight (12%) were also observed. The authors further noted that since the increases in testosterone hydroxylase enzyme activities were generally mild, the hypothalamus-pituitary hormonal feedback loop could be expected to compensate for mild reductions in circulating testosterone *in vivo*.

Eight female $B6C3F_1$ mice per dose were given methyl t-butyl ether (> 99.95% purity in corn oil) by gavage at 0 or 1,800 mg/kg-day for three days (Moser et al., 1996). Food and water were available *ad libitum*. Eighteen hours after the last dose, the mice were sacrificed and hepatocyte cytochromes were isolated. Methyl t-butyl ether induced a statistical increase (37%) in total hepatic cytochrome P450 content, a 9-fold increase in hepatic 7-pentoxy-resorufin-*O*-dealkylase activity (a CYP2B marker) and a 2-fold increase in hepatic 7-ethoxy-resorufin-*O*-deethylase activity compared to controls.

6.4 Elimination/Excretion

The elimination of methyl t-butyl ether and t-butanol in expired air was investigated in seven healthy male volunteers who ingested 2.8 mg methyl t-butyl ether (unspecified purity) in 250 mL Gatorade (Prah et al., 2004). Gatorade was used as the vehicle to mask the unpleasant taste of methyl t-butyl ether. Exhaled air samples were collected after 0, 5, 15, 30, 45, 60, 75, 90, 105, 120, 180, 240, 360, and 1,440 minutes. Mean levels of methyl t-butyl ether and t-butanol in exhaled air were determined using gas chromatography/mass spectrometry.

Elimination of methyl t-butyl ether from expired air was best characterized by a three-compartment model. The mean half-life for methyl t-butyl ether in expired air in the first, second, and third phases was 13.0, 63.1, and 254.0 minutes, respectively. The mean area under the curve ratio of t-butanol to methyl t-butyl ether was 0.175 in exhaled air. Since this study also included the dermal and inhalation routes of exposure, the study authors suggested that these pharmacokinetic estimates were useful in constructing a physiologically-based pharmacokinetic model for methyl t-butyl ether in humans across different routes of administration.

The urinary elimination of methyl t-butyl ether was examined in three healthy human volunteers per sex administered 5 and 15 mg ^{13}C-methyl t-butyl ether (> 98% purity) in spiked tap water samples (Amberg et al., 2001). The different doses were administered four weeks apart. Urine samples were collected for 96 hours after administration in six hour intervals, and blood samples were taken in 60-minute intervals up to four hours, then at 120-minute intervals up to 12 hours, and ultimately at 24 hours. Methyl t-butyl ether and t-butanol concentrations in blood were determined. Urine metabolites, including the parent compound, t-butanol, 2-methyl-1,2-propanediol, and 2-hydroxyisobutyrate were quantified.

At 5 and 15 mg/kg, 46% and 49%, respectively, of the administered dose was eliminated in the urine as unchanged methyl t-butyl ether, t-butanol, 2-methyl-1,2-propanediol, and 2-hydroxyisobutyrate. The authors concluded that the kinetics of excretion after oral exposure were identical to concurrently conducted inhalation exposure studies.

In the same experiment, the respiratory elimination of methyl t-butyl ether was examined in three healthy male volunteers administered 15 mg ^{13}C-methyl t-butyl ether (> 98% purity) in 100 mL tap water samples (Amberg et al., 2001). Approximately 30% of the methyl t-butyl ether dose was cleared by exhalation as unchanged methyl t-butyl ether and as t-butanol. Methyl t-butyl ether exhalation was rapid and maximum concentrations of 100 nM in exhaled air were achieved within 10-20 min. Less than 0.1% of the administered dose was recovered in expired air as ^{13}C-acetone. The study authors concluded that the results indicate that the biotransformation and excretion of methyl t-butyl ether after oral exposure is similar to inhalation exposure and suggested the absence of a significant first-pass metabolism of methyl t-butyl ether in the liver after oral administration.

6.5 Physiologically-based pharmacokinetic models

Although several physiologically-based pharmacokinetic models have been constructed to model the behavior of inhaled methyl t-butyl ether, models describing the behavior of methyl t-butyl

ether after oral exposure are limited and usually include multiple exposure routes. Kim et al. (2007) developed a multiple-route (oral, inhalation and dermal) nine-compartment model of methyl t-butyl ether and t-butanol in humans based on blood measurements of these compounds. Borghoff et al. (1996) developed a multiple-route (oral, inhalation and intravenous) seven-compartment model of methyl t-butyl ether and t-butanol in F344 rats.

7.0 EFFECTS ON HUMANS

7.1 Case Reports

No recent case reports regarding oral exposure to methyl t-butyl ether were identified.

7.2 Epidemiological Studies

Epidemiological studies of human populations exposed under occupational as well as non-occupational conditions, and experimental studies of human volunteers exposed under controlled conditions, have not been able to identify a basis for headache, eye and nose irritation, cough, nausea, dizziness, and disorientation reported by consumers in some areas as a result of fueling with gasoline (IPCS, 1998). Although results are mixed, IPCS (1998) suggested that community studies conducted in Alaska, New Jersey, Connecticut, and Wisconsin provided limited or no evidence of an association between methyl t-butyl ether exposure and the prevalence of health complaints.

In controlled experimental studies on adult volunteers exposed in inhalation chambers to methyl t-butyl ether at concentrations ranging from 5.0 mg/m^3 (1.4 ppm) to 270 mg/m^3 (75 ppm), there were no evident effects on either subjective reports of symptoms or objective indicators of irritation or other effects up to 180 mg/m^3 (50 ppm) for up to two hours (IPCS, 1998). Thus, it appears unlikely that methyl t-butyl ether alone induces adverse acute health effects in the general population after inhalation exposure. However, the potential effects of mixtures of gasoline and methyl t-butyl ether, and the manner in which most persons are exposed to methyl t-butyl ether in conjunction with the use of oxygenated fuels, have not been examined experimentally or through prospective epidemiological methods.

8.0 EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Numerous regulatory organizations, including European Chemicals Bureau (ECB, 2002), Office of Environmental Health Hazard Assessment of the California EPA (OEHHA, 1999), the International Programme on Chemical Safety of the World Health Organization (IPCS, 1998), the European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC, 1997), the Agency for Toxic Substances and Disease Registry (ATSDR, 1996), and Health Canada (1992) have critically reviewed the studies in laboratory animals for methyl t-butyl ether. This section includes only the oral studies for methyl t-butyl ether, due to their significance in the development of lifetime drinking water levels for methyl t-butyl ether, since studies by the inhalation and/or dermal routes have been critically reviewed elsewhere.

No evidence of hepatic peroxisome proliferation was observed in male rats administered methyl t-butyl ether via gavage at 800 mg/kg-day for 14 days, but increased mean relative liver weight and minimal-to-moderate centrilobular hypertrophy were observed in male rats administered methyl t-butyl ether via gavage at 1,000 mg/kg-day and above for 28 days. In male and female rats administered high doses of methyl t-butyl ether (1,250 mg/kg-day) via gavage for 28 days, statistically increased cholesterol levels of at least 20% compared to controls were observed.

Short-term and subchronic gavage exposures to methyl t-butyl ether were associated with increased mean absolute and relative kidney weights in male rats accompanied by hyaline droplet formation in the renal proximal tubules. In rats administered methyl t-butyl ether at 100 mg/kg-day and above via gavage for 13 weeks, statistically increased mean blood urea nitrogen levels of at least 15% compared to controls were observed. Chronic gavage exposure to methyl t-butyl ether was associated with an increase in Leydig cell tumors in male rats and leukemias/lymphomas (combined) in female rats.

8.1 Limited-Exposure Effects

Methyl t-butyl ether was found to be irritating to the eyes and skin of rabbits, but did not induce skin sensitization in guinea pigs.

8.1.1 Irritation and Sensitization Studies

Following the application of 0.5 mL of neat methyl t-butyl ether to the intact and abraded skin of six rabbits for 24 hours, a primary irritation index of 3.36 was reported, which was considered "moderately" irritating to skin (IPCS, 1998). Moderate erythema and edema were observed. Effects were slightly more pronounced on abraded skin. In mice, methyl t-butyl ether can induce slight to severe respiratory irritation following inhalation of 300 to 30,000 mg/m^3, respectively. A 1% induction and challenge concentration of methyl t-butyl ether did not induce skin sensitization in twenty guinea pigs (IPCS, 1998).

8.1.2 Ocular Exposure Studies

Methyl t-butyl ether was irritating to the eyes of rabbits and caused mild, but reversible, changes (IPCS, 1998).

8.2 Single-Exposure Studies

The oral (gavage) LD_{50} for methyl t-butyl ether is approximately 3,800 mg/kg in rats (IPCS, 1998) and 4,000 in mice (OEHHA, 1999). Signs of intoxication after a single oral lethal dose consisted of central nervous system depression, ataxia, labored respiration, and death.

8.3 Short-Term Exposure Studies

8.3.1 Three-Day Gavage Study In Female B6C3F$_1$ Mice

Eight female B6C3F$_1$ mice per dose were given methyl t-butyl ether (> 99.95% purity in corn oil) by gavage at 0 or 1,800 mg/kg-day for three days (Moser et al., 1996). Food and water were available *ad libitum*. Eighteen hours after the last dose, the mice were sacrificed and hepatocytes were isolated for measurement of hepatocyte proliferation *in vitro*, expressed as the amount of 5-bromo-2'-deoxyuridine incorporation into hepatocyte nuclei. The hepatic labeling index was calculated by dividing the number of labeled nuclei by the total number of nuclei and multiplying by 100. Body weight and absolute and relative liver weights were also measured. Body and liver weights were not affected by treatment, but methyl t-butyl ether induced a statistical increase in the hepatocyte labeling index of 6.5% compared to 2.5% in controls.

8.3.2 Fourteen-Day Gavage Study In Male And Female Sprague-Dawley Rats

Ten Sprague-Dawley rats per sex and dose were administered 0, 357, 714, 1,071, or 1,428 mg/kg-day methyl t-butyl ether (99.95% purity in corn oil) by gavage for 14 days (Robinson et al., 1990). The high dose was selected because it was 37% of the LD_{50}. Rats were housed separately by sex and food and water were available *ad libitum*. Mortality and clinical signs were monitored daily. Food and water consumption were measured throughout the study at unspecified intervals. Body weight was measured on Days 0, 4, 6, and 14. Hematology parameters and clinical chemistry were conducted on all rats at study termination. Hematology included hematocrit, hemoglobin, mean corpuscular volume, erythrocytes, leukocytes, differential leukocytes, and reticulocytes. Clinical chemistry included glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, cholesterol, calcium, and phosphorus. Brain, liver, spleen, lung, thymus, kidney, adrenal, heart, ovary, and testes weights were measured at study termination, and relative organ-to- body-weight ratios were calculated. Gross necropsies were conducted on all rats at study termination. Histological examinations were conducted on all control and high-dose rats at study termination, and included unspecified "major organs". If target histopathological organs were identified, these organs were also examined histologically in the remaining dose groups.

At 357 mg/kg-day, two males died, but the deaths were attributed to the gavage treatment. Diarrhea was observed in treated rats. Mean creatinine was statistically increased by 16% in males compared to controls. Mean absolute (15%) and relative (16%) lung weights were statistically lower in females compared to controls.

At 714 mg/kg-day, diarrhea and statistically reduced food intake (unspecified magnitude) were observed in males compared to controls. Mean hemoglobin (6%), hematocrit (4%), differential lymphocytes (6%), and creatinine (16%) were statistically increased in males compared to controls. Mean alanine aminotransferase (21%) and cholesterol (22%) were statistically increased and mean serum calcium (6%) was statistically decreased in females compared to controls. Mean absolute (11%) and relative (11%) lung weights were statistically lower in females compared to controls. Mean absolute (12%) and relative (9%) lung weights were statistically lower in males compared to controls.

At 1,071 mg/kg-day, diarrhea was observed in treated rats. Mean erythrocytes (6%), hemoglobin (6%), aspartate aminotransferase (43%), and lactate dehydrogenase (78%) were statistically increased, and mean differential monocytes (33%) were statistically decreased in males compared to controls. Mean cholesterol (34%) was statistically increased in females compared to controls. Mean absolute (14%) and relative (11%) lung weights were statistically lower in females compared to controls.

At 1,428 mg/kg-day, two males and two females died, but the deaths were attributed to gavage. Diarrhea and profound but transient (< two hours) anesthesia were observed after dosing in male and female rats. Statistically reduced food intake (unspecified magnitude) was observed in females compared to controls. Statistically reduced mean terminal body weight of 10% was observed in females compared to controls. Mean erythrocytes (7%), blood urea nitrogen (14%), aspartate aminotransferase (38%), cholesterol (37%), and lactate dehydrogenase (63%) were statistically increased, and mean differential monocytes (33%) were statistically decreased in males compared to controls. Mean glucose (15%) was statistically increased and mean blood urea nitrogen (27%) and creatinine (20%) were statistically decreased in females compared to controls. Mean absolute (22%) and relative (15%) lung weights were statistically lower in females compared to controls. Mean absolute spleen (18%) and mean absolute (20%) and relative thymus (27%) weights were statistically lower in females compared to controls. Mean relative kidney (8%) and brain (9%) weights were statistically higher in females compared to controls. The incidence of hyaline droplet nephropathy in the renal tubules was "moderately" increased in dosed male rats, but no further details were provided, with the exception that increased hyaline droplets within the cytoplasm of proximal tubular epithelial cells were noted in 7/8 (88%) high-dose males compared with 2/5 (40%) controls.

8.3.3 Fourteen-Day Gavage Studies In Male Sprague-Dawley Rats

In a 14-day gavage study, de Peyster at al. (2003) examined whether methyl t-butyl ether exposure could induce hepatic peroxisome proliferation, since other chemicals that cause Leydig cell tumors in rats were also shown to induce peroxisome proliferation. Six male Sprague-Dawley rats per dose were administered methyl t-butyl ether (> 99.8% purity in corn oil) via gavage at 0 or 800 mg/kg-day via gavage for 14 days. Positive control rats were administered gemfibrozil via the diet. Hepatic peroxisomes were isolated from liver sections and processed for peroxisomal β-oxidation and examined with an electron microscope. Terminal blood samples were collected for measurement of cholesterol, triglyceride, alanine aminotransferase, and aspartate aminotransferease. Liver weights were measured, and relative liver-to-body-weight ratios were calculated. According to the study authors, there were no statistical differences between treated and vehicle control rats, but not all of the data were provided. It should be noted that although the methodology stated that methyl t-butyl ether doses of 800 mg/kg-day were administered, the results section indicated that methyl t-butyl ether doses were 1,000 mg/kg-day.

Ten male Sprague-Dawley rats per dose were administered methyl t-butyl ether (> 99.8% purity in corn oil) via gavage at 0 or 1,200 mg/kg-day for 14 days (de Peyster et al., 2003). This dose was determined in previous experiments to lower circulating testosterone levels without affecting body weight. Liver, testes, accessory sex organs (unspecified), and brain weights were

measured. Total protein content and P-450 content in hepatic microsomes was determined, and hepatic microsomal aromatase activity was measured.

In rats treated with 1,200 mg/kg-day methyl t-butyl ether, a statistical increase in mean relative liver weight of 15% was observed compared to controls. Although hepatic P450 content was comparable to controls, hepatic microsomal aromatase activity was decreased by 36% compared to controls.

8.3.4 Fifteen-Day Gavage Study In Male Sprague-Dawley Rats

Fifteen male Sprague-Dawley rats per dose were administered 0 or 1,500 mg/kg-day methyl t-butyl ether (> 99.9% purity in corn oil) via gavage for 15 days (Williams and Borghoff, 2000; Williams et al., 2000). At study termination, the rats were sacrificed, body, adrenal, kidney, epididymides, testes, prostate, pituitary gland, seminal vesicle, and liver weights were determined, and histopathological examination of the liver, kidneys, testes, and adrenals was conducted.

There were no treatment-related deaths. Deaths attributed to gavage, which were confirmed at necropsy, were primarily limited to the high-dose rats. Statistically increased mean absolute and relative adrenal weights of 15% and 17%, respectively, were observed at 1,500 mg/kg-day compared to controls. Minimal-to-moderate centrilobular hypertrophy was observed in 8/12 treated rats, but not in controls. The hypertrophy was characterized as increased size and cytoplasmic eosinophilia of hepatocytes that were oriented around central veins, which at times extended into the midzonal region of the lobule. The severity was dose-related and ranged from minimal to moderate, and the authors suggested that the effect was similar to that observed with phenobarbital administration. Protein droplet nephropathy of the kidney was observed in 11/12 treated rats and 1/15 controls.

8.3.5 Three-Week Gavage Study In CD-1 Mice

CD-1 mice were administered methyl t-butyl ether via gavage five days per week for three weeks (Ward et al., 1994). This study was not available, but OEHHA (1999) and ATSDR (1996) indicated that no effects on body weight or unspecified reproductive parameters were observed at doses up to 1,000 mg/kg, and thus identified the NOAEL as 1,000 mg/kg (or 714 mg/kg-day).

8.4 Long-Term and Chronic Exposure Studies

Subchronic gavage exposures to methyl t-butyl ether were associated with increased mean absolute and relative kidney weights in male rats accompanied by hyaline droplet formation in the renal proximal tubules. In male and female rats administered methyl t-butyl ether at ≥100 mg/kg-day via gavage for 90 days, statistically increased mean blood urea nitrogen levels in of at least 15% compared to controls were observed. Chronic gavage exposure to methyl t-butyl ether was associated with an increase in Leydig cell tumors in male rats and leukemias/lymphomas (combined) in female rats.

8.4.1 Subchronic Studies

8.4.1.1 Four-Week Studies In Sprague-Dawley Rats

Ten Sprague-Dawley rats per sex and dose were administered methyl t-butyl ether (unspecified purity unspecified in water vehicle) via gavage at 0, 90, 440, or 1,750 mg/kg for five days per week for four weeks (Johnson et al., 1992; Klan et al., 1992). These doses were approximately equivalent to 0, 64, 314, or 1,250 mg/kg-day. Rats were housed individually, and food and water were available *ad libitum*. Mortality and clinical signs were monitored daily. Body weights were measured weekly. Hematology and clinical chemistry were conducted on all rats at study termination. Hematology included erythrocytes, platelets, leukocytes, differential leukocytes, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, globulin, and albumin/globulin ratio. Clinical chemistry included glucose, creatine kinase, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood urea nitrogen, creatinine, sodium, pottasium, calcium, chloride, total protein and bilirubin, albumin, cholesterol and triglycerides. Adrenal, brain, ovary, testes, heart, kidney, liver, and spleen weights were measured, and relative organ-to-body-weight ratios were calculated. Gross necropsies were performed on all rats at study termination. Histological examinations were conducted on all control and high-dose rats at study termination, and included the adrenals, aorta, brain, cecum, colon, duodenum, epididymides, esophagus, eye, heart, ileum, jejunum, kidneys, liver, lung, mammary glands, muscle, nerve, ovaries, pancreas, pituitary, prostate, rectum, salivary gland, seminal vesicle, skin, spleen, stomach, testes, thymus, thyroid/parathyroid, trachea, urinary bladder, and uterus. If effects were noted, the same organs were examined in the lower doses as well.

No non-gavage-related deaths occurred at any dose. At 64 mg/kg-day, transitory (<one hour after dosing) salivation was observed in several rats. Mean corpuscular hemoglobin was statistically increased in females by 4% compared to controls. Mean alkaline phosphatase was statistically increased in males by 15% compared to controls. Mean relative kidney weights were increased in females by 6% compared to controls.

At 314 mg/kg-day, transitory (<one hour after dosing) salivation was observed in all rats, and hypoactivity and/or ataxia was observed in several rats. Mean erythrocytes were statistically increased in males by 6% compared to controls. Mean relative kidney weights were statistically increased in males by 8% compared to controls. Hyaline droplet formation in the proximal convoluted tubules was observed in 7/10 males.

At 1,250 mg/kg-day, transitory (<one hour after dosing) salivation was observed in all rats, and hypoactivity and/or ataxia was observed in several rats. Mean corpuscular hemoglobin was statistically increased in females by 3% compared to controls. Mean total protein was statistically increased by 8% in females compared to controls, and cholesterol was statistically increased in males by 20% and females by 26% compared to controls. Mean relative kidney weights were increased in males by 13% and females by 17% compared to controls. Mean relative liver weights were increased in males by 8% and females by 12% compared to controls. Mean relative adrenal weights were increased in males by 19% compared to controls. Hyaline droplet formation in the proximal convoluted tubules was observed in 9/10 males. Various

effects in the stomach, including submucosal edema, subacute inflammation, epithelial hyperplasia, and ulceration were observed in up to 4/7 males and 5/10 females. The effects were largely confined to the forestomach.

The study authors concluded that the hyaline droplet formation in the proximal tubules in males was attributable to α-2μ-globulin nephropathy, which was not relevant to humans. Further, the stomach lesions were attributable to local irritation, which was not considered a direct result of systemic toxicity.

Fifteen male Sprague-Dawley rats per dose were administered 0, 250, 500, 1,000, or 1,500 mg/kg-day methyl t-butyl ether (> 99.9% purity in corn oil) via gavage for 28 days (Williams and Borghoff, 2000; Williams et al., 2000). At study termination, the rats were sacrificed, body, adrenal, kidney, epididymides, testes, prostate, pituitary gland, seminal vesicle, and liver weights were determined, and histopathological examination of the liver, kidneys, testes, and adrenals was conducted.

There were no treatment-related deaths. Deaths attributed to gavage, which were confirmed at necropsy, were primarily limited to the high-dose rats. At 250 mg/kg-day, statistically increased mean relative kidney weights of 10% were observed compared to controls. Minimal-to-moderate centrilobular hypertrophy was observed in 1/15 treated rats, but not in controls. The hypertrophy was characterized as increased size and cytoplasmic eosinophilia of hepatocytes that were oriented around central veins, which at times extended into the midzonal region of the lobule. The severity was dose-related and ranged from minimal to moderate, and the authors suggested that the effect was similar to that observed with phenobarbital administration. Protein droplet nephropathy of the kidney was observed in 12/15 treated rats, but not in controls.

At 500 mg/kg-day, statistically increased mean relative kidney weights of 9% were observed compared to controls. Minimal-to-moderate centrilobular hypertrophy was observed in 10/15 treated rats, but not in controls. Protein droplet nephropathy of the kidney was observed in 15/15 treated rats, but not in controls.

At 1,000 mg/kg-day, statistically increased mean absolute and relative kidney weights of 10% and 16%, respectively, were observed compared to controls. Statistically increased mean relative liver weights of 10% were observed compared to controls. The increased relative liver weight was accompanied by minimal-to-moderate centrilobular hypertrophy in 11/13 treated rats, but not in controls. Protein droplet nephropathy of the kidney was observed in 12/13 treated rats, but not in controls.

At 1,500 mg/kg-day, mean body weight was reduced by 12% compared to controls. Statistically increased mean relative kidney weights of 18% were observed compared to controls. Statistically increased mean relative liver weights of 14% were observed compared to controls. Statistically increased mean relative testes weights of 15% were observed compared to controls. The increased relative liver weight was accompanied by minimal-to-moderate centrilobular hypertrophy in 11/11 treated rats, but not in controls. Increased mean relative kidney weights, accompanied by protein droplet nephropathy of the kidney, were observed in 10/11 treated rats, but not in controls.

8.4.1.2 Thirteen-Week Or Longer Studies In Sprague-Dawley Rats

Ten Sprague-Dawley rats per sex and dose were administered methyl t-butyl ether (≥ 99.95% purity in corn oil) via gavage at 0, 100, 300, 900, or 1,200 mg/kg-day for 90 days (Robinson et al., 1990). Rats were housed separately by sex and food, and water was available *ad libitum*. Mortality and clinical signs were monitored daily. Food consumption was measured once a week and water consumption was measured three times a week. Body weight was measured twice a week. Hematology and clinical chemistry were conducted on all rats at study termination. Hematology included hematocrit, hemoglobin, mean corpuscular volume, erythrocytes, leukocytes, differential leukocytes, and reticulocytes. Clinical chemistry included glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, cholesterol, calcium, and phosphorus. Brain, liver, spleen, lung, thymus, kidney, adrenal, heart, ovary, and testes weights were measured at study termination, and relative organ-to-body-weight ratios were calculated. Gross necropsies were conducted on all rats at study termination. Histological examinations were conducted on all control and high-dose rats at study termination, and included unspecified "major organs". If target histopathological organs were identified, these organs were also examined histologically in the remaining dose groups.

This study was not designed to meet current U.S. EPA (2007b) Health Effects Testing Guidelines, since hematology did not include a measure of clotting potential, and clinical chemistry did not include albumin, alkaline phosphatase, gamma glutamyl transferase, globulin, sorbitol dehydrogenase, bilirubin, protein, or serum chloride, magnesium, potassium, or sodium. Further, urinalysis was not conducted, and organs examined histologically were specified only as including "major organs".

At 100 mg/kg-day, one male died, but the cause of death was not specified. Diarrhea was observed in male and female rats. Water consumption (unspecified magnitude) was statistically increased in females compared to controls. A statistical decrease in blood urea nitrogen was observed in males (15%) and females (20%).

At 300 mg/kg-day, one female died, but the cause of death was not specified. Diarrhea was observed in male and female rats. A statistical decrease in blood urea nitrogen was observed in males (20%) and females (33%). A statistical decrease in glucose (17%) and lactate dehydrogenase (62%) and an increase in cholesterol (11%) were observed in females. A statistical decrease in creatinine (15%) and an increase in aspartate aminotransferase (34%) were observed in males. Mean absolute (4%) and relative (4%) brain weights were statistically increased in males compared to controls. Mean relative kidney weights (10%) were statistically increased in females compared to controls.

At 900 mg/kg-day, two females and one male died, but the cause of death was not specified. Diarrhea was observed in male and female rats. Food consumption (unspecified magnitude) was statistically increased in females compared to controls. A statistical decrease in blood urea nitrogen was observed in males (18%) and females (35%). A statistical decrease in mean glucose (13%) and lactate dehydrogenase (16%) and an increase in cholesterol (31%) were observed in females compared to controls. A statistical decrease in mean creatinine (26%) and an increase in cholesterol (22%) and lactate dehydrogenase (5%) were observed in males compared

to controls. Mean absolute (14%) and relative (15%) kidney weights were statistically increased in males compared to controls. Mean relative liver weights (13%) were statistically increased in males compared to controls. Mean relative heart (11%), liver (12%), kidney (13%), and thymus (33%) weights were statistically increased in females compared to controls.

At 1,200 mg/kg-day, four females and one male died, but the cause of death was not specified. Diarrhea and a profound but transient (<two hours) anesthetic effect were observed in male and female rats. Water consumption (unspecified magnitude) was statistically increased in males and females compared to controls. A statistical decrease in blood urea nitrogen was observed in males (18%) and females (17%). A statistical decrease in mean glucose (24%) and lactate dehydrogenase (16%) and an increase in cholesterol (20%) were observed in females compared to controls. A statistical decrease in mean creatinine (19%) and an increase in aspartate aminotransferase (33%) were observed in males compared to controls. Terminal mean body weight was statistically reduced by 9% in males compared to controls. Mean absolute (18%) and relative (21%) kidney weights and mean absolute (9%) and relative (13%) lung weights were statistically increased in male rats compared to controls. Mean relative liver weights (12%) in males and kidney (12%) and adrenal (25%) weights in females were statistically increased in male rats compared to controls. According to the authors, microscopic findings included chronic nephropathy in both control and high-dose male rats. These changes, such as renal tubular degeneration, were more severe in treated rats than control rats. Renal tubules plugged with granular casts were found in 5/10 high-dose males, and 10/10 males exhibited slight increases in cytoplasmic hyaline droplets in proximal tubular epithelial cells. No further details regarding the renal changes were provided.

Ten male Sprague-Dawley rats per dose were administered 0, 200, 600, and 1,000 mg/kg methyl t-butyl ether (98.8% purity in soybean oil) by gavage for five days per week for 90 days (Zhou and Ye, 1999). These doses were equivalent to 0, 143, 428, or 857 mg/kg-day, respectively. Body weight and food and water consumption were measured weekly. Clinical chemistry was conducted at study termination and included aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total protein, albumin, globulin, albumin/globulin ratio, blood urea nitrogen, and creatinine. Liver, kidney, testes, and lung weights were measured at study termination. Gross necropsies and histopathological examinations were conducted at study termination, and included the liver, kidney, testes, and lung. Liver sections were also examined under an electron microscope.

This study was not designed to meet current U.S. EPA (2007b) Health Effects Testing Guidelines, since only males were evaluated, hematology was not conducted, and clinical chemistry did not include alkaline phosphatase, gamma glutamyl transferase, glucose, sorbitol dehydrogenase, total bilirubin, total cholesterol, or serum electrolytes. Further, urinalysis was not conducted; spleen, heart, ovary, and brain weights were not measured; and histopathology included only the liver, kidney, testes, and lung.

At 143 mg/kg-day, mean absolute and relative liver weights were statistically increased by 12% and 14%, respectively, compared to controls. Lactate dehydrogenase was statistically decreased (32%) at the low, but not mid or high doses compared to controls. Aspartate aminotransferase was statistically increased by 31% compared to controls, but within historical control ranges.

Histopathological examination in treated rats was comparable to controls. Electron microscopy of the liver revealed nuclear condensation, fat droplets, lysosome appearance in cells, and smooth endoplasmic reticulum disintegration, but the magnitude and number of animals affected was not specified. The study authors did, however, indicate that more severe changes were observed at higher doses.

At 428 mg/kg-day, mean absolute and relative liver weights were statistically increased by 18% and 15%, respectively, compared to controls. Mean relative kidney weight was statistically increased by 6% compared to controls, but no accompanying renal pathology was observed. Aspartate aminotransferase was statistically increased by 29% compared to controls, but within historical control ranges. Histopathological examination in treated rats was comparable to controls. Electron microscopy of the liver revealed nuclear condensation, fat droplets, lysosome appearance in cells, and smooth endoplasmic reticulum disintegration, but the magnitude and number of animals affected was not specified. However, the study authors indicated that more severe changes were observed at higher doses.

At 857 mg/kg-day, mean absolute and relative liver weights were statistically increased by 21% and 22%, respectively, compared to controls. Mean absolute and relative kidney weights were statistically increased by 12% and 13%, respeetively, compared to controls, but no accompanying renal pathology was observed. Aspartate aminotransferase was statistically increased by 27% compared to controls, but within historical control ranges. Histopathological examination in treated rats was comparable to controls. Electron microscopy of the liver revealed nuclear condensation, fat droplets, lysosome appearance in cells, and smooth endoplasmic reticulum disintegration, but the magnitude and number of animals affected was not specified. However, the study authors indicated that more severe changes were observed at higher doses.

8.4.2 Chronic Studies

Sixty Sprague-Dawley rats per sex and dose were administered 0, 250, or 1,000 mg/kg methyl t-butyl ether (> 99% purity in extra virgin olive oil) by gavage four times a week for 104 weeks on a weekly schedule of two days dosing, one day without dosing, two days dosing, and two days without dosing (Belpoggi et al., 1995; 1997). These doses were approximately equivalent to daily doses of 0, 143, or 571 mg/kg-day. The animals were housed five per cage and kept under observation until natural death. Food and water were available *ad libitum*. Mortality and clinical signs were monitored daily. Food and water consumption and body weight were measured weekly for the first 13 weeks and twice monthly thereafter until 112 weeks. Thereafter, body weights were measured every eight weeks until death. Gross necropsies were performed on all rats after natural death. Histopathological examinations, which were performed on all rats after natural death, included the aorta, adrenals, bone, bone marrow, brain, bronchi, cecum, colon, diaphragm, duodenum, esophagus, eye, Harderian gland, heart, ileum, jejunum, kidneys, liver, lung, lymph nodes (mediastinal, subcutaneous, mesenteric), mammary glands, muscles, nerve, ovaries, pancreas, pharynx, larynx, pituitary, prostate, salivary gland, seminal vesicle, subcutaneous tissue, skin, subcutaneous tissue, spinal cord, spleen, stomach, testes, thymus, thyroid/parathyroid, tongue, trachea, urinary bladder, uterus, Zymbal gland, and gross lesions.

This study was not designed to meet current U.S. EPA (2007b) Health Effects Testing Guidelines, since the dosing occurred on a four-day per week schedule, with two days dosing, one day without dosing, two days dosing, and two days without dosing. Further, since no results for hematology, clinical chemistry, urinalysis, or organ weights were reported, it was presumed that these parameters were not examined. Histology did not include the aorta, bone, bone marrow, eye, mammary glands, muscles, nerve, seminal vesicle, or spinal cord. The tumor incidences reported in this study were reviewed by Belpoggi et al. (1998) after a re-evaluation of the histopathology slides.

At the low dose, survival at the end of the treatment period (104 weeks) was 35% in treated females compared to 48% in controls. Survival at the end of the treatment period (104 weeks) was 30% in low-dose males compared to 30% in controls. There was a statistical increase in lymphomas and leukemias combined (7/51) in female rats compared to controls (2/58). The individual incidence of lymphomas or leukemias was not indicated. The lymphatic tumors were accompanied by an increase in dysplastic proliferation of lymphoreticular tissue, which was characterized as hyperplastic lymphoid tissues at various sites, in which atypical lymphoid cells, usually lymphoimmunoblasts, isolated and/or aggregated in small clusters, were observed. An increased incidence of uterine sarcomas was observed in low-dose females, but not high-dose females, compared to controls.

At the high-dose, survival at the end of the treatment period (104 weeks) was 28% in treated females compared to 48% in controls. Survival at the end of the treatment period (104 weeks) was 42% in high-dose males compared to 30% in controls. There was a statistical increase in the incidence of testicular Leydig cell (interstitial cell) tumors in male rats compared to controls. The incidence was 3/26, 5/25, and 11/32 in control, low-, and high-dose males (based on the number of rats surviving at the occurrence of the first Leydig tumor, which was 96 weeks). In female rats, there was a dose-related statistical increase in lymphomas and leukemias combined (12/47) compared to controls (2/58), and an increase in dysplastic proliferation of lymphoreticular tissue. The study authors reported that the range of the lymphatic tumors in females in this study was within the historical control incidence for these tumors in female Sprague-Dawley rats from studies in their laboratory (below 10%).

The study authors reported that "no treatment-related non-oncological pathological changes were detected by gross inspection and histological examination", but the data were not provided.

8.5 Studies of Genotoxicity and Related End-Points

The genotoxicity data for methyl t-butyl ether have been critically reviewed by ECB (2002), OEHHA (1999), IPCS (1998), ECETOC (1997), and ATSDR (1996). The weight of evidence suggests that methyl t-butyl ether has some genotoxic potential. Methyl t-butyl ether has been tested in mutagenicity, chromosomal aberration, micronucleus, sister chromatid exchange, DNA damage and repair, and DNA strand break assays. Methyl t-butyl ether was not mutagenic in several *Salmonella* reverse mutation assays, although one assay was positive in TA102. Methyl t-butyl ether was also positive in a mouse lymphoma cell forward mutation assay, possibly due to the metabolism of methyl t-butyl ether to formaldehyde. Methyl t-butyl ether was negative in *in vivo* and *in vitro* chromosomal aberration assays, but equivocal results were observed in a sister

chromatid exchange assay *in vitro*. Methyl t-butyl ether was negative in *in vivo* and *in vitro* mouse micronucleus assays and unscheduled DNA synthesis assays, and an *in vivo* DNA repair assay, although methyl t-butyl ether was positive in a DNA strand break assay in rat lymphocytes *in vivo* and human lymphocytes *in vitro*. DNA adduct formation was observed in mice given a single gavage dose of methyl t-butyl ether.

8.5.1 Mutagenicity Assays

Methyl t-butyl ether was not mutagenic in *Salmonella* reverse mutation assays and tissue culture mutation assays, and was negative in a *Drosophila* sex-linked recessive assay (OEHHA, 1999). Methyl t-butyl ether was positive in one *Salmonella* reverse mutation assay in strain TA102 and negative in eight other *Salmonella* reverse mutation assays, two of which included TA102 (ECB, 2002). In a study by Williams-Hill et al. (1999), methyl t-butyl ether (99.9% purity) was weakly and moderately positive in TA102 without and with metabolic activation, respectively. Addition of formaldehyde dehydrogenase reduced the mutagenic potential, suggesting that the formaldehyde metabolite was partially responsible for the positive result. A well-conducted study by McGregor et al. (2005) failed to replicate the positive result for methyl t-butyl ether in *Salmonella* TA102.

According to ECB (2002), methyl t-butyl ether was evaluated in an *in vitro* forward mutation assay in mouse L5178Y TK+/- lymphocytes at concentrations of 0.39 to 6.25 µl/ml with and without metabolic activation with the liver S9 fraction from Fisher-344 rats (ARCO, 1980; Mackerer et al., 1996). After a two- to three-day recovery and expression period, lymphocytes were plated and incubated with methyl t-butyl ether (96% or 99% purity) for 10 days. The total number of resistant colonies was counted, and the ratio to cells growing in non-selective medium was determined and characterized as the mutant frequency. Five parallel assays were conducted. Methyl t-butyl ether showed a statistically and dose-dependently increased mutation frequency in the presence of metabolic activation when compared to controls. Mackerer et al. (1996) then investigated the possible role of formaldehyde in the mutagenic events. The authors exposed mouse lymphoma cells to concentrations of methyl t-butyl ether from 1 to 4 µl/ml for three hours and added formaldehyde dehydrogenase with its co-factor NAD+, both of which convert formaldehyde to non-mutagenic formic acid, thereby eliminating possible mutagenicity resulting from formaldehyde. The results showed that the mutation frequency did not increase when formaldehyde dehydrogenase and its coenzyme were present, while there was a five-fold increase in its absence.

ECB (2002) reported that methyl t-butyl ether was evaluated in two separate studies for the ability to induce mutations at the hypoxanthine-guanine phosphoribosyl transferase locus in Chinese hamster V79 cells with and without metabolic activation. In the studies by Life Science Research (1989) and Cinelli et al. (1992), no statistical increase in mutation frequency was observed compared to controls.

8.5.2 Assays of Chromosomal Damage

Methyl t-butyl ether was negative in *in vivo* and *in vitro* chromosomal aberration assays (ECB, 2002; OEHHA, 1999), and in an *in vitro* sister chromatid exchange assay (OEHHA, 1999). ECB

(2002) considered the results from the *in vitro* sister chromatid exchange assay to be equivocal, since there was a significant increase of sister chromatid exchange frequency in one of the two replicates at 1µl/ml methyl t-butyl ether (99% purity). However, because there was only a small increase of sister chromatid exchange induction with the positive control, the test was repeated, and repeat tests failed to confirm the positive result (Litton Bionetics, 1980). Further, a concurrent assay using methyl t-butyl ether of 95% purity failed to demonstrated a statistical increase in sister chromatid exchange frequency compared to controls.

8.5.3 Other Assays of Genetic Damage

Methyl t-butyl ether was negative in *in vivo* and *in vitro* mouse micronucleus assays (ECB, 2002; OEHHA, 1999), *in vivo* and *in vitro* unscheduled DNA synthesis assays, and an *in vivo* DNA repair assay (OEHHA, 1999).

ECB (2002) reported that methyl t-butyl ether was positive in one and negative in two unscheduled DNA synthesis assays in primary rat hepatocytes and *in vitro*. In the positive study, methyl t-butyl ether was evaluated for unscheduled DNA synthesis in primary rat hepatocytes isolated from two male Sprague-Dawley rats (Zhou et al., 2000). Hepatocytes were incubated with 0, 200, 600 or 1,000 ug/ml methyl t-butyl ether (98.8% in dimethylsulfoxide) and 5 µCi/mL [^{3}H]-methylthymidine for three hours at 37°C. Radioactivity was measured with a liquid scintillation spectrometer. Concurrent negative, vehicle (dimethylsulfoxide) and positive controls (mechlorethamine) were included. At 0, 0.2, 0.6 or 1 mg/mL, the radioactivity (counts per minute) was 712, 777, 1,311, and 1,437 CPM, respectively. The highest dose was statistically significant when compared to vehicle controls.

Methyl t-butyl ether was evaluated in the single cell gel electrophoresis assay (comet assay) *in vitro* for the ability to induce DNA strand breaks in human lymphocytes (Chen et al., 2007). The assay was conducted under neutral and alkaline pH conditions. Lymphocytes isolated from the blood of one healthy female donor were incubated with methyl t-butyl ether (unspecified purity in dimethylsulfoxide) at 0, 0.05, 0.1, or 0.2 mM for one hour. After cell viability was determined to be >95%, one hundred comets on each of triplicate slides were scored visually according to the relative intensity of the tail. An intensity score from class 0 (undamaged) to class 4 (severely damaged) was assigned to each cell. Thus, the total score for the 100 comets could range from 0 to 400. The extent of DNA damage was analyzed and scored by the same experienced person. Solvent and positive controls were included. The mean DNA damage score was statistically increased at all doses compared to controls (18%, 24%, and 26%, respectively, under alkaline conditions and 47%, 65%, and 78%, respectively, under neutral conditions).

Methyl t-butyl ether was evaluated in the alkaline single cell gel electrophoresis assay (comet assay) *in vivo* for the ability to induce DNA strand breaks in rat lymphocytes (Lee et al., 1998). Nine male Sprague-Dawley rats per dose were administered methyl t-butyl ether via gavage at 0, 40, 400, or 800 mg/kg for 28 days. Lymphocytes isolated from trunk blood were analyzed for DNA strand breaks and scored for apoptosis frequency. Cytotoxicity (or viability) was determined by the trypan blue exclusion method. Viability was greater than 90% in all groups. Measures of DNA-strand breakage, such as tail length and tail moment, were significantly

increased at 800 mg/kg compared to controls. As this publication was an abstract, and a full publication was not identified, no further details were available.

The potential DNA adduct formation has been examined in male Kunming mice given ^{13}C-methyl t-butyl ether (>95% purity) at up to 1.9 mg/kg (Yuan et al., 2007) or 6.18 mg/kg (Du et al., 2005) via gavage. DNA was extracted six hours post-dosing from lung, liver and kidney samples. DNA adducts were detected in a dose-related manner in the kidney and lung at 1.33 mg/kg and above. The methyl group of methyl t-butyl ether was shown to be the predominant binding moiety in liver, while the methyl group and the tert-butyl group gave comparable contributions to adduct formation in lung and kidney (Yuan et al., 2007).

Iavicoli et al. (2002) investigated the ability of methyl t-butyl ether to induce cytotoxicity, transformation, or apoptosis of rat fibroblasts *in vitro*. In the cell proliferation and cytoxicity assay, rat-1 normal rat fibroblasts were incubated with methyl t-butyl ether (99.8% purity) at 8.4 x 10^{-6} to 8.4 mM for 48 hours. After rinsing, the cultures were then exposed to 3-(4,5-)-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) for two hours. The amount of the colored formazan derivative that was formed was measured to determine cytotoxicity. Cell viability after a two-day incubation was also determined. DNA content was measured using flow-assisted cell sorting. Cell cycle analysis, to measure apoptosis, was conducted after a 48-hour exposure to methyl t-butyl ether at the IC_{50} or 1/10 of the IC_{50} (0.84 or 0.084 mM, respectively). Twenty-four hour cell transformation assays were also conducted in C3H/10T$_{1/2}$ Cl 8 mouse embryo fibroblasts at methyl t-butyl ether concentrations of 0.336 and 0.672 mM, with cigarette tobacco smoke serving as a positive control. These doses were selected since they did not cause cell loss after 24 hours. All assays were performed in triplicate.

The 50% inhibitory concentration (IC_{50}) of methyl t-butyl ether on growth of rat fibroblasts was determined to be 0.84 mM. Cell viability at the IC_{50} or 1/10 of the IC_{50} (0.84 or 0.084 mM, respectively) after 24 and 48 hours was statistically and dose- and time-dependently reduced compared to controls. Methyl t-butyl ether also caused a dose-dependent reduction in the number of cells in the G2/M phase of the cell cycle and an increase in the percentage of cells in the S-phase, indicating increased apoptosis. At 0.336 and 0.672 mM methyl t-butyl ether, a statistical increase in the number of transformed cell foci in mouse embryo fibroblasts of 2.1 and 2.5 times the control, respectively, was observed.

8.6 Reproductive and Developmental Toxicity Studies

No *in vivo* oral two-generation reproduction or developmental studies were identified for methyl t-butyl ether. In an attempt to characterize a possible mode of action for the Leydig cell tumors observed in male rats after chronic gavage dosing, reproductive effects in male rats have recently been investigated in non-standardized reproduction studies. A single gavage dose of methyl t-butyl ether at approximately 500 mg/kg-day resulted in reduced circulating testosterone in male rats during the hours immediately following dosing. In male rats treated with 1,200 mg/kg-day methyl t-butyl ether for 14 days, decreased mean testosterone and luteinizing hormone and increased estradiol were observed, along with decreased testicular microsomal aromatase activity. Repeated exposure to 800 mg/kg-day methyl t-butyl ether via gavage in male rats was associated with statistical reductions in circulating testosterone after 28 days. High doses (> 50

mM) of methyl t-butyl ether were also found to reduce basal and human Chorionic Gonadotropin (hCG)-stimulated testosterone production in Leydig cells *in vitro*.

One- and two-generation inhalation reproductive studies in rats and four inhalation developmental studies in rats, mice, and rabbits are available for methyl t-butyl ether. These studies have been reviewed by ECB (2002), OEHHA (1999), IPCS (1998), ECETOC (1997), and ATSDR (1996). Specific reproductive effects were not observed in rats at concentrations up to 28,800 mg/m^3. Methyl t-butyl ether did not induce developmental effects at concentrations below those that were maternally toxic. Decreases in uterine weight and increases in estrogen metabolism in mice have been observed at 28,800 mg/m^3 (IPCS, 1998).

Since the reproductive and developmental studies for methyl t-butyl ether have been extensively reviewed by several other regulatory agencies, this section includes only the oral reproductive and developmental studies for methyl t-butyl ether, including those published since the various regulatory reviews. However, none of the oral studies were standardized two-generation reproduction or developmental studies.

8.6.1 Reproduction Studies

No oral one- or two-generation reproduction studies were identified for methyl t-butyl ether, but effects on the reproductive organs have been investigated following oral exposure to methyl t-butyl ether in non-standardized reproduction studies.

Potential testicular toxicity associated with methyl t-butyl ether was assessed in five male CD-1 mice per dose that received gavage doses of methyl t-butyl ether (unspecified purity in canola oil) on Days 1, 3, and 5 at 0, 400, 1,000 or 2,000 mg/kg (Billitti et al., 2005). Testosterone levels were measured on Day 6 fecal samples collected from all mice. Thereafter, mice were injected with human chorionic gonadotrophin to stimulate maximum testosterone production and fecal samples were collected after one day. Body weight and serum testosterone were measured and histological examination of the testes was included at study termination. Two high-dose mice died as a result of dosing error. All examined parameters in the treated mice that survived were comparable and/or not statistically different compared to controls.

Eight female B6C3F$_1$ mice per dose were given methyl t-butyl ether (> 99.95% purity in corn oil) by gavage at 0 or 1,800 mg/kg-day for three days (Moser et al., 1996). Food and water were available *ad libitum*. Twenty-four hours after the last dose, the mice were sacrificed and hepatocytes were isolated for measurement of estrogen metabolism *in vitro*, which was expressed as the amount (nM) of 17-β–estradiol metabolized/ mg protein/ minute. Methyl t-butyl ether induced a two-fold statistical increase in the rate of estrogen metabolism *in vitro* compared to controls.

Six to eleven female CD-1 mice per dose were administered methyl t-butyl ether via gavage at 0, 600, or 1,500 mg/kg-day for five days either with or without subcutaneous administration of 1 ug estradiol on Days 3-5 (Okahara et al., 1998). The authors reported that methyl t-butyl ether had some mild, but in some cases, seemingly opposite, activity under these conditions, but no further details were provided. At 1,500 mg/kg-day, delayed vaginal opening by Postnatal Day 26 was

observed in half of the treated females. Mean relative uterine weights were statistically increased in the methyl t-butyl ether/estradiol group compared to the estradiol alone control group, but the dose level or magnitude was not specified. According to the authors, no clear or consistent effect was observed in uterine peroxidase activity or in ovarian, liver, or kidney weights compared to controls. No further details were available in this abstract, and a full publication was not located.

Twelve male Sprague-Dawley rats per dose were administered methyl t-butyl ether (> 99.8% purity in corn oil) via gavage at 0, 1,000, or 1,500 mg/kg every other day for a total of 14 doses over 28 days (de Peyster et al., 2003). The 1,000 mg/kg dose was selected since it was the highest dose in the Belpoggi et al. (1995) chronic gavage study, and since this dose induced a statistical increase in Leydig cell tumors in male rats compared to controls. The 1,500 mg/kg dose was chosen since it was approximately the highest dose from a 90-day gavage study for methyl t-butyl ether by Robinson et al. (1990). The experiment originally included an untreated and a vehicle-treated control group, but the results were ultimately combined into one control group. Due to excess weight loss and one death, the 1,000 and 1,500 mg/kg doses were reduced to 500 and 750 mg/kg, respectively, starting on Day 13. The terminal doses were approximately equivalent to 0, 357, or 536 mg/kg-day. This study was conducted to investigate the mechanism of Leydig cell tumors induced in male rats after chronic gavage exposure to methyl t-butyl ether in a study by Belpoggi et al. (1995). It has been suggested that increased hepatic metabolism through P450 enzymes results in increased steroid catabolism, resulting in reduced testosterone circulation.

Testosterone concentrations were measured on Day 1 and 14 (tail blood) and 28 (cardiac puncture). If the serum sample volume was sufficient, terminal corticosterone was also measured to determine whether the Leydig tumors were induced through an increased stimulation of testicular glucocorticoid receptors, which can impair testosterone production. Liver, kidney, testes, seminal vesicles, and epididymides weights were measured, and mean organ-to-body weight ratios were calculated. Total protein and total P450 were measured from isolated liver microsomes.

At study termination, mean body weight gain was 8, 3, 1, and 0% in the negative control, vehicle control, 357 mg/kg-day, and 536 mg/kg-day groups, respectively. The Day 1 testosterone concentration in rats administered 537 mg/kg-day methyl t-butyl ether was statistically reduced by approximately 70% compared to pooled controls (vehicle and negative, n=4 only). The Day 14 and 28 testosterone concentrations in treated rats were not statistically different compared to controls. At study termination, mean absolute liver weight and total microsomal protein in treated rats were comparable to controls, but mean liver P450 content (nmol/mg protein and nmol/g liver weight) was slightly, but statistically, increased in rats administered 537 mg/kg-day compared to controls. There was a 24% increase in nmol/mg P450 protein and a 35% increase in nmol P450/g liver weight compared to pooled controls. Mean corticosterone levels on Day 1, 14, and 28 were not statistically different compared to pooled controls, but the sample size was only about 4-5 rats per dose. The authors concluded that high gavage doses of methyl t-butyl ether result in reduced circulating testosterone in rats during the hours immediately following dosing (4-5 hours). However, the increase in hepatic P450 content did not result in reduced

circulating testosterone, as originally hypothesized by the study authors, but the authors could not rule out other hormonal or metabolic compensatory mechanisms.

Twelve male Sprague-Dawley rats per dose were administered methyl t-butyl ether (> 99.8% purity in corn oil) via gavage at 0, 40, 400, or 800 mg/kg-day for 28 days (de Peyster et al., 2003; Day et al., 1998). This study was conducted to further investigate the mechanism of Leydig cell tumors induced in male rats after chronic gavage exposure to methyl t-butyl ether in a study by Belpoggi et al. (1995). Luteinizing hormone, prolactin, testosterone, and corticosterone concentrations were measured on Day 1 and 14 (tail blood) and 28 (trunk). Liver, pituitary, testes, epididymides, thyroid, adrenal, prostate, and brain weights were measured, and mean organ-to-body and brain weight ratios were calculated.

At 40 mg/kg-day, mean plasma corticosterone was statistically reduced by 28% compared to controls on Day 14, but the corticosterone was not statistically different from controls at study termination.

At 400 mg/kg-day, terminal mean body weight was statistically reduced by 7% compared to controls. Mean plasma corticosterone was statistically reduced by 42% compared to controls on Day 14, but the corticosterone was not statistically different from controls at study termination. Mean pituitary weight was statistically reduced by 23% compared to controls.

At 800 mg/kg-day, terminal mean body weight was statistically reduced by 13% compared to controls. Mean plasma corticosterone was statistically reduced by 43% compared to controls on Day 14. At study termination, mean plasma testosterone was statistically reduced by 35% and mean plasma corticosterone was statistically reduced by 44% compared to controls. The mean adrenal-to-body-weight ratio was statistically reduced by 20% compared to controls. The mean thyroid-to-body-weight ratio was statistically reduced by 29% compared to controls.

Six male Sprague-Dawley rats per dose were administered methyl t-butyl ether (> 99.8% purity in corn oil) via gavage at 0 or 800 mg/kg-day for five days (de Peyster et al., 2003). This study was conducted to further investigate the mechanism of Leydig cell tumors induced in male rats after chronic gavage exposure to methyl t-butyl ether in a study by Belpoggi et al. (1995). The effect of castration on the hypothalamic-pituitary axis was investigated using testosterone implants in phosphate buffered saline (PBS) and four experimental groups of male rats. The four groups consisted of sham implant (PBS) and 800 mg/kg-day methyl t-butyl ether via gavage, sham implant (PBS) and corn oil vehicle gavage, testosterone implant and 800 mg/kg-day methyl t-butyl ether via gavage, and testosterone implant and corn oil vehicle gavage. The amount of testosterone in each implant was intended to result in average circulating testosterone as in normal non-castrated rats. Lutenizing hormone, prolactin, and testosterone concentrations from the tail vein were measured four hours after the initial dose (Day 1) and two hours after the final dose (Day 5). Terminal prostate and seminal vesicle weights were measured. The experiment was repeated with a younger set of animals, reportedly to reduce the amount of body weight variation, since each testosterone implant contained a standard amount of testosterone.

In the first experiment, the authors found that circulating testosterone was higher and lutenizing hormone was lower in rats with testosterone implants compared to controls, but the differences

were not statistically significant. Since each testosterone implant contained a standard amount of testosterone, the authors suggested that the results were confounded by the difference in body weights between the rats after the 3-day recovery period from the surgical implant, even though prior to surgery, the rats were of comparable body weights. Thus, the experiment was repeated with a younger set of animals, but the results of the first experiment could not be duplicated and may have been confounded by a small sample size, since one control rat gained a large amount of body weight. Recognizing confounding factors, the authors concluded that there was no clear evidence of an effect on the hypothalamic-pituitary axis in either experiment.

Ten male Sprague-Dawley rats per dose were administered methyl t-butyl ether (> 99.8% purity in corn oil) via gavage at 0 or 1,200 mg/kg-day for 14 days (de Peyster et al., 2003). This dose was determined in previous experiments to lower circulating testosterone levels without affecting body weight. Terminal plasma estradiol, luteinizing hormone, and testosterone concentrations were measured from trunk blood samples. Testes and accessory sex organs (unspecified) weights were measured. Total protein content in testicular microsomes was determined, and testicular microsomal aromatase activity was also measured.

In rats treated with 1,200 mg/kg-day methyl t-butyl ether, a statistical decrease in mean testosterone and luteinizing hormone of 51% and 10%, respectively, was observed compared to controls, and a statistical increase in mean estradiol of 26% was observed compared to controls. Testicular microsomal aromatase activity was decreased by 55% compared to controls.

Williams and Borghoff (2000) and Williams et al. (2000) investigated the hypothesis that methyl t-butyl ether-induced decrease in serum testosterone levels in male rats may be due in part to the ability of methyl t-butyl ether to induce the metabolism of endogenous testosterone and, hence, enhance its clearance. Male Sprague-Dawley rats were administered 0, 250, 500, 1,000, or 1,500 mg/kg-day methyl t-butyl ether (> 99.9% purity in corn oil) via gavage for 15 or 28 days. Rats were sacrificed one hour following the last dose, and serum and interstitial fluid testosterone, and serum dihydrotestosterone, 17-β-estradiol, prolactin, triiodothyronine (T3), thyroxin (T4), thyroid stimulating hormone, follicle stimulating hormone, and luteinizing hormone levels were measured. Histopathology of the testes was performed in all rats.

After 15 days at 1,500 mg/kg-day, interstitial fluid and serum testosterone levels (approximately 60% each, estimated from graph) and serum prolactin levels (56%) were statistically decreased compared to controls.

After 28 days at 1,000 mg/kg-day, serum triiodothyronine (T3) was statistically decreased by 19% compared to controls.

After 28 days at 1,500 mg/kg-day, serum triiodothyronine (T3; 19%), luteinizing hormone (approximately 20%, estimated from graph), and dihydrotestosterone (45%) were statistically decreased compared to controls.

No testicular lesions were observed at any dose level. The authors concluded that methyl t-butyl ether causes mild perturbations in T3 and prolactin; however, the short-term (15-day), but not longer-term (28-day), decrease in testosterone and the mild increase in luteinizing hormone

levels did not fit the pattern caused by known Leydig cell tumorigens, since larger increases in luteinizing hormone have been caused by chemicals known to cause Leydig cell tumors.

Ten CD-1 mice per sex and dose were given 0, 1, 10, 100 or 1,000 mg/kg methyl t-butyl ether (purity unspecified in corn oil) by gavage for five days per week for three weeks (Ward et al., 1994). As this study was not available, this summary was based on IPCS (1998). These doses were approximately equivalent to 0, 0.7, 7, 71, or 714 mg/kg-day. At study termination, the mice were sacrificed and one testis from each male and both ovaries from each female were sectioned for cytological evaluation. In males, sperm number, Sertoli cells, spermatogonia, spermatocytes, and capped spermatids were evaluated. In females, oocyte quality was assessed. There were no effects of methyl t-butyl ether on any of the cell types examined, but no further details were provided. OEHHA (1999) and ATSDR (1996) indicated that the reproductive NOAEL for this study was 1,000 mg/kg-day, but no further details were available. It should be noted that OEHHA (1999) and ATSDR (1996) likely did not adjust for the less than daily dosing regimen, and likely should have indicated the reproductive NOAEL as 714 mg/kg-day.

The effect of methyl t-butyl ether on the testosterone production of Leydig cells in culture was examined *in vitro* by de Peyster et al. (2003). Leydig cells were isolated from adult male Sprague-Dawley rats and incubated for three hours with 0, 50, or 100 mM methyl t-butyl ether (> 99.8% purity) or t-butanol, a major metabolite of methyl t-butyl ether. The same concentrations were also tested with human Chorionic Gonadotropin (hCG), added to stimulate testosterone production. Cell viability at the tested concentrations was at least 85%. Testosterone production after the three-hour exposure was measured by radioimmunoassay. Aminoglutethimide was used as a positive control, and the experiment was conducted in triplicate.

A statistical reduction in basal testosterone production of 56% and 76%, compared to controls, was observed at 50 and 100 mM methyl t-butyl ether, respectively. A statistical reduction in human Chorionic Gonadotropin-stimulated testosterone production of 51% and 60%, compared to controls, was observed at 50 and 100 mM methyl t-butyl ether, respectively. T-butanol induced a statistical reduction in basal testosterone production of 72% and 66% at 50 mM and 100 mM compared to controls, respectively. T-butanol induced a statistical reduction in human Chorionic Gonadotropin-stimulated testosterone production of 73% and 83% at 50 mM and 100 mM compared to controls, respectively. The positive control, aminoglutethimide (5 mM) induced a statistical reduction of basal and human Chorionic Gonadotropin-stimulated testosterone production of 80% and 75% compared to controls, respectively.

In a 14- and 90-day systemic gavage study in Sprague-Dawley rats by Robinson et al. (1990), effects on ovary weight and histology and testes weight and histology were examined, and no effects were reported.

8.6.2 Developmental Toxicity Studies

No oral developmental studies were identified for methyl t-butyl ether.

8.7 Studies of Immunological and Neurological Effects

No standardized immunological or neurological assays were identified for methyl t-butyl ether, but some immunological or neurological effects have been reported in systemic studies for methyl t-butyl ether. Reported immunological effects were limited to reduced circulating corticosterone levels and thyroid weights in rats after short-term gavage exposures. Reported neurological effects were limited to transitory salivation after a single gavage dose of 90 mg/kg-day and higher and transitory hypoactivity and/or ataxia at higher doses in rats.

8.7.1 Immunological Effects

Twelve male Sprague-Dawley rats per dose were administered methyl t-butyl ether (> 99.8% purity in corn oil) via gavage at 0, 1,000, or 1,500 mg/kg every other day for a total of 14 doses over 28 days (de Peyster et al., 2003). After an adjustment of doses due to excess weight loss, the terminal doses were approximately equivalent to 0, 357, or 536 mg/kg-day. Terminal corticosterone was measured on Day 1, 14, and 28. Mean corticosterone levels on Day 1, 14, and 28 were not statistically different compared to controls, but the sample size was only about 4-5 rats per dose, due to other analyses concurrently requiring blood volume.

Twelve male Sprague-Dawley rats per dose were administered methyl t-butyl ether (> 99.8% purity in corn oil) via gavage at 0, 40, 400, or 800 mg/kg-day for 28 days (de Peyster et al., 2003). Corticosterone concentrations were measured on Day 1 and 14 (tail blood) and 28 (trunk). Thyroid weights were measured, and mean organ-to-body and brain weight ratios were calculated.

At 40 mg/kg-day, mean plasma corticosterone was statistically reduced by 28% compared to controls on Day 14, but the corticosterone was not statistically different from controls at study termination.

At 400 mg/kg-day, mean plasma corticosterone was statistically reduced by 42% compared to controls on Day 14, but the corticosterone was not statistically different from controls at study termination.

At 800 mg/kg-day, mean plasma corticosterone was statistically reduced by 43% compared to controls on Day 14. At study termination, mean plasma corticosterone was statistically reduced by 44% compared to controls. The mean thyroid-to-body- weight ratio was statisrically reduced by 29% compared to controls.

In a 14-day and 90-day systemic gavage study in Sprague-Dawley rats by Robinson et al. (1990), effects on spleen and thymus weight and histology were examined, and no effects were reported. Although some statistical reductions in monocyte differential counts were observed, the effect was not dose- or duration-related and did not occur in both sexes.

In a 28-day gavage study by Lee et al. (1998), methyl t-butyl ether (unspecified purity in corn oil) was administered to male Sprague-Dawley rats at 0, 40, 400, or 800 mg/kg-day via gavage. At 800 mg/kg-day, high corticosterone levels were observed, but the magnitude and statistical

significance were not specified. Limited details were available in this published abstract and a full publication was not located.

8.7.2 Neurological Effects

In rats, reported neurological effects were limited to transitory salivation reported after a single gavage dose of 90 mg/kg-day and higher and transitory hypoactivity and/or ataxia at higher doses (Johnson et al., 1992).

Martin et al. (2002) studied the effect of 200 and 400 mM methyl t-butyl ether (unspecified purity) on binding at the gamma-aminobutyric acid receptor site in cerebral cortex membrane preparations isolated from male Sprague-Dawley rats. The gamma-aminobutyric acid receptor was probed using the ^{3}H-t-butylbicycloorthobenzoate, which binds to the convulsant recognition site of the receptor. The experiment was conducted in triplicate.

The 50% inhibitory concentration (IC_{50}) of methyl t-butyl ether and its metabolite, t-butanol, on the binding of ^{3}H-t-butylbicycloorthobenzoate at the gamma-aminobutyric acid(A) receptor site was 120 and 69 mM, respectively. In additional saturation binding assays, 200 and 400 mM methyl t-butyl ether statistically reduced apparent density of convulsant binding, or B_{max}, to 36 and 17% of the control value, respectively. The study authors suggested that their results indicate that direct effects on the gamma-aminobutyric acid(A) receptor site by methyl t-butyl ether or its metabolite t-butanol could explain some of the neurotoxicological or neurobehavioral effects observed after methyl t-butyl ether exposures in humans and laboratory animals.

9.0 RISK CHARACTERIZATION

9.1 *Hazard Identification*

Oral LOAEL and NOAEL values from the animal studies reviewed are shown in Table 2.

9.1.1 Evaluation of Major Non-Cancer Effects and Mode of Action

9.1.1.1 Major Non-Cancer Effects

The scientific literature for methyl t-butyl ether in humans and laboratory animals has been reviewed extensively by several national and international regulatory agencies, including the European Chemicals Bureau (ECB, 2002), Office of Environmental Health Hazard Assessment of the California EPA (OEHHA, 1999), the International Agency for Research on Cancer (IARC, 1999), the International Programme on Chemical Safety of the World Health Organization (IPCS, 1998), the European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC, 1997), the Agency for Toxic Substances and Disease Registry (ATSDR, 1996), and Health Canada (1992). Thus, this risk assessment to determine drinking water action levels for methyl t-butyl ether focuses mainly on the oral exposure studies included in these reviews or that have been published since these reviews.

1 Table 2. Summary of non-cancer LOAEL and NOAEL values from repeated-dose oral studies with methyl t-butyl ether
2

Study Type (Species)	Route of Exposure	NOAEL mg/kg-day	LOAEL mg/kg-day	Non-Cancer Biological Effect(s)	Reference
Two-Week (Sprague-Dawley Rat)	Gavage	None (Females) 357 (Males)	357 (Females) 714 (Males)	↓ mean absolute and relative lung weights in male and female rats and altered clinical parameters in male rats. Limited endpoints evaluated.	Robinson et al., 1990
Two-Week (Sprague-Dawley Rat)	Gavage	800 (Males only)	None (Males only)	No effect on hepatic clinical chemistry or peroxisomal proliferation. Limited endpoints evaluated.	DePeyster et al., 2003
Three-Week (CD-1 Mouse)	Gavage	714[a]	None	No effects on body weight or reproductive parameters (sperm number, Sertoli cells, spermatogonia, spermatocytes, and capped spermatids in males and oocyte quality in females). Limited endpoints evaluated.	Ward et al., 1994[b]; 1995[b]
Four-Week (Sprague-Dawley Rat)	Gavage	250 (Males only)	500 (Males only)	↑ mean relative liver weight and minimal-to-moderate centrilobular hypertrophy. ↑ mean relative kidney weight and protein droplet nephropathy in renal tubules. Limited endpoints evaluated.	Williams and Borghoff, 2000; Williams et al., 2000
Four-Week (Sprague-Dawley Rat)	Gavage	314 (Males and Females)[a]	1,250 (Males and Females)[a]	↑ mean cholesterol and relative liver weight. Gastric inflammation, edema, hyperplasia, and ulcers. ↑ mean relative kidney weight and hyaline droplet formation in renal tubules of males. Limited endpoints evaluated.	Johnson et al., 1992; Klan et al., 1992
Four-Week (Sprague-Dawley Rat)	Gavage	357 (Males only)	536 (Males only)	↓ circulating testosterone concentration immediately following dosing; ↑ mean liver P450 content. Limited endpoints evaluated.	DePeyster et al., 2003
Four-Week (Sprague-Dawley Rat)	Gavage	400 (Males only)	800 (Males only)	↓ body weight and ↓ plasma testosterone and corticosterone. Limited endpoints evaluated.	DePeyster et al., 2003; Day et al., 1998
Four-Week (Sprague-Dawley Rat)	Gavage	None (Males only)	1,200 (Males only)	↑ mean relative liver weight, ↓ mean testosterone and luteinizing hormone, ↑ mean estradiol, ↓ hepatic and testicular microsomal aromatase activity. Limited endpoints evaluated.	DePeyster et al., 2003
13-Week (Sprague-Dawley Rat)	Gavage	None (Males only)	143 (Males only)[a]	↑ liver weights and aspartate aminotransferase, hepatic nuclear condensation, fat droplets, lysosome appearance in cells, and smooth endoplasmic reticulum disintegration. Limited endpoints evaluated.	Zhou and Ye, 1999
13-Week (Sprague-Dawley Rat)	Gavage	None (Males and Females)	100 (Males and Females)	↓ blood urea nitrogen in males and females. Limited endpoints evaluated.	Robinson et al., 1990

Study Type (Species)	Route of Exposure	NOAEL mg/kg-day	LOAEL mg/kg-day	Non-Cancer Biological Effect(s)	Reference
104-Week (Sprague-Dawley Rat)	Gavage	Not determined		Although study authors reported "no treatment-related nononcological pathological changes were detected by gross inspection and histological examination," data were not provided. Limited endpoints evaluated (no hematology, clinical chemistry, or urinalysis).	Belpoggi et al., 1995; 1997; 1998

[a] Doses were adjusted to account for a less than 7-day dosing regimen.
[b] Study not available, and thus as cited in OEHHA (1999) and ATSDR (1996).

No evidence of hepatic peroxisome proliferation was observed in male rats administered methyl t-butyl ether via gavage at 800 mg/kg-day for 14 days (de Peyster et al., 2003), but increased mean relative liver weight and minimal-to-moderate centrilobular hypertrophy were observed in male rats administered methyl t-butyl ether via gavage at 1,000 mg/kg-day and above for 28 days (Williams and Borghoff, 2000; Williams et al., 2000). In male and female rats administered high doses of methyl t-butyl ether (1,250 mg/kg-day) via gavage for 28 days, statistically increased cholesterol levels of at least 20% compared to controls were observed (Johnson et al., 1992).

Short-term and subchronic gavage exposures to methyl t-butyl ether were associated with increased mean absolute and relative kidney weights in male rats accompanied by hyaline droplet formation in the renal proximal tubules. In male and female rats administered methyl t-butyl ether at 100 mg/kg-day and above via gavage for 13 weeks, statistically increased mean blood urea nitrogen levels of at least 15% compared to controls were observed (Robinson et al., 1990). Statistically increased liver weights and aspartate aminotransferase, along with hepatic nuclear condensation, fat droplets, lysosome appearance in hepatocytes, and smooth endoplasmic reticulum disintegration were observed after subchronic gavage doses of 143 mg/kg-day and higher (Zhou and Ye, 1999). After chronic gavage exposure to methyl t-butyl ether at doses up to 571 mg/kg-day, Belpoggi et al. (1995) reported that "no treatment-related nononcological pathological changes were detected by gross inspection and histological examination". However, the data were not provided. Thus, increases in liver weight, aspartate aminotransferase, blood urea nitrogen, and cholesterol and the centrilobular hepatocyte hypertrophy observed in rats after short-term and subchronic oral exposures to methyl t-butyl ether could not be critically assessed following chronic oral exposures.

No *in vivo* oral two-generation reproduction or developmental studies were identified for methyl t-butyl ether. Reproductive effects in male rats have been investigated in non-standardized reproduction studies. A single gavage dose of methyl t-butyl ether at approximately 500 mg/kg-day resulted in reduced circulating testosterone in male rats during the hours immediately following dosing (de Peyster et al., 2003). In male rats treated with 1,200 mg/kg-day methyl t-butyl ether for 14 days, decreased mean testosterone and luteinizing hormone and increased estradiol were observed, along with decreased testicular microsomal aromatase activity (de Peyster et al., 2003). Repeated exposure to 800 mg/kg-day methyl t-butyl ether via gavage in male rats was associated with statistical reductions in circulating testosterone after 28 days (de Peyster et al., 2003). High doses (> 50 mM) of methyl t-butyl ether were also found to reduce basal and human Chorionic Gonadotropin (hCG)-stimulated testosterone production in Leydig cells *in vitro*.

No standardized immunological or neurological assays were identified for methyl t-butyl ether, but some immunological or neurological effects have been reported in systemic studies for methyl t-butyl ether. Reported immunological effects were limited to reduced circulating corticosterone levels and thyroid weights in rats after short-term gavage exposures. Studies for other chemicals have demonstrated that the effects of a chemical stressor on selected immunological parameters can be predicted on the basis of the area under the corticosterone concentration versus time curve (Pruett et al., 2003). Reported neurological effects were limited

to transitory salivation after a single gavage dose of 90 mg/kg-day and higher and transitory hypoactivity and/or ataxia at higher doses in rats.

9.1.1.2 Mode of Action (Non-Cancer Effects)

In vivo and *in vitro* assays by de Peyster et al. (2003) demonstrated that single and repeated gavage exposures to methyl t-butyl ether can reduce circulating testosterone levels. Williams and Borghoff (2000) demonstrated that methyl t-butyl ether induced mild increases in testosterone hydroxylase enzymes. Further, increases in UDP-glucuronosyltransferase observed were consistent with the centrilobular hypertrophy observed in rodents after repeated methyl t-butyl ether exposures. Collectively, the study authors suggested that the decrease in serum testosterone observed following methyl t-butyl ether administration might be the result of enhanced testosterone metabolism and subsequent clearance.

No evidence of hepatic peroxisome proliferation was observed in male rats administered methyl t-butyl ether via gavage at 800 mg/kg-day for 14 days (de Peyster et al., 2003). Hepatic nuclear condensation, fat droplets, lysosome appearance in hepatocytes, and smooth endoplasmic reticulum disintegration were observed after subchronic gavage doses of 143 mg/kg-day and higher (Zhou and Ye, 1999). Recent *in vivo* metabolism data indicate that oral exposure to methyl t-butyl ether induces various CYP450 isozymes. Thus, based on the CYP450 data and the lack of reported hepatic histopathology in the chronic gavage study by Belpoggi et al. (1995), the weight of evidence with respect to hepatotoxicity suggests that although methyl t-butyl ether induces various CYP450 isozymes, which may lead to centrilobular hepatocyte hypertrophy, the effect does not progress upon chronic oral exposure. The effects are likely an adaptive mechanism by the liver to metabolizing high doses of methyl t-butyl ether and are likely reversible upon discontinuation of exposure. However, it must be noted that a critical assessment of the progression of the liver effects from short-term or subchronic-to-chronic exposures could not be made, since the non-neoplastic data from Belpoggi et al. (1995) were not available for review, although the authors indicated that no non-neoplastic effects were observed. ECB (2002) concluded that the liver weight increases, hepatic hypertrophy, and changes in smooth endoplasmic reticulum observed after repeated oral exposures to methyl t-butyl ether are typical of other chemicals that are considered to cause adaptive, but reversible, responses by the liver in order to metabolize the chemical.

All investigations on nephrotoxicity associated with methyl t-butyl ether exposure in laboratory rats are consistent with ∀-2μ-globulin nephropathy (IPCS, 1998). ∀-2μ-Globulin nephropathy is considered an effect specific to male rats and, therefore, of questionable relevance to humans.

9.1.2 Weight-of-Evidence Evaluation and Cancer Characterization

Chronic gavage exposure to methyl t-butyl ether was associated with an increase in Leydig cell tumors in male rats and leukemias/lymphomas (combined) in female rats (Belpoggi et al., 1995; 1997; 1998). Although there are no chronic data in humans, there is "*suggestive evidence of carcinogenic potential*" after chronic oral exposure to methyl t-butyl ether in rats.

The genotoxicity data for methyl t-butyl ether have been critically reviewed by ECB (2002), OEHHA (1999), IPCS (1998), ECETOC (1997), and ATSDR (1996). The weight of evidence suggests that methyl t-butyl ether has some genotoxic potential. Methyl t-butyl ether has been tested in mutagenicity, chromosomal aberration, micronucleus, sister chromatid exchange, DNA damage and repair, and DNA strand break assays *in vivo* and/or *in vitro*. Methyl t-butyl ether was not mutagenic in several *Salmonella* reverse mutation assays, although one assay was positive in TA102. Subsequently, a well-conducted study failed to replicate the positive result for methyl t-butyl ether in *Salmonella* TA102 (McGregor et al., 2005). Methyl t-butyl ether was also positive in a mouse lymphoma cell forward mutation assay, possibly due to the metabolism of methyl t-butyl ether to formaldehyde. Methyl t-butyl ether was negative in *in vivo* and *in vitro* chromosomal aberration assays, but equivocal results were observed in a sister chromatid exchange assay *in vitro*. Methyl t-butyl ether was negative in *in vivo* and *in vitro* mouse micronucleus assays and unscheduled DNA synthesis assays, and an *in vivo* DNA repair assay, although methyl t-butyl ether was positive in a DNA strand break assay in rat lymphocytes *in vivo* and in human lymphocytes *in vitro* (Chen et al., 2007). DNA adduct formation was observed in mice given a single gavage dose of methyl t-butyl ether (Du et al., 2005; Yuan et al., 2007).

9.1.3 Mode of Action (Carcinogenic Effects)

The mode of action of the Leydig cell tumors in rats is unclear. There are plausible mechanisms for the chemical induction of Leydig cell tumors, as typified by agonists of estrogen, gonadotropin releasing hormone (GnRH), and dopamine receptors, androgen receptor antagonists, and inhibitors of 5α-reductase, testosterone biosynthesis, and aromatase (Cook et al., 1999). Most of these ultimately involve elevation in serum luteinizing hormone and/or Leydig cell responsiveness to luteinizing hormone. The pathways for regulation of the hypothalamo-pituitary-testis axis of rats and humans are similar, such that compounds that either decrease testosterone or estradiol levels or their recognition will increase luteinizing hormone levels.

Compounds that induce Leydig cell tumors in rats by disruption of the hypothalamo-pituitary-testis axis pose a risk to human health (Cook et al., 1999). However, several lines of evidence suggest that human Leydig cells are quantitatively less sensitive than rats in their proliferative response to luteinizing hormone, and hence in their sensitivity to chemically induced Leydig cell tumors (Cook et al., 1999). This evidence includes the following: (1) the human incidence of Leydig cell tumors is much lower than in rodents even when corrected for detection bias; (2) several comparative differences exist between rat and human Leydig cells that may contribute, at least in part, to the greater susceptibility of the rat to both spontaneous and xenobiotic-induced Leydig cell tumors; (3) endocrine disease states in humans (such as androgen-insensitivity syndrome and familial male precocious puberty) underscore the marked comparative differences that exist between rats and humans in the responsiveness of their Leydig cells to proliferative stimuli; and (4) several human epidemiology studies are available on a number of compounds that induce Leydig cell tumors in rats, such as 1,3-butadiene, cadmium, ethanol, lactose, lead, and nicotine, and that demonstrate no association between human exposure to these compounds and induction of Leydig cell hyperplasia or adenomas (Cook et al., 1999).

Although endocrine-mediated modes of action have been suggested for the induction of testicular tumors by methyl t-butyl ether in rats, OEHHA (1999) and ECB (2002) felt there were insufficient data to support these hypotheses. Based on the available evidence, it seems that the typical mode of action for Leydig cell tumors, which involves elevated luteinizing hormone, is not the case for methyl t-butyl ether (ECB, 2002). Further, testicular cancer is a relatively uncommon cancer in humans. Most human testicular cancers originate either from germ or from Sertoli cells. Tumors of the testes constitute about 1% of all human neoplasm; only 2-3% of all testicular tumors are of Leydig cell origin. Further, methyl t-butyl ether-induced Leydig cell tumors appear in rats only at high doses. ECB (2002) concluded that no definitive conclusion could be drawn about the relevance of the Leydig tumors to humans due to the lack of knowledge of the possible mode of action. Considering all the available data, the relevance to man was not considered very significant by ECB (2002).

In the chronic gavage study by Belpoggi et al. (1995), a reduced incidence of mammary tumors was reported. Such a tumor profile in male and female rats would suggest reduced serum estradiol levels or reduced prolaction secretion, which would cause luteinizing hormone-receptor down-regulation and a subsequent increase in luteinizing hormone (Cook et al., 1999). However, prolactin receptors are either not expressed or are expressed at very low levels in the testes in humans, and thus the induction of Leydig cell tumors in rats by dopamine agonists would appear not to be relevant to humans (Cook et al. 1999).

Methyl t-butyl ether induced mild increases in testosterone hydroxylase enzymes, suggesting that the decrease in serum testosterone observed following repeated oral exposures to methyl t-butyl ether in rats might be the result of enhanced testosterone metabolism and subsequent clearance. Williams et al. (2000) reported decreased serum testosterone and luteinizing hormone after 15- but not 28-day gavage exposures to methyl t-butyl ether, but concluded that these changes in hormone levels did not fit the pattern caused by known Leydig cell tumorigens.

Peroxisome proliferating chemicals have also been known to cause Leydig cell tumors (Klaunig et al., 2003). Peroxisome proliferating chemicals are nongenotoxic carcinogens that mediate their actions through the peroxisome proliferator receptor α. Klaunig et al. (2003) postulated that one mechanism of Leydig cell tumorigenesis begins with peroxisome proliferator receptor α activation in the liver, followed by two possible pathways--one secondary to liver induction and the other direct inhibition of testicular testosterone biosynthesis. Both proposed pathways involved changes in the metabolism and quantity of related hormones and hormone precursors. Klaunig et al. (2003) however, noted that rodents are more responsive than primates in their response to peroxisome proliferators *in vivo*. When de Peyster et al. (2003) administered methyl t-butyl ether at 800 mg/kg-day to rats for two weeks, no effects on hepatic clinical chemistry or peroxisomal proliferation were observed.

The mode of action of the lymphohematopoietic cancers observed in female rats after chronic gavage exposures is unknown. However, the proposed metabolite of methyl t-butyl ether, formaldehyde, has also produced lymphohematopoietic cancers in Sprague-Dawley rats exposed orally (OEHHA, 1998).

9.1.4 Selection of Key Study and Critical Effect

The key study was considered the chronic gavage study by Belpoggi et al. (1995) in which Leydig cell tumors in male rats and hemolymphoreticular leukemias/lymphomas (combined) in female rats were observed at statistically increased incidence compared to controls. Although the study did not meet current U.S. EPA (2007b) Health Effects Testing Guidelines and the study results may have been confounded by early mortality in control and treated rats, it was considered to be adequate for use in a lifetime oral risk assessment for methyl t-butyl ether, since it was conducted by the most appropriate route and duration for a lifetime oral risk assessment for methyl t-butyl ether.

Carcinogenicity of methyl t-butyl ether has been observed after oral and inhalation administration in laboratory animals. Other than the tumors observed in Sprague-Dawley rats from the chronic gavage study by Belpoggi et al. (1995; 1997; 1998), renal tubular tumors and Leydig interstitial cell tumors were observed in male Fischer 344 rats in a 24-month inhalation study (Chun et al., 1992; Bird et al., 1997), and hepatocellular adenomas and/or carcinomas were observed in male and female CD-1 mice in an 18-month inhalation study (Burleigh-Flayer et al., 1992; Bird et al., 1997). The leukemia/lymphomas were not observed consistently in the after inhalation exposure in rats (IPCS, 1998). Increases in Leydig cell tumors occurred at the highest gavage dose (537 mg/kg-day) in Sprague-Dawley rats, but interpretation of the increases in Fischer-344 rats after inhalation exposure was complicated by the very high concurrent and historical control incidences (IPCS, 1998).

The historical control incidence of Leydig cell tumors from studies conducted by Belpoggi were not reported. The historical control incidence of Leydig cell tumors in male rats of various strains has been reported by Cook et al. (1999). In male Sprague-Dawley rats, Leydig cell adenomas were observed in 16/349 (4.8%) of control rats in studies terminated at 24 months (Cook et al., 1999). Other laboratories using Sprague-Dawley rats in 24-month studies have reported historical control incidences of 11/340 (0.8%) and 1/340 (0.1%) for Leydig cell adenomas and carcinomas, respectively (Cook et al., 1999). The route of administration for these studies was not indicated. These historical control incidences are below those observed in control, low- and high-dose males from the Belpoggi et al. (1995) gavage study with methyl t-butyl ether (12, 20, and 34%, respectively).

In male Fischer 344 rats, Leydig cell adenomas were observed in 39,253/51,230 (76.6%) of control rats in studies terminated at 24 months (Cook et al., 1999). The route of administration for these studies was not indicated. This incidence is similar to those observed in control, low-, mid- and high-dose males from the 24-month inhalation study with methyl t-butyl ether (Chun et al., 1992; Bird et al., 1997) (64, 70, 82, and 94%, respectively).

The historical control incidence for lymphomas and leukemias (combined) in the Belpoggi laboratory was reported to be less than 10% in female Sprague-Dawley rats (Belpoggi et al., 1995). This historical control incidence is below the incidence of lymphomas and leukemias (combined) observed in control, low- and high-dose females from the Belpoggi et al. (1995) study with methyl t-butyl ether (3, 14, and 26%, respectively).

In the Belpoggi et al. (1995) study, the animals were observed until natural death, although treatment ended at 104 weeks. Survival at 104 weeks was less than 50%, which is the minimum recommended survival rate according to current U.S. EPA (2007b) Health Effects Testing Guidelines. Survival at the end of treatment was 35% and 28% in low- and high-dose females, respectively, compared to 48% in controls. Survival at the end of treatment was 30% and 42% in low- and high-dose males, respectively, compared to 30% in controls. Further, this study does not meet current U.S. EPA (2007b) Health Effects Testing Guidelines since the dosing occurred on a four-day per week schedule and no results for hematology, clinical chemistry, urinalysis, or organ weights were reported.

Recognizing the deficiencies in the Belpoggi et al. (1995) study, using a chronic oral study to estimate lifetime cancer risk from oral exposure to methyl t-butyl ether was considered more appropriate than using a chronic inhalation study and conducting an inhalation-route-to-oral-route extrapolation to estimate a lifetime cancer risk from oral exposure to methyl t-butyl ether. Further, the historical control incidences for Leydig cell adenomas as reported by Cook et al. (1999) were well below those observed in control, low- and high-dose males from the Belpoggi et al. (1995) gavage study. Likewise, the historical control incidence for lymphomas and leukemias (combined) in the Belpoggi laboratory were below those observed in control, low- and high-dose females from the Belpoggi et al. (1995) gavage study with methyl t-butyl ether. However, as reported by IPCS (1998), the diagnostic criteria for the distinction between Leydig cell tumors and hyperplasia were not indicated by Belpoggi et al. (1995; 1997; 1998), and the latter were not reported at all, which was considered unusual by IPCS (1998) for old Sprague-Dawley rats showing Leydig cell tumors.

9.1.5 Identification of Susceptible Populations

There are no data by which to identify any subpopulations (e.g., the elderly, pregnant women, children, or people with allergies or asthma) that might be at special risk to methyl t-butyl ether exposure (IPCS, 1998).

9.2 Dose-Response Assessment

For the dose-response assessment, the statistical 95% lower confidence limit of the 10% effect level, also known as the $BMDL_{10}$, was estimated using default settings in the Benchmark Dose Program (Version 1.4.1c, U.S. EPA, 2007a). In the Belpoggi et al. (1995; 1997; 1998) study, Sprague-Dawley rats were administered methyl t-butyl ether via gavage at 0, 250, or 1,000 mg/kg-day for four days a week for 24 months. These doses were approximately equivalent to daily doses of 0, 143, or 571 mg/kg-day. In male rats, the incidence of Leydig cell tumors was statistically increased at the high dose compared to the controls, and there was a statistically significant dose-related trend at the mid and high dose. In female rats, the combined incidence of lymphomas and leukemias was statistically increased at the high dose compared to the controls, and there was a statistically significant dose-related trend at the mid- and high-dose.

9.2.1 Dose-response assessment based on tumor data in male rats

The administered doses in male rats were converted to human equivalent doses of 0, 42.5, or 170 mg/kg-day, based on the following equation.

$$\text{Human Equivalent Dose} = \text{dose (mg/kg-day)} \times (\text{kg wt. rat}/70 \text{ kg wt. human})^{0.25}$$

Mean terminal body weight for low-dose male Sprague-Dawley rats from Belpoggi et al. (1995; 1997; 1998) = 0.550 kg (data not provided; estimated from graph at 104 weeks, time at which dosing ended, although animals were observed until natural death). Mean terminal body weight for high-dose male Sprague-Dawley rats from Belpoggi et al. (1995; 1997; 1998) = 0.550 kg (data not provided; estimated from graph at 104 weeks, time at which dosing ended, although animals were observed until natural death). In male rats, the incidence of Leydig cell tumors was statistically increased at the high dose compared to the controls (Table 3).

Table 3. Leydig cell tumors in male rats after chronic gavage exposure to methyl t-butyl ether (Belpoggi et al., 1995; 1997; 1998)

methyl t-butyl ether dose (mg/kg-day; human equivalent dose)	Incidence of Leydig cell tumors[a]	Incidence of Leydig cell tumors[b]
0	3/26 (12%)	3/37.8 (8%)
42.5	5/25 (20%)	5/37.6 (13%)
170	11/32 (34%)*	11/40.4 (27%)

[a] Number of rats affected/number surviving at appearance of first tumor (96 weeks) based on Belpoggi et al. (1995, 1998)
[b] Number of rats affected/effective number at risk after Poly-3 adjustment for survival based on Kippling et al. (2007)
* $p<0.05$

Since there was a statistically significant dose-related trend at the mid- and high-dose, a benchmark dose level at the lower 95% confidence interval (BMDL) for methyl t-butyl ether will be determined based on the incidence of Leydig cell tumors in male rats. The $BMDL_{10}$ was defined as the lower 95% confidence interval of the dose at which one could expect a 10% increased incidence in a given population (Table 4).

Table 4. Results of benchmark dose modeling of Leydig cell tumors from male rats (all alive at 96 weeks, first observed tumor)

Model	P value	AIC	Chi square residuals	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma	0.8224	88.8501	-0.107, 0.187, -0.063	60	32
Logistic	0.6578	88.9955	-0.278, 0.340, -0.060	83	56
Multistage[1]	NA	90.8002	0, 0, 0	45	12
Probit	0.6760	88.9739	-0.256, 0.324, -0.063	80	53
Quantal Linear/Weibull[2]	0.8224	88.8501	-0.107, 0.187, -0.063	60	32

P value = Global measurement of goodness-of-fit (P > 0.1)
AIC (Akaike's Information Criterion) = Model comparison (lowest value preferred)
Chi square = Local measurement of goodness-of-fit (< ±2.0).
[1] Multistage Cancer BMDU = 279 mg/kg-day (restrict beta) and Cancer Slope Factor = 0.0032
[2] BMD program defaulted Quantal Linear model to Weibull model

The Gamma, Quantal Linear and Weibull models provided the best fit, based on the highest p value, lowest AIC value, local Chi^2 values of less than the absolute value of two for all data points, and a good fit of both the BMD and BMDL dose-response plots (see Appendix). The calculated BMD (60 mg/kg-day) and BMDL (32 mg/kg-day) were in close approximation of each other.

9.2.2 Dose-response assessment based on tumor data in female rats

Alternately, the $BMDL_{10}$ for methyl t-butyl ether can be calculated based on the combined incidence of lymphomas and leukemias in female rats from the Belpoggi et al. (1995; 1997; 1998) study. The doses were equivalent to human oral doses of 0, 38.7, or 152 mg/kg-day, based on the following equation.

$$\text{Human Equivalent Dose} = \text{dose (mg/kg-day)} \times (\text{kg wt. rat}/70 \text{ kg wt. human})^{0.25}$$

Mean terminal body weight for low-dose female Sprague-Dawley rats from Belpoggi et al. (1995; 1997; 1998) = 0.375 kg (data not provided; estimated from graph at 104 weeks, time at which dosing ended, although animals were observed until natural death). Mean terminal body weight for high-dose female Sprague-Dawley rats from Belpoggi et al. (1995; 1997; 1998) = 0.355 kg (data not provided; estimated from graph at 104 weeks, time at which dosing ended, although animals were observed until natural death). In female rats, the combined incidence of lymphomas and leukemias was statistically increased at the high dose compared to the controls (Table 5).

Table 5. Combined incidence of hemolymphoreticular lymphomas and leukemias in female rats after chronic gavage exposure to methyl t-butyl ether (Belpoggi et al., 1995; 1997; 1998)

methyl t-butyl ether dose (mg/kg-day human equivalent dose)	Incidence of hemolymphoreticular lymphomas and leukemias[a]
0	2/58 (3%)
38.7	7/51 (14%)
152	12/47 (26%)[b]

[a] Number of rats affected/number surviving at appearance of first tumor (56 weeks)
[b] $p<0.05$

Since there was a statistically significant dose-related trend at the mid- and high-dose, a benchmark dose level at the lower 95% confidence interval ($BMDL_{10}$) for methyl t-butyl ether will be determined based on the combined incidence of lymphomas and leukemias in female rats (Table 6).

Table 6. Results of benchmark dose modeling of hemolymphoreticular lymphomas and leukemias from female rats (all alive at 56 weeks, first observed tumor)

Model	P value	AIC	Chi square residuals	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma	0.4246	116.208	-0.284, 0.675, -0.318	57	36
Logistic	0.1604	117.587	-0.894, 1.066, -0.186	91	70
Multistage[1]	NA	117.596	0, 0, -0	36	16
Probit	0.1779	117.413	-0.831, 1.039, -0.213	87	65
Quantal Linear/Weibull[2]	0.4246	116.208	-0.284, 0.675, -0.318	57	36

P value = Global measurement of goodness-of-fit (P > 0.1)
AIC (Akaike's Information Criterion) = Model comparison (lowest value preferred)
Chi square = Local measurement of goodness-of-fit (< |2.0|).
[1] Multistage Cancer BMDU = 279 mg/kg-day (restrict beta) and Cancer Slope Factor = 0.0032
[2] BMD program defaulted Quantal Linear model to Weibull model

The Gamma, Quantal Linear and Weibull models provided the best fit, based on the highest p value, lowest AIC value, local Chi^2 values of less than the absolute value of two for all data points, and a good fit of both the BMD and BMDL dose-response plots (see Appendix). The calculated BMD (57 mg/kg-day) and BMDL (36 mg/kg-day) were in close approximation of each other.

4.2.3 Oral Slope Factor Calculation

Formatted: Bullets and Numbering

There were insufficient data to support a mode of action for the Leydig cell or lymphatic tumors. In the absence of mode of action information, the U.S. EPA (2003) generally takes a conservative, or public health-protective, default position regarding the interpretation of toxicological data. This conservative approach assumes that the animal tumor findings are relevant to humans and that cancer risks are assumed to conform with low dose linearity (U.S. EPA, 2003). Elucidation of a mode of action for a particular cancer response in animals or humans is a data-rich determination. Significant information should be developed to ensure that a mode of action underlies the process leading to cancer at a given site (U.S. EPA, 2003). Based on this approach, both the lymphatic and Leydig cell tumors in rats were assumed to be relevant to humans and the associated cancer risks were assumed to conform to low dose linearity. Thus, a 10^{-5} risk level will be calculated for methyl t-butyl ether based on the $BMDL_{10}$ of 32 mg/kg-day (the lower of the two $BMDL_{10}$ values, recognizing that they were both essentially the same). The slope of the dose-response line, known as the slope factor, is an upper-bound estimate of risk per increment of dose that can be used to estimate risk probabilities for different exposure levels (U.S. EPA, 2003c). The slope factor is equal to $0.01/LED_{01}$ if the LED_{01} is used as the point of departure (U.S. EPA, 2003c). Since the 10% benchmark dose level was used in this risk assessment, then the oral slope factor was determined according to the following equation.

$$\text{Oral Slope Factor} = \frac{0.1}{BMDL_{10}}$$

$$\text{Oral Slope Factor} = \frac{0.1}{32 \text{ mg/kg-day}}$$

Oral Slope Factor = 0.003125 $(mg/kg\text{-}day)^{-1}$

The Cancer Slope Factor of 0.003125 $(mg/kg\text{-}day)^{-1}$ as estimated by NSF International is essentially the same as the Cancer Slope Factor of 0.0032 $(mg/kg\text{-}day)^{-1}$ estimated by the Multistage model of the Benchmark Dose Software Version 1.4.1c (U.S. EPA, 2007a). A 10^{-5} (or 1 in 100,000) cancer risk level can determined from the $BMDL_{10}$ according to the following linear extrapolation:

$$\frac{0.1}{BMDL_{10}} = \frac{0.00001}{10^{-5}\text{ risk level}}$$

$$\frac{0.1}{32\text{ mg/kg-day}} = \frac{0.00001}{10^{-5}\text{ risk level}}$$

$$10^{-5}\text{ risk level} = 0.003125\text{ mg/kg-day}$$

Formatted: Bullets and Numbering

Drinking Water Unit Risk Calculation

The unit risk, defined as the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L (U.S. EPA, 2003a), may be calculated from the slope factor. Risk-specific doses are derived from the slope factor or unit risk to estimate the dose associated with a specific risk level, for example, a one-in-a-million increased lifetime risk (U.S. E.P.A., 2003c). The unit risk is calculated from the slope factor using the default 70 kg body weight and 2 L/day drinking water consumption of an adult:

$$\text{Unit Risk} = \frac{0.003125\text{ kg-day}}{\text{mg}} \times \frac{1}{70\text{ kg}} \times \frac{2\text{ L}}{\text{day}} \times \frac{1\text{ mg}}{1{,}000\ \mu\text{g}} = 9.0 \times 10^{-8}\ (\mu g/L)^{-1}$$

$$= 0.009 \times 10^{-5}\ (\mu g/L)^{-1}$$

or

$$= 0.09 \times 10^{-6}\ (\mu g/L)^{-1}$$

Therefore, drinking water containing 1 µg/L of methyl t-butyl ether consumed for a lifetime is estimated to result in development of 0.009 excess tumors per 100,000 people, and drinking water containing 1 µg/L of methyl t-butyl ether consumed for a lifetime is estimated to result in development of 0.09 excess tumors per 1,000,000 people. Alternately, drinking water containing 90 µg/L of methyl t-butyl ether consumed for a lifetime is estimated to result in development of 1 excess tumor per 100,000 people, or drinking water containing 9 µg/L of methyl t-butyl ether consumed for a lifetime is estimated to result in development of 1 excess tumor per 1,000,000 people.

9.3 Exposure Assessment

The presence of methyl t-butyl ether in ambient air as a result of the manufacture and distribution of oxygenated fuel, vehicle refueling processes, and evaporative and tailpipe emissions from motor vehicles, is likely to be the principal source of human exposure (OEHHA, 1999). Methyl t-butyl ether is infrequently detected in public drinking water systems from groundwater (IPCS, 1998). There are inadequate data to characterize the concentration of methyl t-butyl ether in public drinking water systems from surface water. Methyl t-butyl ether has been found at high levels (i.e. ≥ 1,000 µg/L) in a few private wells used for drinking water (IPCS, 1998). Exposure of the public to methyl t-butyl ether can be principally by inhalation of fumes while refueling motor vehicles and drinking contaminated water (McGregor, 2006). Maximum internal doses resulting from such exposures are unlikely to exceed 0.05 mg/kg-day and will normally be very much lower.

9.4 TAC Derivation

The Total Allowable Concentration (TAC), is used to evaluate the results of extraction testing normalized to static at-the-tap conditions and is defined as the RfD multiplied by the 70 kg weight of an average adult assumed to drink two liters of water per day. A relative source contribution (RSC), applied when calculating a TAC for non-carcinogens, is used to ensure that the RfD is not exceeded when food and other non-water sources of exposure to the chemical are considered. Since the TAC value for methyl t-butyl ether is based on a carcinogenic endpoint, a RSC will not be applied. The TAC for methyl t-butyl ether will be set to the 10^{-5} cancer risk level for methyl t-butyl ether.

$$\text{TAC} = \frac{10^{-5}\ \text{risk level} \times 70\ \text{kg}}{2\ \text{L/day}}$$

$$= \frac{(0.003\ \text{mg/kg-day})(70\ \text{kg})}{2\ \text{L/day}}$$

$$= 0.105\ \text{mg/L}\ \textbf{(100 ppb rounded)}$$

9.5 STEL Derivation

NSF/ANSI 60 (2005) and 61 (2007) allow for the derivation and use of a STEL for materials that are initially present in potable water at relatively high concentrations, but rapidly decline in concentration because they are volatile or because they chemically or biologically degrade. The STEL is generally calculated from a repeated dose study in laboratory animals of 14 to 90 days in duration, adjusted for the default 10 kg body weight and 1 L/day drinking water consumption of a child. A product can initially contribute up to the STEL if the at-the-tap concentration decreases to a level at or below the TAC or SPAC within 90 days. Since methyl t-butyl ether is being evaluated as a genotoxic carcinogen, exposure to drinking water levels higher than the TAC, set at the 10^{-5} risk level, cannot be justified and it is not appropriate to derive a STEL for this chemical.

10.0 RISK MANAGEMENT

10.1 SPAC Derivation

The SPAC is set at the 10^{-6} cancer risk level of 0.01 mg/L (or 100 ppb) for methyl t-butyl ether. This is based on the default 10 sources of the chemical in the water distribution system in the absence of data on the actual number of sources.

11.0 RISK COMPARISONS AND CONCLUSIONS

The scientific literature for methyl t-butyl ether in humans and laboratory animals has been reviewed extensively by several national and international regulatory agencies. Table 7 provides a summary of the most recent and major reviews along with the major conclusions from each assessment regarding the non-cancer and cancer human health risks from exposure to methyl t-butyl ether.

Although the conclusions from the various agencies regarding non-cancer effects are largely in agreement with each other, the conclusions regarding the carcinogenic potential in rats after oral exposure are divergent. The American Conference of Governmental Industrial Hygienists (ACGIH, 2005) has classified methyl t-butyl ether as a Class A3: Animal Carcinogen. The International Agency for Research on Cancer (IARC) has reported that there is limited evidence in humans and in experimental animals for the carcinogenicity of methyl t-butyl ether. Thus, it was concluded by IARC (1999) that methyl t-butyl ether is not classifiable as to its carcinogenicity to humans (Group 3).

Based on a critical review of the genotoxicity data for methyl t-butyl ether, ECB (2002) concluded that methyl t-butyl ether cannot be considered a mutagen. OEHHA (1999) concluded that that the data are weak and there is no clear evidence that methyl t-butyl ether or its metabolites are involved in the carcinogenic response in laboratory animals. IPCS (1998) concluded that the weight of evidence suggests that methyl t-butyl ether is not genotoxic. ECETOC (2003 and 1997) concluded that genotoxicity of methyl t-butyl ether is unlikely to play a role in neoplastic findings reported in chronic studies with methyl t-butyl ether. Further, the inhaled concentrations causing neoplastic effects are equal to or greater than those inducing non-neoplastic effects in female mouse liver and male rat kidney. Thus, protection against non-neoplastic effects should also protect from any theoretical carcinogenic effect (ECETOC (2003).

1 **Table 7. Summary of international and national regulatory risk assessments or literature reviews for methyl t-butyl ether**
2

Organization/ Reference	Month/ Year	Conclusions from Non-Cancer Assessment of Oral Exposure	Conclusions from Cancer Assessment of Oral Exposure	Regulatory Risk Level Derived?
Caldwell et al. (2007)	12/2007	Not assessed	Hemolymphoreticular tumors of Belpoggi et al., (1995) were considered to be exposure-related and relevant to humans.	No
Cruzan et al. (2007)	2007	Not assessed	There were weak tumorigenic response in the testes and kidneys of male rats and liver in female mice. The weight of the evidence does not support a genotoxic mode of action. Non-genotoxic mode of actions have been demonstrated or suggested that correspond to the weak tumorigenic responses. These mode of actions either do not occur in humans or humans are much less susceptible to these. It is, therefore, unlikely that humans would be exposed to sufficient levels of methyl t-butyl ether to cause these tumorigenic responses.	No
McGregor, 2006	2006	Not assessed	Evidence for carcinogenicity in rodents of methyl t-butyl ether or it's metabolite t-butanol is unconvincing, with the strongest being for a low-level incidence of renal tubule-cell adenomas by a mechanism that is specific to male rats and has no human relevance.	No
American Conference of Governmental Industrial Hygienists (ACGIH, 2005)	2005	Reproductive and kidney effects were reported but not specified.	Classified methyl t-butyl ether as a Class A3: Animal Carcinogen (classification not route-specific)	No
National Institute of Public Health & Environmental Protection, The Netherlands (Baars, 2004; RIVM, 2004)	11/2004	RIVM (2004) adopted the conclusions of ECB (2002)		0.3 mg/kg-day tolerable daily intake (non-cancer)
European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC, 2003 and 1997)	12/2003 and 6/1997	Non-cancer conclusions of oral exposure were not indicated.	Methyl t-butyl ether was not considered carcinogenic. Rat Leydig cell tumors after chronic gavage were not considered predictive of hazard to humans. Further, the importance of the combined lymphoma/leukemia incidence from this study was considered to be unclear due to deficiencies in the study report.	No

Organization/ Reference	Month/ Year	Conclusions from Non-Cancer Assessment of Oral Exposure	Conclusions from Cancer Assessment of Oral Exposure	Regulatory Risk Level Derived?
European Chemicals Bureau (ECB, 2002)	9/2002	Based on the effects in the rat "liver" from the 90-day gavage study by Robinson et al. (1990), the subchronic NOAEL was considered 300 mg/kg-day. Note that it is presumed by the authors of this risk assessment that ECB (2002) was referring to the effects in the rat kidney, rather than liver. The chronic oral LOAEL was considered 250 mg/kg (or 143 mg/kg-day; see cancer assessment)	Due to lack of direct evidence of genotoxicity, the chronic oral LOAEL was considered 250 mg/kg (143 mg/kg-day) based on the Leydig cell tumors in male rats and lymphatic tumors in female rats, recognizing limitations and uncertainties due to the inadequacies of the chronic oral study by Belpoggi et al. (1995). The LOAEL of 250 mg/kg with a total daily uptake of 0.0021 mg/kg determined the margin of safety to be 125,000. Methyl t-butyl ether was considered borderline between a Carcinogen Category of 3 or non-classification.	No
International Agency for Research on Cancer (IARC, 1999)	9/1999	Not assessed.	Methyl t-butyl ether was tested for carcinogenicity in a non-standard protocol in rats by gavage. The incidences of Leydig-cell tumors of the testis in males and of lymphomas and leukemias combined in females were increased. There is *inadequate evidence* in humans for the carcinogenicity of methyl *t*-butyl ether. There is *limited evidence* in experimental animals for the carcinogenicity of methyl *t*-butyl ether (note that conclusions were not route-specific). Thus, methyl *t*-butyl ether is *not classifiable as to its carcinogenicity to humans (Group 3).*	No
California EPA Office of Environmental Health Hazard Assessment (OEHHA, 1999)	3/1999	Based on the effects in the rat kidney from the 90-day gavage study by Robinson et al. (1990), the oral NOAEL was considered 100 mg/kg-day. This study was used to determine a public health goal for non-cancer effects of 47 ppb in drinking water.	Methyl t-butyl ether is an animal carcinogen and possible human carcinogen (note that conclusion was not route-specific). The Belpoggi et al. (1995) study was determined to be adequate for risk assessment purposes. This study, along with two chronic inhalation studies, was used to determine a public health goal for cancer effects of 13 ppb in drinking water (based on 10^{-6} risk level and 3 L/day water intake).	47 ppb in drinking water (non-cancer); 13 ppb in drinking water (cancer)

Organization/ Reference	Month/ Year	Conclusions from Non-Cancer Assessment of Oral Exposure	Conclusions from Cancer Assessment of Oral Exposure	Regulatory Risk Level Derived?
WHO International Programme on Chemical Safety (IPCS, 1998)	1998	Based on the increased male absolute and relative kidney weight, chronic nephropathy, and increase in hyaline droplets in proximal tubular cells effects in the rat liver from the 90-day gavage study by Robinson et al. (1990), the subchronic oral NOAEL was considered 300 mg/kg. The chronic oral LOEL was considered 1,000 since no adverse non-neoplastic effects were reported by Belpoggi et al. (1995). A chronic NOAEL or LOAEL for non-cancer effects was not identified.	Leydig cell tumors in rats have been induced by non-genotoxic carcinogens that disturb the hormonal balance of testosterone, luteinizing hormone, and luteinizing hormone-releasing factor in rats. Owing to differences between rats and humans in the regulation of gonadotropins, it is questionable that a similar effect will occur in humans. Although such a mechanism may be relevant, this is not substantiated by experimental evidence, since these hormones were not determined in any of the studies with methyl t-butyl ether. In female rats, lymphomas and leukemias (combined) were increased. This observation was not supported by preneoplastic effects on the lymphoid system in other studies. Moreover, the study description made it difficult to evaluate adequately the results. However, since the effect appeared rather pronounced, it is not justified to neglect it, based on presumed experimental deficiencies. For a proper evaluation, additional information is required. Thus, methyl t-butyl ether should be considered a rodent carcinogen at high doses, which also induces other adverse effects. The available data are inconclusive and prohibit its use for human carcinogenic risk assessment until outstanding complications in its interpretation have been addressed.	No
U.S. Environmental Protection Agency (US EPA, 1997)	12/1997	The recommended level in drinking water of 20-40 ppb based on averting taste and odor provides a sufficient margin of exposure for cancer and non-cancer effects observed in laboratory animals. A level based on cancer risk level or a non-cancer RfD was not developed due to data limitations.		20-40 ppb in drinking water
Agency for Toxic Substances and Disease Registry (ATSDR, 1996)	8/1996	An acute minimum risk level was based on a 40 mg/kg NOAEL for lack of drowsiness in rats after a single gavage dose in a study by Bioresearch Laboratories (1990). An intermediate minimum risk level was based on a 100 mg/kg LOAEL for decreased blood urea nitrogen in rats from the Robinson et al. (1990) subchronic gavage study. (1990). Chronic minimal risk level (> 365 days) was not determined, since chronic oral exposure in female rats was associated with increased mortality and lymphatic tumors.	Chronic minimal risk level (> 365 days) was not determined for methyl t-butyl ether, since chronic oral exposure in female rats was associated with increased mortality and lymphatic tumors.	Minimum risk levels of 0.4 mg/kg-day for acute exposures (<14 days); 0.3 mg/kg-day for intermediate duration exposures (15-364 days)

Organization/ Reference	Month/ Year	Conclusions from Non-Cancer Assessment of Oral Exposure	Conclusions from Cancer Assessment of Oral Exposure	Regulatory Risk Level Derived?
Health Canada (1992; 1996)	1992; 1996	The predicted concentrations of methyl t-butyl ether in the Canadian environment do not constitute a danger to human life or health. Methyl t-butyl ether is not considered to be "toxic" as defined under Section 11 of the Canadian Environmental Protection Act (Health Canada, 1992).	Carcinogenicity Class VI. Tolerable Daily Intake for cancer effects not determined (Health Canada, 1996).	0.01 mg/kg-day Oral Tolerable Daily Intake for non-cancer effects.

Since the Belpoggi et al. (1995) chronic gavage study in rats was not designed to meet a standardized protocol, the study was considered by some regulatory agencies to have deficiencies that would impact a human health risk assessment for methyl t-butyl ether. In summary, some agencies or organizations considered the Belpoggi et al. (1995) study to be inadequate for a human health risk assessment for oral exposure while other agencies considered the study to be adequate, although flawed.

Among the agencies or organizations that considered the Belpoggi et al. (1995) study or the overall evidence to be inadequate to assess the carcinogenic potential in humans from oral exposure to methyl t-butyl ether were the European Chemicals Bureau (ECB, 2002), the International Agency for Research on Cancer (IARC, 1999), the International Programme on Chemical Safety (IPCS, 1998), and the European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC, 2003 and 1997). IPCS (1998) critically reviewed the Belpoggi et al. (1995) study and noted several confounding factors, such as:

(1) there is limited description of the results, particularly the histopathological findings;
(2) diagnostic criteria are not given for the distinction between Leydig cell tumors and hyperplasia (the latter were not reported at all, which is unusual for old Sprague-Dawley rats showing Leydig cell tumors);
(3) diagnostic criteria are not given for the distinction between dysplastic hyperplasia and lymphoma;
(4) lymphomas and leukemias are pooled; specific tumor type and incidences were not reported;
(5) historical control data might aid the evaluation of lymphomas and leukemias, particularly if they are available for these rats within different age ranges; and
(6) chronic progressive nephropathy was not observed in these Sprague-Dawley rats, although these lesions might be expected, on the basis of data from a number of other studies with this strain of rat.

IPCS (1998) concluded that owing to differences between rats and humans in the regulation of gonadotropins, it is questionable that the Leydig cell tumors observed in rats would be seen in humans. IPCS (1998) further indicated that these tumors have been reported to be induced by non-genotoxic carcinogens that disturb the hormonal balance of testosterone, luteinizing hormone, and luteinizing hormone releasing factor in rats, and that although such a mechanism may be relevant in humans, it was not substantiated by experimental evidence, since these hormones were not determined in any of the studies with methyl t-butyl ether (IPCS, 1998). However, since the IPSC review, recent *in vivo* and *in vitro* studies by de Peyster et al. (2003) have demonstrated that single and repeated gavage exposures to methyl t-butyl ether can reduce circulating testosterone levels. Further, studies by Williams et al. (2000) indicated that methyl t-butyl ether can induce mild increases in testosterone hydroxylase enzymes, suggesting that the decrease in serum testosterone observed following repeated oral exposures to methyl t-butyl ether in rats may be the result of enhanced testosterone metabolism and subsequent clearance. However, Williams et al. (2000) noted that the changes in testosterone and luteinizing hormone levels after short-term gavage exposures to methyl t-butyl ether in rats did not fit the pattern caused by known Leydig cell tumorigens.

US EPA (1997) recommended a drinking water level for methyl t-butyl ether of 20–40 ppb based on averting taste and odor, and considered this level to provide a sufficient margin of exposure for cancer and non-cancer effects observed in laboratory animals. Under the U.S. EPA (2008) IRIS Program, the draft re-assessment of methyl t-butyl ether is currently undergoing the "Agency Review" step with an estimated completion date of February 17, 2008. The next stages are "Interagency Review" and "External Peer Review".

The National Institute of Public Health and Environmental Protection of the Netherlands (Baars, 2004; RIVM, 2004), Agency for Toxic Substances and Disease Registry (ATSDR, 1996) and Health Canada (1996; 1991) have not derived chronic regulatory values for methyl t-butyl ether based on cancer effects, although values for less than chronic exposure and/or non-cancer effects have been derived (Table 7). RIVM (2004; Baars, 2004) considered the subchronic gavage study by Robinson et al. (1990) as the key study and applied 1,000x uncertainty factor (10 each for inter- and intraspecies differences, and 10 total for limited duration of the study and database deficiences) to the NOAEL of 300 mg/kg-day to determine a tolerable daily intake of 0.3 mg/kg-day. Note that NSF considered the reduced lung weights treatment-related at all exposure doses in females and thus, could not identify a NOAEL for female rats in this study.

Among the organizations or authors that considered the Belpoggi et al. (1995) study to be adequate, although flawed, to assess the carcinogenic potential in humans from oral exposure to methyl t-butyl ether were Caldwell et al. (2007) and the Office of Environmental Health Hazard Assessment of California EPA (OEHHA, 1999). OEHHA (1999) reported that the National Academy of Sciences (NRC, 1996) reviewed the chronic gavage study by Belpoggi et al. (1995) and 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) the incomplete description of tumor pathology and diagnostic criteria; and
(5) the lack of mortality adjusted analysis to account for differences in survival times.

OEHHA (1999) considered these criticisms and concluded that although these experiments, like the others available for methyl t-butyl ether, do have certain limitations or difficulties of interpretation, they contribute considerably to the overall evidence available for methyl t-butyl ether risk assessment. Further, OEHHA (1999) concluded that the study was valid, not critically flawed, and consistent with other reported results. Caldwell et al. (2007) considered the background incidence of hemolymphoreticular tumors in female rats from Belpoggi et al. (1995) to be consistent with other studies. Further, the hemolymphoreticular tumors were considered to be exposure-related, relevant to humans, and unlikely to be due to infections. The review authors also supported the combination of lymphoblastic leukemias and lymphomas reported by Belpoggi et al. (1995) for the purposes of risk assessment.

Goodman et al. (2007) and NTP (Kissling et al., 2007) provided recent insight into the lack of mortality-adjusted analysis to account for differences in survival times noted as a deficiency by NRC (1996). Goodman et al. (2007) do not consider the increase in Leydig cell tumors in treated male rats to be statistically significant when these data are re-evaluated with a statistical adjustment (Poly-3 test) for the increased survival in the high-dose males, which provides an increased opportunity for the occurrence of tumors. However, NTP (Kissling et al., 2007) rebutted that the Poly-3 analysis was developed by the NTP (Bailer and Portier, 1988; Portier and Bailer, 1989) based on survival rates from 104-week (two-year) studies and was not designed to encompass longer-term studies like Belpoggi et al. (1995) in which rats were observed until natural death of up to 174 weeks. Kissling et al. (2007) demonstrated that the increase in Leydig tumors in male rats exposed to methyl t-butyl ether was statistically significant according to the Poly-3 test based on survival at 104 weeks, for which the test was designed. When the Leydig cell tumor data were evaluated in the Poly-3 test based on the exact death times obtained through communications with Dr. Belpoggi, Kissling et al. (2007) reported the incidence of Leydig cell tumors to be 3/37.8 (8%), 5/37.6 (13%), and 11/40.4 (27%) in control, low-, and high-dose rats, respectively, based on the effective number of rats at risk after adjustment for survival at 104 weeks. These data compare to the incidences of 3/26 (12%), 5/25 (20%), and 11/32 (34%), respectively, based on the total number of rats alive at the appearance of the first Leydig tumor (96 weeks) reported by Belopoggi et al. (1995). A $BMDL_{10}$ of 67 mg/kg-day (data not shown) was estimated by NSF International based on the adjusted survival reported by Kissling et al. (2007). Note that the Benchmark Dose program (V.1.4.1c., 2007a) rounds the number of rats in each dose group to 38, 38 and 40, respectively. This $BMDL_{10}$ of 67 mg/kg-day compares to the $BMDL_{10}$ of 32 mg/kg-day based on the survival at 96 weeks, time of first Leydig tumor. The $BMDL_{10}$ for Leydig tumors based on Poly-3-adjusted survival is provided as a comparison only, as no regulatory guidance is available regarding this Poly-3-based approach to estimate the $BMDL_{10}$. Further, the performance of the Poly-3 test depends on how closely it represents the correct specification of the time-at-risk weight in the data (Moon et al., 2003). A similar mortality-adjusted analysis for the lymphatic tumors in female rats was not identified in the published literature.

As noted above, a key difference in the methodology of the Belpoggi et al. (1995) study compared to NTP chronic studies is that the treatment duration and sacrifice time are the same (104 weeks) for NTP rat studies. Whereas, Belpoggi et al. (1995) observed the rats until natural death in order to assess late-appearing tumors, although the treatment duration was 104 weeks. NSF used the total number of rats alive at the appearance of the first Leydig tumor (96 weeks) reported by Belopoggi et al. (1995) in order to estimate the $BMDL_{10}$. NSF did not feel it was appropriate to include all sixty animals per dose in the $BMDL_{10}$ estimation, since the late-appearing Leydig cell tumors may have been spontaneous, particularly considering the high spontaneous incidence of this tumor and the fact that Portier et al. (1986) found spontaneously-occurring Leydig cell tumors in control rats, albeit the F344 strain, to be clearly non-lethal. Note that a $BMDL_{10}$ based on Poly-3 adjustment for survival at 104 weeks for the lymphatic tumors in female rats could not be estimated by NSF International, because survival data at 104 weeks was not reported by Belpoggi et al. (1995).

Two inhalation studies in rats (Burleigh-Flayer et al., 1992; Chun et al., 1992; Bird et al., 1997) and the gavage study (Belpoggi et al. 1995; 1997; 1998) in rats were used by OEHHA (1999) to

develop a public health goal (PHG) of 13 ppb for methyl t-butyl ether in drinking water. The value was derived from the geometric mean of the cancer slope factors of the combined male rat kidney adenomas and carcinomas after inhalation exposure, the male rat Leydig cell tumors after gavage and inhalation exposure, and the leukemia and lymphomas in female rats after gavage exposure. The value was set at the 10^{-6} cancer risk level and assumed three liters of water consumption per day. OEHHA (1999) indicated that while some reviews have given less weight to the Belpoggi et al. (1995; 1997; 1998) studies, OEHHA (1999) found that they contributed to the overall weight of evidence.

OEHHA (1999) did not consider the renal tubule tumors observed in male rats after chronic inhalation of methyl t-butyl ether to be associated with α-2μ-globulin nephropathy, and cited investigations by NSTC (1997) and U.S. EPA (1997). These reviews reported that the possibility of male rat-specific α-2μ-globulin nephropathy playing a significant role in the pathogenesis of methyl t-butyl ether rat kidney tumors is unlikely. According to OEHHA (1999), these reviews conclude that the data indicate only mild accumulation of α-2μ-globulin and mild or partial expression of α-2μ-globulin associated nephropathy in male rats, while clearly exacerbating the expression of non- α-2μ-globulin rat nephropathy in both males and females. Further, 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 by Bird et al. (1997). However, the IPCS (1998) considered all investigations on nephrotoxicity associated with methyl t-butyl ether exposure in laboratory rats to be consistent with α-2μ-globulin nephropathy and of questionable relevance to human health.

Due to the limited oral data for methyl t-butyl ether, Dourson and Felter (1997) reviewed the toxicokinetic data for methyl t-butyl ether and suggested that there are sufficient data to conduct an inhalation-to-oral route extrapolation for methyl t-butyl ether. Based on the two-year inhalation toxicity study by Chun et al. (1992), in which rats were exposed to 0, 400, 3,000, or 8,000 ppm methyl t-butyl ether for six hours per day and five days per week, human equivalent oral doses of 0, 130, 940, or 2,700 mg/kg-day were estimated. These doses were estimated using a physiologically-based pharmacokinetic model that compared the differences between the absorption, distribution, metabolism, and elimination of methyl t-butyl ether after inhalation compared to oral exposure. After a review of the kinetic and metabolism data, Dourson and Felter (1997) concluded that the ratio of inhalation-to-oral absorption was between 0.4 to 1, and thus chose 0.5 for the absorption component of the physiologically-based pharmacokinetic model. It was also concluded that the ratios between inhalation-to- oral distribution, metabolism, and elimination of methyl t-butyl ether in rats were each one, since these parameters were considered equivalent between the inhalation and oral routes. The human equivalent oral doses that were estimated based on the the Chun et al. (1992) chronic inhalation study were proposed for use in oral non-cancer and cancer risk assessments for methyl t-butyl ether. In this study, renal tubular tumors and Leydig interstitial cell tumors were observed at an increased incidence in male rats compared to controls.

Based on the physiologically based pharmacokinetic model proposed by Dourson and Felter (1997), the proposed human equivalent oral doses of 0, 130, 940, or 2,700 mg/kg-day were used to estimate a BMDL for methyl t-butyl ether based on the incidence of Leydig cell tumors in male rats inhaling methyl t-butyl ether for two years (Appendix A Section 14.3). Ar human

equivalent oral doses of 0, 130, 940, and 2,700 mg/kg-day, the incidence of Leydig cell tumors was 32/50, 35/50, 41/50, and 47/50, respectively.

The Gamma, Multistage, Quantal Linear, and Weibull models provided the best fits, based on the same lowest AIC value, local Chi^2 values of less than the absolute value of two for all data points, and a good fit of both the BMD and BMDL dose-response plots (Appendix A). The calculated BMD (158.8 mg/kg-day) and BMDL (102.4 mg/kg-day) for all four models were identical and in close approximation of each other. As an alternate to a 10^{-5} cancer risk level for methyl t-butyl ether based on Leydig tumors in male rats or lymphatic tumors after gavage exposure, the BMDL of 102.4 mg/kg-day, based on Leydig tumors after inhalation exposure, can be used to calculate the 10^{-5} cancer risk level for methyl t-butyl ether.

$$10^{-5} \text{ risk level in rats} = \frac{\text{BMDL } (0.00001)}{0.1}$$

$$10^{-5} \text{ risk level in rats} = \frac{102.4 \text{ mg/kg-day } (0.00001)}{0.1}$$

$$10^{-5} \text{ risk level in rats} = 0.01 \text{ mg/kg-day}$$

This 10^{-5} risk level dose of 0.01 mg/kg-day based on Leydig tumors in rats after inhalation exposure is three times higher than the 10^{-5} risk level dose of 0.003 mg/kg-day based on Leydig tumors in rats after gavage exposure.

Similarly, the proposed human equivalent oral doses of 0, 130, 940, or 2,700 mg/kg-day from Dourson and Felter (1997) were used to estimate a BMDL for methyl t-butyl ether based on the combined incidence of renal tubule adenoma and carcinomas in male rats observed after chronic inhalation. As suggested by OEHHA (1999), this approach considers that the renal tubule tumors are not associated with α-2μ-globulin nephropathy (Appendix A, Section 14.4). At human equivalent oral doses of 0, 130, 940, and 2,700 mg/kg-day, the combined incidence of renal tubule adenoma and carcinomas was 1/35, 0/32, 8/31, and 3/21, respectively.

Since none of the models provided a good fit, data for the highest dose level were omitted and the models were re-run (Appendix A, Section 14.5). The results of the BMDL modeling with the highest dose omitted provided a better fit than with all the dose levels. In general, however, the fits for all models using the data for renal tubole tumors in male rats after inhalation exposure were not as good as when using the data for the Leydig tumors in male rats after inhalation exposure.

When data for the highest dose level were omitted, the Multistage and Quantal Quadratic models provided the best fits, based on the same lowest AIC value, local Chi^2 values of less than the absolute value of two for all data points, and a good fit of both the BMD and BMDL dose-response plots (Appendix A). Since the calculated BMD (580 mg/kg-day) and BMDL (439 mg/kg-day) for the Quantal Quadratic model were in closer approximation of each other, the BMDL from the Quantal Quadratic model of 439 mg/kg-day was preferred over the BMDL of 303 mg/kg-day from the Multistage model. As an alternate to a 10^{-5} cancer risk level for methyl

t-butyl ether based on Leydig tumors in male rats after gavage exposure or Leydig tumors in male rats after inhalation exposure, the BMDL of 439 mg/kg-day, based on combined incidence of renal tubule adenoma and carcinomas in male rats after inhalation exposure, can be used to calculate the 10^{-5} cancer risk level for methyl t-butyl ether.

$$10^{-5} \text{ risk level in rats} = \frac{\text{BMDL } (0.00001)}{0.1}$$

$$10^{-5} \text{ risk level in rats} = \frac{439 \text{ mg/kg-day } (0.00001)}{0.1}$$

$$10^{-5} \text{ risk level in rats} = 0.04 \text{ mg/kg-day}$$

This 10^{-5} risk level dose of 0.04 mg/kg-day, based on renal tubule adenomas and carcinomas in rats after inhalation exposure, is more than one order of magnitude higher than the 10^{-5} risk level dose of 0.003 mg/kg-day, based on Leydig tumors in rats after gavage exposure, and four times higher than the 10^{-5} risk level dose of 0.01 mg/kg-day, based on Leydig tumors in rats after inhalation exposure. Overall, data for the Leydig tumors in male rats after inhalation exposure in the Chun et al. (1992) study provided the best fit for the BMDL models as compared to the data for Leydig tumors after gavage exposure from the Belpoggi et al. (1995; 1997; 1998) study or the renal tumors after inhalation exposure in the Chun et al. (1992) study.

However, recognizing the deficiencies in the Belpoggi et al. (1995) study, using a chronic oral study to estimate lifetime cancer risk from oral exposure to methyl t-butyl ether was considered more appropriate than using a chronic inhalation study and conducting an inhalation-route-to-oral-route extrapolation to estimate a lifetime cancer risk from oral exposure to methyl t-butyl ether. Although there are no chronic oral data in humans, there is "*suggestive evidence of carcinogenic potential*" after chronic gavage exposure to methyl t-butyl ether in rats. Further, the weight of genotoxicity evidence suggests that methyl t-butyl ether has some genotoxic potential and there were insufficient data to support a non-genotoxic mode of action. In the absence of mode of action information, the U.S. EPA (2003) generally takes a conservative, or public health-protective, default position, which assumes that the animal tumor findings are relevant to humans, and cancer risks are assumed to conform to low dose linearity. Based on this approach, the Leydig cell tumors in rats were assumed to be relevant to humans and the associated cancer risks were assumed to conform to low dose linearity. Thus, a 10^{-5} cancer risk level for methyl t-butyl ether was extrapolated from the chronic gavage $BMDL_{10}$ of 32 mg/kg-day for the Leydig cell tumors in male rats, which was essentially the same as the $BMDL_{10}$ of 36 mg/kg-day for leukemias/lymphomas (combined) in female rats. The Belpoggi et al. (1995) study was considered adequate for the purposes of risk assessment. The drinking water action levels developed in this risk assessment are protective of public health, since they were based on the tumor incidences observed in a chronic gavage study.

12.0 REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2005. TLVs® and BEIs®: Based on the Documentation of the Threshold limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH. P. 38.

Amberg, A., E. Rosner, and W. Dekant. 2001. Toxicokinetics of methyl tert-butyl ether and its metabolites in humans after oral exposure. Toxicol Sci. 61(1):62-7.

ARCO (1980). Methyl tertiary-butyl ether: acute toxicological studies. Unpublished study for ARCO Research and Development for ARCO Chemical Company. Glenolden, Pennsylvania: ARCO Chemical Company. As cited in ECB (2002).

ATSDR (Agency for Toxic Substances and Disease Registry). 1996. Toxicological Profile for methyl t-butyl ether. U.S. Department of Health and Human Sevices. Public Health Service. Agency on Toxic Substances and Disease Registry. August.

Baars, A.J., P.J.C.M. Janssen, and W.C. Mennes. 2004. Human-Toxicological Maximum Permissible Risk Levels for Methyl-tertiary-butylether (MTBE). Unpublished report. National Institute of Public Health and the Environment, Bilthoven, The Netherlands. June. Available at http://www.tera.org/iter/rivm/mtbereport.htm.

Bailer, A.J., and C.J. Portier. 1988. Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. Biometrics. 44:417-431.

Barnes, D.G., and M. Dourson. 1988. Reference Dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

Belpoggi, F., M. Soffritti, and C. Maltoni. 1998. Pathological characterization of testicular tumors and lymphomas-leukaemias and of their precursors observed in Sprague-Dawley rats exposed to methyl tertiary-butyl ether (MTBE) Eur. J. Oncol. 3(3):201-206.

Belpoggi, F., M. Soffritti, and C. Maltoni. 1995. Methyl-tertiary-butyl ether (MTBE) - a gasoline additive - causes testicular and lympho-haematopoietic cancers in rats. Toxicol. Ind. Health. 11(2):119-149.

Belpoggi, F., M. Soffritti, F. Filippini, and C. Maltoni. 1997. Results of long-term experimental studies on the carcinogenicity of methyl tert-butyl ether. Ann. N.Y. Acad. Sci. 837:77-95.

Billitti, J.E., B.C. Faulkner, and B.W. Wilson. 2005. Absence of acute testicular toxicity of methyl-tert butyl ether and breakdown products in mice. Bull Environ Contam Toxicol. 75(2):228-35.

Bioresearch Laboratories. 1990. Pharmacokinetics of methyl tert-butyl ether (MTBE) and tert-butanol (TBA) in male and female Fischer 344 rats after administration of MTBE by the intravenous, oral, and dermal routes. Report No. 38842. Senneville, Quebec, Canada. As cited by ATSDR (1996).

Bird, M.G., H.D. Burleigh-Flayer, J.S. Chun, J.F. Douglas, J.J. Kneiss, and L.S. Andrews. 1997. Oncogenicity studies of inhaled methyl tertiary-butyl ether (MTBE) in CD-1 mice and F-344 rats. J. Appl. Toxicol. 17 (S1): S45-S55. May. As cited in OEHHA (1999).

Borghoff, S.J., J.E. Murphy, and M.A. Medinsky. 1996. Development of physiologically based pharmacokinetic model for methyl tertiarybutyl ether and tertiary-butanol in male Fisher-344 rats. Fundam Appl. Toxicol. 30:264–275.

Burleigh-Flayer, H.D., J.S. Chun, and W.J. Kintigh. 1992. Methyl tertiary butyl ether: vapor inhalation oncogenicity study in CD-1 mice. Bushy Run Research Center Report No. 91N0013A. October 15. Union Carbide Chemicals and Plastics Company, Inc. submitted to the U.S. EPA under TSCA Section 4 Testing Consent Order 40 CFR 799.5000 with cover letter dated October 29, 1992. EPA/OPTS#42098. Export, Pennsylvania: Bushy Run Research Center. As cited in OEHHA (1999).

Caldwell, J.C., J. Jinot, D. Devoney, and J.S. Gift. 2007. Evaluation of evidence for infection as a mode of action for induction of rat lymphoma. Environ Mol Mutagen (In Press).

Chen, C.S., Y.C. Hseu, S.H. Liang, J.-Y. Kuo, and S.C. Chen. 2007. Assessment of genotoxicity of methyl-tert-butyl ether, benzene, toluene, ethylbenzene, and xylene to human lymphocytes using comet assay. J Hazard Mater. (In Press) doi:10.1016/j.jhazmat.2007.08.053.

Chun, J.S., H.D. Burleigh-Flayer, and W.J. Kintigh. 1992. Methyl tertiary ether: vapor inhalation oncogenicity study in Fisher 344 rats. Bushy Run Research Center Report No. 91N0013B. November 13. Union Carbide Chemicals and Plastics Company, Inc. submitted to the U.S. EPA under TSCA Section 4 Testing Consent Order 40 CFR 799.5000 with cover letter dated November 19, 1992. EPA/OPTS#42098. Export, Pennsylvania: Bushy Run Research Center. As cited in OEHHA (1999).

Cinelli, S., P. Ciliutti, A. Falezza, C. Meli, L. Caserta, S. Marchetti, A.H. Seeberg, and J.A. Vericat. 1992. Absence of mutagenicity of methyl-tertiary-butyl ether [abstract No. P36/P10]. Toxicol. Lett. Suppl. 1-356: 300. As cited in ECB (2002).

Cook, J.C., G.R. Klinfelter, J.F. Hardisty, R.M. Sharpe, and P.M.D. Foster. 1999. Rodent Leydig Cell Tumorigenesis: A Review of the Physiology, Pathology, Mechanisms, and Relevance to Humans. Crit. Rev. Toxicol. 29(2):169-261.

Cruzan, G., S.J. Borghoff, A. de Peyster, G.C. Hard, M. McClain, D.B. McGregor, and M.G. Thomas. 2007. Methyl *tertiary*-butyl ether mode of action for cancer endpoints in rodents. Reg Toxicol Pharmacol. 47:156–165.

Day, K.J., A. de Peyster, B.S. Allgaier, A. Luong, J.A. MacGregor. 1998. Methyl t-butyl ether (MTBE) effects on the male rat reproductive endocrine axis [abstract]. Toxicol. 42(1-S):174.

Dekant, W., U. Bernauer, E. Rosner, and A. Amberg. 2001. Biotransformation of MTBE, ETBE, and TAME after inhalation or ingestion in rats and humans. Res. Rep. Health Eff. Inst. 102:29-71; discussion 95-109.

de Peyster, A., K.J. MacLean, B.A. Stephens, L.D. Ahern, C.M. Westover, and D. Rozenshteyn. 2003. Subchronic studies in Sprague-Dawley rats to investigate mechanisms of MTBE-induced Leydig cell cancer. Toxicol Sci. 72(1):31-42.

Dourson, M.L. 1994. Methods for establishing oral reference doses (RfDs). In Risk Assessment of Essential Elements. W. Mertz, C.O. Abernathy, and S.S. Olin (editors), pages 51-61, ILSI Press Washington, D.C.

Dourson, M.L. and S.P. Felter. 1997. Route-to-route extrapolation of the toxic potency of MTBE. Risk Anal. 17(6):717-25.

Dourson, M.L., S.P. Felter, and D. Robinson. 1996. Evolution of science-based uncertainty factors in noncancer risk assessment. Regul Toxicol Pharmacol 24:108-120.

Du, H.F., L.H. Xu, H.F. Wang, Y.F. Liu, X.Y. Tang, K.X. Liu, and S.X. Peng. 2005. Formation of MTBE-DNA adducts in mice measured with accelerator mass spectrometry. Environ Toxicol. 20(4):397-401.

European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC). 1997. Technical Report No. 72. Methyl tert-Butyl Ether (MTBE) Health Risk Characterisation CAS No.1634-4-4 (EINECS No. 216.653.1). ISSN-0773-8072-72. June.

European Chemicals Bureau (ECB). 2002. European Union Risk Assessment Report. Tert-Butyl Methyl Ether. CAS No. 1634-04-4. EINECS No. 216-653-1. 3rd Priority List. Volume 19. Institute for Health and Consumer Protection, European Chemicals Bureau, Europena Commission. EUR 20417 EN. September 9.

Goodman, J.E., D. Gaylor, L.A. Beyer, L.R. Rhomberg, and B.D. Beck. 2007. Effects of MTBE on Leydig cell tumors in Sprague-Dawley rats: Range of possible Poly-3 results. Regul Toxicol Pharmacol. (In Press).

Health Canada. 1992. Canadian Environmental Protection Act. Priority Substances List Assessment Report No. 5. Methyl tertiary-butyl ether. Government Canada. Environment Canada. Health and Welfare Canada. Health Canada. ISBN 0-662-19941-3.

Health Canada. 1996. Health-Based Tolerable Daily Intakes/Concentrations and Tumorigenic Doses/Concentrations for Priority Substances. Environmental Health Directorate. Health Protection Branch. Health Canada. ISBN 0-662-24858-9.

IARC (International Agency for Research on Cancer). 1999. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Vol. 73, pp 339. September 30.

Iavicoli, I., G. Carelli, R. Ardito, A. Cittadini, and A. Sgambato. 2002. Methyl-tertiary-butyl ether (MTBE) inhibits growth and induces cell transformation in rodent fibroblasts. Anticancer Res. 22(4):2173-7.

IPCS (International Programme On Chemical Safety). 1998. Environmental Health Criteria 206. Methyl Tertiary-Butyl Ether. United Nations Environment Programme. International Labour Organisation. World Health Organization. Available from: http://www.inchem.org/documents/ehc/ehc/ehc206.htm#PartNumber:1.

Johnson, W.D., J. Findlay, and R.A. Boyne. 1992. 28-day oral (gavage) toxicity study of methyl t-butyl ether in rats. Prepared for Amoco. Illinois Institute of Technology Research. ITT Research Institute Project No. L08100. Chicago, Illinois. 48 pp.

Kim, D., M. E. Andersen, J.D. Pleil, L.A. Nylander-French, and J.D. Prah. 2007. Refined PBPK model of aggregate exposure to methyl tertiary-buryl ether. Toxicol Lett. 169(3):222-35.

Kissling, G.E., C.J. Portier, and J. Huff. 2007. MtBE and cancer in animals: Statistical issues with poly-3 survival adjustments for lifetime studies. Regul Toxicol Pharmacol. (In Press).

Klan, M.J. W. Johnson, N.S. Hatoum, and J.K. Yermakoff. 1992. 28-day oral (gavage) toxicity study of methyl t-butyl ether in rats [abstract]. Toxicol. 12(1):117.

Klaunig, J.E., M.A. Babich, K.P. Baetcke, J.C. Cook, J.C. Corton, R.M. David, J.G. DeLuca, D.Y. Lai, R.H. McKee, J.M. Peters, R.A. Roberts, P.A. Fenner-Crisp. 2003. PPARalpha agonist-induced rodent tumors: modes of action and human relevance. Crit. Rev. Toxicol. 33(6):655-780.

Lee, L.C., P.J.E. Quintana, and A. de Peyster. 1998. Comet assay evaluation of the effect of methyl t-butyl ether (MTBE) on rat lymphocytes [abstract]. Toxicol. 42(1-S):187.

Le Gal, A., Y. Dreano, P.G. Gervasi, and F. Berthou. 2001. Human cytochrome P450 2A6 is the major enzyme involved in the metabolism of three alkoxyethers used as oxyfuels. Toxicol Lett. 124(1-3):47-58.

Life Science Research Roma Toxicology Centre S.P.A. 1989. Gene mutation in Chinese hamster V79 cells, test substance: MtBE. Report No. 216002-M-03589. Rome, Italy: Roma Toxicology Centre S.P.A. As cited in ECB (2002).

Litton Bionetics Inc. 1980. Mutagenicity Evaluation of TBME A995 (Tert-Butyl Methyl Ether) in an in-vitro Cytogenetic Assay Measuring Sister Chromatid Exchange and Chromosome Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells. Kensington, Maryland: Litton Bionetics, Inc. As cited in ECB (2002).

Mackerer, C.R., F.A. Angelosanto, G.R. Blackburn, and C.A. Schreiner. 1996. Identification of formaldehyde as the metabolite responsible for the mutagenicity of methyl tertiary-butyl ether in the activated mouse lymphoma assay. Proc. Soc. Exp. Biol. Med. 212(4):338-41. As cited in ECB (2002).

Martin, J.V., N.M. Bilgin, and M.M. Iba. 2002. Influence of oxygenated fuel additives and their metabolites on the binding of a convulsant ligand of the gamma-aminobutyric acid(A) (GABA(A)) receptor in rat brain membrane preparations. Toxicol Lett. 129(3):219-26.

McGregor, D. G. Cruzan, R.D. Callander, K. May, and M. Banton. 2005. The mutagenicity testing of tertiary-butyl alcohol, tertiary-butyl acetate and methyl tertiary-butyl ether in Salmonella typhimurium. Mutat Res. 565(2):181-9.

McGregor, D. 2006. Methyl *tertiary*-Butyl Ether: Studies for Potential Human Health Hazards. Crit Rev Toxicol. 36(4):319-358.

Moon, H., H. Ahn, R.L. Kodell, and J.J. Lee. 2003. Estimation of k for the poly-k test with application to animal carcinogenicity studies. Stat Med. 22(16):2619-36.

Moser, G.J., B.A. Wong, D.C. Wolf, O.R. Moss, and T.L. Goldsworthy. 1996. Comparative short-term effects of methyl tertiary butyl ether and unleaded gasoline vapor in female B6C3P1 mice. Fundam Appl Toxicol. 31:173-183.

National Research Council (NRC). 1996. Toxicological and Performance Aspects of Oxygenated Motor Vehicle Fuels. 160 pp. Committee on Toxicological and Performance Aspects of Oxygenated Motor Vehicle Fuels, Board on Environmental Studies and Toxicology, Committee on Life Sciences, National Research Council (NRC), National Academy of Sciences (NAS), Washington, D.C.: National Academy Press. As cited in OEHHA (1999).

National Research Council (NRC). 1983. Risk Assessment in the Federal Government: Managing the Process. National Academy Press.

NSF/ANSI 60. 2005. Drinking Water Treatment Chemicals - Health Effects. NSF International, Ann Arbor, MI.

NSF/ANSI 61. 2007. Drinking Water System Components - Health Effects. NSF International, Ann Arbor, MI.

NSTC (National Science and Technology Council). 1997. Interagency Assessment of Oxygenated Fuels. June. National Science and Technology Council, Committee on Environment and Natural Resources (CENR) and Interagency Oxygenated Fuels Assessment Steering Committee. White House Office of Science and Technology Policy (OSTP) through the CENR of the Executive Office of the President. Washington, D.C.: NSTC. Available at: http://www.whitehouse.gov/WH/EOP/OSTP/html/OSTP_Home.html. As cited by OEHHA (1999).

OEHHA (Office of Environmental Health Hazard Assessment). 1998. Evidence on the Carcinogenicity of Methyl Tertiary Butyl Ether (MTBE) Draft. Reproductive and Cancer Hazard Assessment Section. California Environmental Protection Agency. September.

OEHHA (Office of Environmental Health Hazard Assessment). 1999. Public Health Goal for Methyl Tertiary-Butyl Ether (MTBE) in Drinking Water. Pesticide and Environmental Toxicology Section. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. March.

Okahara, N. A. de Peyster, S.E. McPherson, and J.A. MacGregor. 1998. Effect of MTBE on estrogen-sensitive tissues of immature female CD-1 mice [abstract].. Toxicol. 42(1-S):174-175.

Portier, C.J., J.C. Hedges, and D.G. Hoel. 1986. Age-specific models of mortality and tumor onset for historical control animals in the National Toxicology Program's carcinogenicity experiments. Cancer Res. 46:4372–4378.

Portier, C.J. A.J. and Bailer. 1989. Testing for increased carcinogenicity using a survival-adjusted quantal response test. Fundam. Appl. Toxicol. 12:731-737.

Prah, J., D. Ashley, B. Blount, M. Case, T. Leavens, J. Pleil, and F. Cardinali. 2004. Dermal, Oral, and Inhaltion Pharmacokinetics of Methyl Tertiary Butyl Ether (MTBE) in Human Volunteers. Toxicol. Sci. 77:195-205.

Presidential/Congressional Commission on Risk Assessment and Risk Management. 1997a. Framework for environmental health risk management. Final report Volume 1.

Presidential/Congressional Commission on Risk Assessment and Risk Management. 1997b. Risk assessment and risk management in regulatory decision-making. Final report Volume 2.

Pruett, S.B., R. Fan, Q. Zheng, L.P. Myers. and P. Hebert. 2003. Modeling and predicting immunological effects of chemical stressors: characterization of a quantitative biomarker for immunological changes caused by atrazine and ethanol. Toxicol. Sci. 75(2):343-54.

RIVM. 2004. Risicogrenzen voor MTBE (Methyl tertiair-Butyl Ether) in bodem, sediment, grondwater, oppervlaktewater, drinkwater en voor drinkwaterbereiding (Risk limits for MTBE in soil, sediment, groundwater, surface water, drinking water, and for drinking water preparation). (Report in Dutch, Evaluation in English). (Swartjes FA, Baars AJ, Fleuren RHLJ, and Otte PF). Report no. 711701039/2004. National Institute of Public Health and the Environment, Bilthoven, The Netherlands, November 2004. p. 55-68 (English section). Available at http://www.rivm.nl/bibliotheek/rapporten/711701039.html.

Robinson, M., R.H. Bruner, and G.R. Olson. 1990. Fourteen- and ninety-day oral toxicity studies of methyl tertiary-butyl ether in Sprague-Dawley rats. J. Am. Coll. Toxicol. 9(5):525-540.

Suffet, I.H. 2007. A re-evaluation of the taste and odour of methyl tertiary butyl ether (MTBE) in drinking water. Water Sci Technol. 55(5):265-73.

U.S. Environmental Protection Agency. 1986. Guidelines for carcinogen risk assessment. Federal Register 51(185):33992-34040.

U.S. Environmental Protection Agency. 1988. Recommendations for and documentation of biological values for use in risk assessment. EPA 600/6-87/008, NTIS PB88-179874/AS, February 1988.

U.S. Environmental Protection Agency. 1991a. National primary drinking water regulations: Final Rule. Federal Register 56(20):3526-3614.

U.S. Environmental Protection Agency. 1991b. Guidelines for developmental toxicity risk assessment. Federal Register 56(234):63798-63826.

U.S. Environmental Protection Agency. 1993. Reference Dose (RfD): Description and use in health risk assessment. Integrated Risk Information System (IRIS) background document 1A. http://www.epa.gov/ngispgm3/iris/rfd.htm

U.S. Environmental Protection Agency. 1995. Methods for the Determination of Organic Compounds in Drinking Water-Supplement III. Method 502.2. VOCs by Purge and Trap Capillary GC with Photoionization and Electrolytic Conductivity Detectors in Series. EPA/600/R-95-131, NTIS Pub. No. PB95-261616.

U.S. Environmental Protection Agency. 1996a. Proposed guidelines for carcinogen risk assessment. Federal Register 61(79):17960-18011.

U.S. Environmental Protection Agency. 1996b. Guidelines for reproductive toxicity risk assessment. Federal Register 61(212):56274-56322.

U.S. Environmental Protection Agency. 1997. Drinking Water Advisory: Consumer Acceptability Advice and Health Effects Analysis on Methyl tertiary-Butyl Ether (MtBE). EPA 822-F-97-008. December.

U.S. Environmental Protection Agency. 1998. Guidelines for neurotoxicity risk assessment. Federal Register 63(93):26926-26954.

U.S. Environmental Protection Agency. 1999. draft revised Guidelines for carcinogen risk assessment. NCEA-F-0644, July 1999. http://cfpub.epa.gov/ncea/raf/rafguid.cfm

U.S. Environmental Protection Agency. 2002. A Review of the Reference Dose and Reference Concentration Process. EPA/630/P-02/002F. 01 Dec 2002. U.S. EPA, Risk Assessment Forum, Washington, DC, 192 pp.

U.S. Environmental Protection Agency. 2003a. Glossary of IRIS terms. Integrated Risk Information System (IRIS). http://www.epa.gov/ngispgm3/iris/gloss8.htm.

U.S. Environmental Protection Agency. 2003b. Draft final guidelines for carcinogen risk assessment (external review draft, February 2003). NCEA-F-0644A. 03 Mar 2003. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. 125 pp.

U.S. Environmental Protection Agency. 2005a. Glossary of IRIS terms. Integrated Risk Information System (IRIS). http://www.epa.gov/ngispgm3/iris/gloss8.htm.

U.S. Environmental Protection Agency. 2005b. Guidelines for carcinogen risk assessment. EPA/630/P-03/001B. March 2005. http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=116283

U.S. Environmental Protection Agency. 2007a. Benchmark Dose Software Version 1.4.1c. National Center for Environmental Assessment, Office of Research and Development. http://www.epa.gov/ncea/bmds.htm.

U.S. Environmental Protection Agency. 2007b. Health effects testing guidelines. U.S. Code of Federal Regulations, Title 40, Part 798. U.S. Environmental Protection Agency.

U.S. Environmental Protection Agency. 2007c. Office of Pollution Prevention and Toxics. ChemRTK HPV Challenge Program. http://www.epa.gov/hpv/hpvis/index.html. Last Updated December 4, 2007.

U.S. Environmental Protection Agency. 2008. IRIS Track. Status Report for Methyl tert-Butyl Ether (MTBE). Integrated Risk Information System. http://cfpub.epa.gov/ncea/iristrac/index.cfm?fuseaction=listChemicals.showList&letter=M. Last Updated January 28, 2008.

U.S. Food and Drug Administration. 2007. U.S. Code of Federal Regulations. Title 21 (Food and Drugs). http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. April 1.

Ward Jr., J.B., W.W. Au, E.B. Whorton, et al. 1994. Genetic toxicity of methyl tertiary-butyl ether. Division of Environmental Toxicology, Department of Preventive Medicine and Community Health. Galveston, Texas: University of Texas Medical Branch. As cited in IPCS (1998).

Ward Jr., JB, D.H. Daiker, D.A. Hastings, M.M. Ammenheuser, and M.S. Legator. 1995. Assessment of the mutagenicity of methyl tertiary-butyl ether at the HPRT gene in CD-1 mice [abstract]. Toxicol. 15:79. As cited in OEHHA (1999) and ATSDR (1996).

Williams, T.M. and S.J. Borghoff. 2000. Induction of testosterone biotransformation enzymes following oral administration of methyl tert-butyl ether to male Sprague-Dawley rats. Toxicol. Sci. 57(1):147-55.

Williams, T.M., R.C. Cattley, and S.J. Borghoff. 2000. Alterations in endocrine responses in male Sprague-Dawley rats following oral administration of methyl tert-butyl ether. Toxicol. Sci. 54(1):168-76.

Yuan, Y., H.F. Wang, H.F. Sun, H.F. Du, L.H. Xu, Y.F. Liu, X.F. Ding, D.P. Fu, and K.X. Liu. 2007. Adduction of DNA with MTBE and TBA in mice studied by accelerator mass spectrometry. Environ Toxicol. 22(6):630-5.

Zhou,W. D. Yuan, G. Huang, H. Zhang, and S. Ye. 2000. Mutagenicity of Methyl Tertiary Butyl Ether. J. Environ. Pathol., Toxicol. Oncol. 19(1-2):35-39.

Zhou,W. and S. Ye. 1999. Subchronic oral methyl tertiary-butyl ether exposure (MTBE) in male Sprague-Dawley rats and effects on health of MTBE exposed workers. J. Occup. Health. 41:33-38.

13.0 APPENDIX A

13.1 Benchmark Dose for Leydig Cell Tumors after Gavage Exposure

Formatted: Bullets and Numbering

Formatted: Bullets and Numbering

```
==========================================================
        Gamma Model. (Version: 2.11; Date: 10/31/2007)
        Input Data File: C:\BMDS\UNSAVED1.(d)
        Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
                                        Thu Jan 24 13:29:50 2008
==========================================================
BMDS MODEL RUN
----------------------------------------------------------------
  The form of the probability function is:

  P[response]= background+(1-background)*CumGamma[slope*dose,power],
  where CumGamma(,) is the cummulative Gamma distribution function

  Dependent variable = COLUMN2
  Independent variable = COLUMN1
  Power parameter is restricted as power >=1

  Total number of observations = 3
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

            Default Initial (and Specified) Parameter Values
              Background =     0.12963
                 Slope =  0.00333091
                 Power =        1.3

        Asymptotic Correlation Matrix of Parameter Estimates

( *** The model parameter(s) -Power have been estimated at a boundary point, or have been specified by
the user, and do not appear in the correlation matrix )

          Background      Slope
Background        1      -0.58

   Slope      -0.58          1

                    Parameter Estimates

                                  95.0% Wald Confidence Interval
    Variable      Estimate     Std. Err.   Lower Conf. Limit   Upper Conf. Limit
  Background     0.122284    0.0572279       0.0101192           0.234448
     Slope     0.00175848   0.000886228     2.15052e-005        0.00349546
     Power          1          NA
```

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-42.4001	3			
Fitted model	-42.4251	2	0.0499075	1	0.8232
Reduced model	-44.6509	1	4.50163	2	0.1053

AIC: 88.8501

Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.1223	3.179	3	26	-0.107
42.5000	0.1855	4.637	5	25	0.187
170.0000	0.3491	11.171	11	32	-0.063

Chi^2 = 0.05 d.f. = 1 P-value = 0.8224

Benchmark Dose Computation

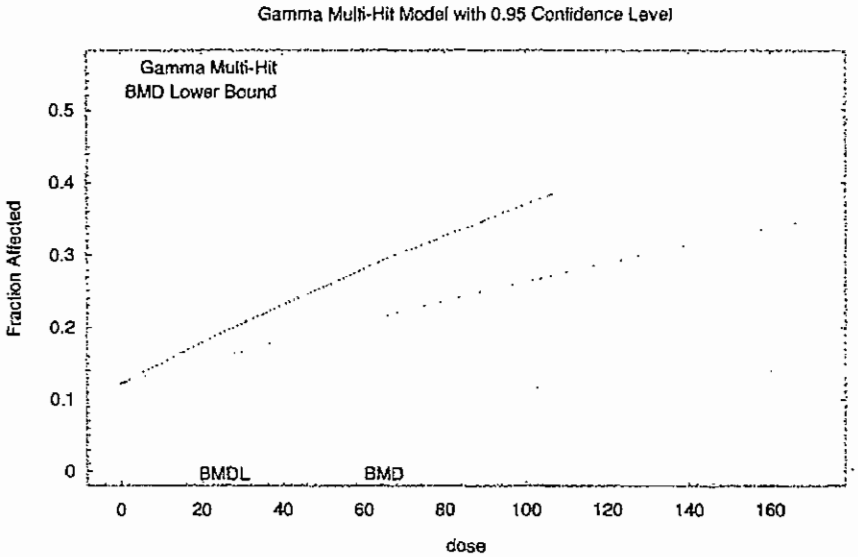
Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 59.9156

BMDL = 31.5687



13:29 01/24 2008

13.2 Benchmark Dose for Lymphomas/Leukemias after Gavage Exposure

Formatted: Bullets and Numbering

```
==========================================================================
        Gamma Model. (Version: 2.11:  Date: 10/31/2007)
        Input Data File: C:\BMDS\UNSAVED1.(d)
        Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                        Thu Jan 24 13:52:15 2008
==========================================================================
BMDS MODEL RUN
--------------------------------------------------------------------------
  The form of the probability function is:

  P[response]= background+(1-background)*CumGamma[slope*dose,power],
  where CumGamma(.) is the cumulative Gamma distribution function

  Dependent variable = COLUMN2
  Independent variable = COLUMN1
  Power parameter is restricted as power >=1

  Total number of observations = 3
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
```

Default Initial (and Specified) Parameter Values
Background = 0.0423729
Slope = 0.00460149
Power = 1.3

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Power have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	Background	Slope
Background	1	-0.49
Slope	-0.49	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0419587	0.0264021	-0.00978844	0.0937059
Slope	0.00184323	0.00061981	0.000628423	0.00305803
Power	1	NA		

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-55.798	3			
Fitted model	-56.1041	2	0.612346	1	0.4339
Reduced model	-61.6305	1	11.665	2	0.002931

AIC: 116.208

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0420	2.434	2	58	-0.284
38.7000	0.1079	5.504	7	51	0.675
152.0000	0.2761	12.974	12	47	-0.318

Chi^2 = 0.64 d.f. = 1 P-value = 0.4246

Benchmark Dose Computation

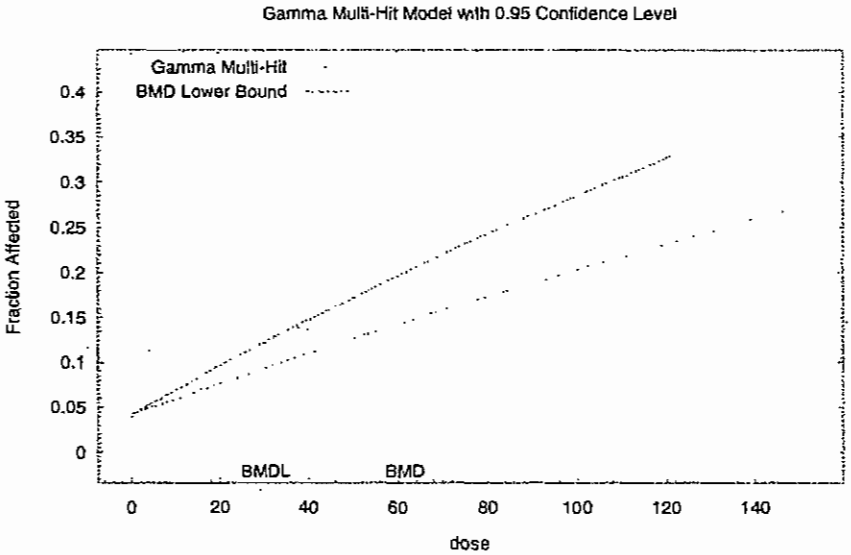
Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 57.1609

BMDL = 35.7657



13:52 01/24 2008

10.3 Benchmark Dose for Leydig Cell Tumors after Inhalation Exposure

Formatted: Bullets and Numbering

Results of benchmark dose modeling of Leydig cell tumors from male rats inhaling methyl t-butyl ether for two years

Model	Local Chi[2] scaled residuals <[2]?	p-value[a]	AIC	BMD (mg/kg-day)	BMDL (mg/kg-day)
Gamma	Yes	0.9391	200.39	158.8	102.4
Logistic	Yes	0.6394	202.485	188.7	37.9
Multistage[c]	Yes	0.9391	200.39	158.8	102.4
Probit	Yes	0.8460	200.599	292.7	177.8
Quantal Linear	Yes	0.9391	200.39	158.8	102.4
Quantal Quadratic	Yes	0.3745	202.28	652.5	503.5
Weibull	Yes	0.9391	200.39	158.8	102.4

[a] p value should be greater than 0.1
[b] Graph was considered a good visual fit if the standard deviation for each dose fell within the estimated dose response curve
[c] Multistage degree of polynomial = 3
Note that Benchmark Dose Software Version 1.3.1 used

```
=================================================================
        SRevision: 2.2 $ SDate: 2001/03/14 01:17:00 $
        Input Data File: C:\BMDS\DATA\MTBE_CHUN_LEYDIG.(d)
        Gnuplot Plotting File:  C:\BMDS\DATA\MTBE_CHUN_LEYDIG.plt
                                                  Fri Nov 07 15:47:21 2003
=================================================================

BMDS MODEL RUN
-----------------------------------------------------------------

 The form of the probability function is:

 P[response]= background+(1-background)*CumGamma[slope*dose,power],
 where CumGamma(.) is the cummulative Gamma distribution function

 Dependent variable = COLUMN3
 Independent variable = COLUMN1
 Power parameter is restricted as power >=1

 Total number of observations = 4
 Total number of records with missing values = 0
 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

          Default Initial (and Specified) Parameter Values
            Background =    0.637255
               Slope =  0.00109377
               Power =        1.3

      Asymptotic Correlation Matrix of Parameter Estimates

      ( *** The model parameter(s)  -Power have been estimated at a boundary point, or have been specified by the
      user, and do not appear in the correlation matrix )

        Background      Slope
Background        1      -0.48
   Slope      -0.48          1

                Parameter Estimates
    Variable        Estimate        Std. Err.
  Background        0.656225        0.0492578
     Slope        0.000663687      0.000200204
     Power              1            NA

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard
error.
                Analysis of Deviance Table

    Model     Log(likelihood)  Deviance  Test DF    P-value
  Full model      -98.1322
 Fitted model      -98.195     0.125725    2        0.9391
Reduced model     -106.633     17.0012    3        0.0007063

      AIC:        200.39
```

Goodness of Fit

Dose	Est. Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.6562	32.811	32	50	-0.2415
130.0000	0.6846	34.232	35	50	0.2337
940.0000	0.8158	40.789	41	50	0.07694
2700.0000	0.9427	47.136	47	50	-0.08262

Chi-square = 0.13 DF = 2 P-value = 0.9391

Benchmark Dose Computation

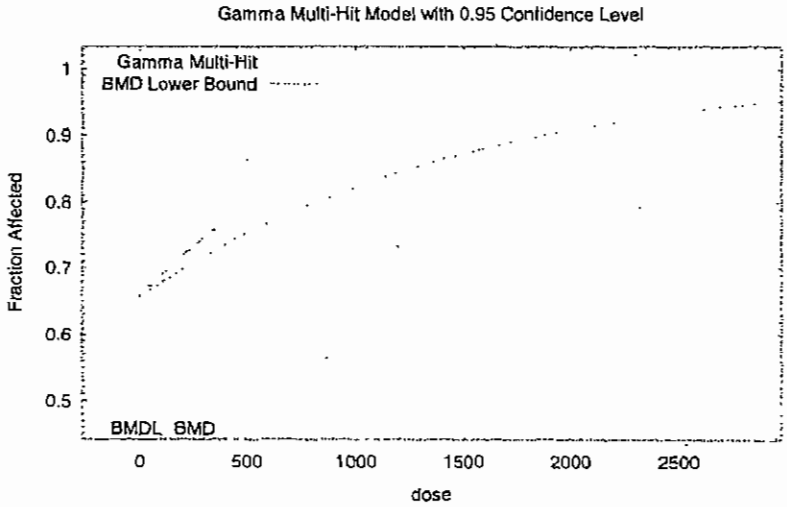
Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 158.75

BMDL = 102.395



15:47 11/07 2003

13.1 Benchmark Dose for Renal Tumors after Inhalation Exposure

Formatted: Bullets and Numbering

Results of benchmark dose modeling of renal tubule adenomas and carcinomas (combined) from male rats inhaling methyl t-butyl ether for two years

Model	Local Chi² scaled residuals <[2]?	p-value[a]	AIC	BMD (mg/kg-day)	BMDL (mg/kg-day)
Gamma	No	0.0136	74.7039	922	536
Logistic	No	0.0210	74.1405	816	444
Multistage[c]	Yes	0.0136	74.7039	922	538
Probit	No	0.0010	79.0339	1132	735
Quantal Linear	No	0.0136	74.7039	922	536
Quantal Quadratic	Yes	0.0005	79.8644	2108	1249
Weibull	No	0.0136	74.7039	922	536

[a] p value should be greater than 0.1
[b] Graph was considered a good visual fit if the standard deviation for each dose fell within the estimated dose response curve
[c] Multistage degree of polynomial = 3
Note that Benchmark Dose Software Version 1.3.1 used

```
Quantal Quadratic Model SRevision: 2.2 $ $Date: 2000/03/17 22:27:16 $
Input Data File: C:\BMDS\DATA\MTBE_CHUN_RENAL_OMIT_HIGH.(d)
Gnuplot Plotting File:  C:\BMDS\DATA\MTBE_CHUN_RENAL_OMIT_HIGH.plt
                                        Mon Nov 10 11:00:55 2003

BMDS MODEL RUN
------------------------------------------------------------

  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(-slope*dose^2)]

  Dependent variable = COLUMN3
  Independent variable = COLUMN1

  Total number of observations = 3
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

          Default Initial (and Specified) Parameter Values
            Background =   0.0416667
               Slope =  3.0124e-007
               Power =          2  Specified

       Asymptotic Correlation Matrix of Parameter Estimates

( *** The model parameter(s)  -Power have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix )

        Background     Slope
Background       1     -0.15
```

Slope -0.15 1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.015063	0.0149491
Slope	3.13042e-007	1.18417e-007

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-22.2426			
Fitted model	-23.0703	1.65528	1	0.1982
Reduced model	-30.0632	15.6411	2	0.0004014

AIC: 50.1405

Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0151	0.527	1	35	0.6561
130.0000	0.0203	0.648	0	32	-0.8135
940.0000	0.2531	7.845	8	31	0.06399

Chi-square = 1.10 DF = 1 P-value = 0.2951

Benchmark Dose Computation

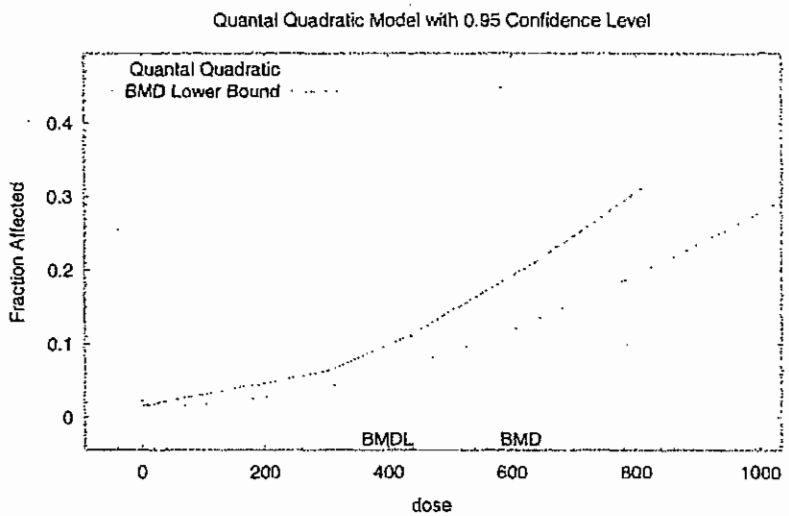
Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 580.147

BMDL = 439.007



11:00 11/10 2003

13.5 Benchmark Dose for Renal Tumors after Inhalation Exposure (omit highest dose)

Formatted: Bullets and Numbering

Results of benchmark dose modeling of renal tubule adenomas and carcinomas (combined) from male rats inhaling methyl t-butyl ether for two years (omit highest dose)

Model	Local Chi² scaled residuals <[2]?	p-value[a]	AIC	BMD (mg/kg-day)	BMDL (mg/kg-day)
Gamma	Yes	NA	51.7978	773	323
Logistic	Yes	NA	51.7978	833	314
Multistage[c]	Yes	0.2951	50.1405	580	303
Probit	Yes	NA	51.7978	743	363
Quantal Linear	Yes	0.1422	52.1041	413	235
Quantal Quadratic	Yes	0.2951	50.1405	580	439
Weibull	Yes	NA	51.7978	839	324

[a] p value should be greater than 0.1
[b] Graph was considered a good visual fit if the standard deviation for each dose fell within the estimated dose response curve
[c] Multistage degree of polynomial = 3
Note that Benchmark Dose Software Version 1.3.1 used

```
==========================================================
        Quantal Quadratic Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
        Input Data File: C:\BMDS\DATA\MTBE_CHUN_RENAL_OMIT_HIGH.(d)
        Gnuplot Plotting File:  C:\BMDS\DATA\MTBE_CHUN_RENAL_OMIT_HIGH.plt
                                        Mon Nov 10 11:00:55 2003
==========================================================

BMDS MODEL RUN
-------------------------------------------------------------
```

The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-slope*dose^2)]

Dependent variable = COLUMN3
Independent variable = COLUMN1

Total number of observations = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values
Background = 0.0416667
Slope = 3.0124e-007
Power = 2 Specified

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Power have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	Background	Slope
Background	1	-0.15
Slope	-0.15	1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.015063	0.0149491
Slope	3.13042e-007	1.18417e-007

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-22.2426			
Fitted model	-23.0703	1.65528	1	0.1982
Reduced model	-30.0632	15.6411	2	0.0004014

AIC: 50.1405

Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0151	0.527	1	35	0.6561
130.0000	0.0203	0.648	0	32	-0.8135
940.0000	0.2531	7.845	8	31	0.06399

Chi-square = 1.10 DF = 1 P-value = 0.2951

Benchmark Dose Computation

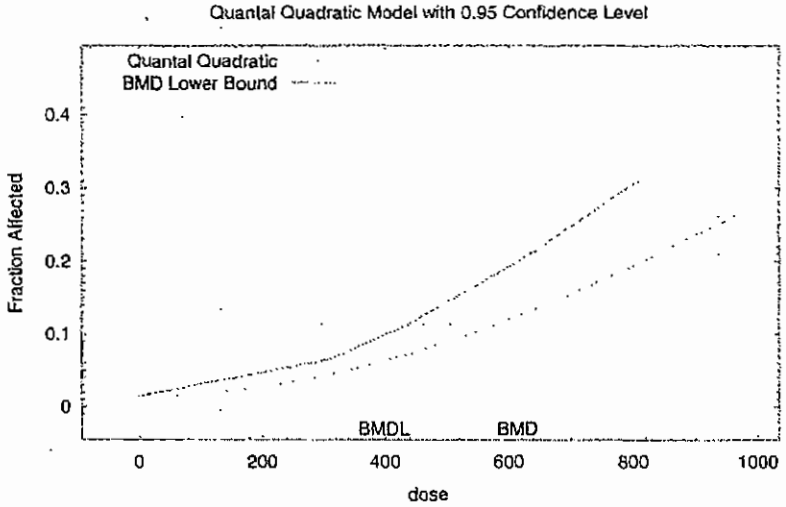
Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 580.147

BMDL = 439.007



11:00 11/10 2003

14.0 PEER REVIEW HISTORY

Formatted: Bullets and Numbering

This document has not undergone external peer review.

Appendix C

Addendum to MTBE Oral Risk Assessment—NSF International

April 2010 ADDENDUM to Draft Methyl *teritary*-Butyl Ether Oral Risk Assessment Document, NSF International, February 2008

The February 2008 draft risk assessment for methyl *teritary*-butyl ether (MTBE) by NSF International did not include the calculation of a risk value based on non-cancer endpoints. Non cancer endpoints were considered in the evaluation but were determined to be a less sensitive endpoint, compared to the cancer endpoint, and was therefore not included in the original assessment. This addendum represents the quantitative determination of non-cancer effects associated with oral exposure to MTBE.

The NSF International (2008) assessment for MTBE determined that there is "suggestive evidence of carcinogenic potential" after gavage exposure to MTBE in rats. This determination was based on an increase in Leydig cell tumors in male SD rats and leukemias/lymphomas (combined) in female SD rats that received MTBE via gavage for two years (Belpoggi et al., 1995). The non cancer assessment was based on a NOAEL from a ninety-day oral toxicity studies of methyl tertiary-butyl ether in Sprague-Dawley rats.

The Total Allowable Concentration (TAC) for MTBE based on non-cancer effects of 0.7 mg/L was calculated and exceeds the Total Allowable Concentration (TAC) for MTBE of 0.1 mg/L based on the cancer endpoint. For the purpose of evaluating cross linked polyethylene tubing/pipe for residential applications to NSF/ANSI Standard 61, the Total Allowable Concentration (TAC) for MTBE of 0.1 mg/L will be used because it is protective of both cancer and non cancer endpoints.

TABLE OF CONTENTS

1.0 PHYSICAL AND CHEMICAL PROPERTIES 1

1.1 Organoleptic Properties 1

2.0 PRODUCTION AND USE 2

2.1 Production 2

2.2 Use 2

3.0 ANALYTICAL METHODS 2

3.1 Analysis in Water 2

3.2 Analysis in Biological Matrices 3

4.0 SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE 3

4.1 Sources of Human Exposure 3

4.2 Sources of Environmental Exposure 3

5.0 COMPARATIVE KINETICS AND METABOLISM IN HUMANS AND LABORATORY ANIMALS 4

5.1 Absorption 6

5.2 Distribution 6

5.3 Metabolism 7

5.4 Elimination/Excretion 9

5.5 Physiologically-based pharmacokinetic models 10

6.0 EFFECTS ON HUMANS 10

6.1 Case Reports 10

6.2 Epidemiological Studies 10

7.0 EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS 11

7.1 Limited-Exposure Effects 12

7.2 Single-Exposure Studies 13

7.3 Short-Term Exposure Studies 13

7.4 Long-Term and Chronic Exposure Studies 18

7.5 Reproductive and Developmental Toxicity Studies 25

7.6 Studies of Immunological and Neurological Effects 33

8.0 RISK CHARACTERIZATION 35

8.1 Hazard Identification 35

8.2 TAC Derivation 42

8.3 SPAC Derivation 43

9.0 RISK COMPARISONS AND CONCLUSIONS 43

10.0 ADDENDUM REFERENCES: 44

ADDENDUM EXECUTIVE SUMMARY

Methyl tertiary-Butyl Ether (MTBE) – Oral Risk Assessment CAS # 1634-04-4			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
NOAEL (no observed adverse effect level)	300	mg/kg-day	From a 13-week gavage study in SD rats
Oral RfD (oral reference dose)	0.1	mg/kg-day	From the NOAEL with a 3000x total uncertainty factor
TAC (total allowable concentration)	0.7	mg/L	For a 70 kg adult drinking 2 L/day with a 20% Relative Source Contribution
SPAC (single product allowable concentration)	0.07	mg/L	From the TAC, assuming 10 potential sources of MTBE in drinking water
STEL (short term exposure level)	Not determined	mg/L	Not applicable

KEY STUDY	Robinson, M., R.H. Bruner, and G.R. Olson. 1990. Fourteen- and ninety-day oral toxicity studies of methyl tertiary-butyl ether in Sprague-Dawley rats. J Am Coll Toxicol. 9(5):525-540.
CRITICAL EFFECT(S)	The NOAEL was based on the approximate threshold associated with the induction of adaptive liver responses after subchronic gavage exposure to MTBE.
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD include: • 10x for interspecies extrapolation • 10x for intraspecies extrapolation • 1x for LOAEL to NOAEL extrapolation • 10x for subchronic to chronic extrapolation • 3x for database deficiencies The total uncertainty factor is therefore 3000x.
TOXICITY SUMMARY	Oral toxicity data for MTBE in humans were limited to sensory irritation effects after occupational exposure or kinetic parameters after single-dose exposures. Gavage but not drinking water exposure to MTBE in laboratory rodents was associated with increased liver weights and altered blood parameters (blood urea nitrogen and cholesterol) accompanied by centrilobular hepatocyte hypertrophy. Increased mean kidney weights, hyaline droplet formation, and α-2μ-globulin immunoreactivity were observed in the proximal tubules of male rats after drinking water or gavage exposure. All investigations on nephrotoxicity associated with MTBE exposure are consistent with α-2μ-globulin nephropathy, which was not considered relevant to humans. The liver effects observed after subchronic gavage exposure were attributed to an adaptive mechanism by the liver to metabolizing bolus doses of MTBE since they were not observed after drinking water exposure. The effect of long-term exposure to MTBE at levels below the threshold that would elicit such adaptive responses is unknown. While adaptive mechanisms to metabolizing high-dose chemical exposures are usually reversible upon cessation of treatment, these mechanisms, if provoked for a sufficiently prolonged duration, may result in irreversible changes that are considered adverse and potentially relevant to humans. The NOAEL was considered 300 mg/kg-day based on the threshold associated with the induction of adaptive liver responses that occurred at 900 mg/kg-day after subchronic gavage exposure to MTBE. Although standardized chronic inhalation bioassays are available for MTBE, insufficient kinetics data are available to reliably extrapolate an inhalation concentration in rats to human equivalent oral doses.
CONCLUSIONS	A physiologically-based pharmacokinetic model extrapolating oral rat doses to humans and additional studies examining potential modes of action would increase the confidence and reduce the uncertainty associated with the non-cancer risk levels derived herein. The relevance of the drinking water levels derived herein should be re-evaluated when the results of an ongoing two-year drinking water study becomes available.

1.0 PHYSICAL AND CHEMICAL PROPERTIES

MTBE is an aliphatic dialkyl ether with synonyms of 2-methoxy-2-methylpropane; 2-methyl-2-methoxypropane; ether, tert-butyl methyl; MTBE; methyl 1,1-dimethylethyl ether; methyl tert-butyl ether; methyl tertiary-butyl ether; propane, 2-methoxy-2-methyl-; t-butyl methyl ether; tert-butyl methyl ether (ChemIDPlus, 2003). It has trade names of 3 D Concord, Driveron, HSDB 5487, and UN 2398 (IPCS, 1998). It has the following structure, and physical and chemical properties listed in Table 1:

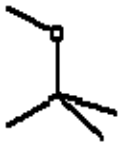


Table 1. The physical and chemical properties of MTBE

Property	Data	Reference
Empirical Formula	$C_5H_{12}O$	OEHHA, 1999
CAS#	1634-04-4	OEHHA, 1999
Molecular Weight	88.15	OEHHA, 1999
Physical State and Color	colorless liquid at room temperature	IPCS, 1998
Melting Point	-109°C	OEHHA, 1999
Boiling Point	55.2°C	IPCS, 1998
Density	0.7404 at 20°C	IPCS, 1998
Vapor Pressure	33,500 Pa at 25°C	IPCS, 1998
Water Solubility	51 g/L at 25°C	OEHHA, 1999
Dissociation Constant (pK_a)	Not reported	
n-Octanol/Water Partition Coefficient (log K_{ow})	0.94-1.3[a] 1.43 (estimated)[b]	[a] IPCS, 1998 [b] http://esc.syrres.com
Henry's Law Constant (air/water partition)	5.87×10^{-4} atm-m^3/mole at 25°C	OEHHA, 1999

1.1 Organoleptic Properties

MTBE has a terpene-like odor (IPCS, 1998). Individual variability in sensitivity to taste and odor make it difficult to identify odor and taste thresholds for MTBE in water (ECB, 2002). IPCS (1998) has reported that the taste threshold for MTBE in water is 134 ppb. OEHHA (1999) has cited various sources that report odor thresholds for MTBE in water of between 2.5 to 680 ppb. The U.S. EPA (1997) recommended a drinking water level of 20-40 ppb for MTBE, based on averting taste and odor. More recent data by Suffet et al. (2007) suggests that the odor threshold for MTBE in water is ≥ 15 ppb.

2.0 PRODUCTION AND USE

2.1 Production

Industrially, MTBE is derived from the catalytic reaction of methanol and isobutylene over an acidic ion-exchange resin catalyst such as sulfonated styrene cross-linked with divinyl benzene in the liquid phase at 38-93°C and 100-200 psi (IPCS, 1998). It can also be prepared from methanol, t-butanol, and diazomethane.

MTBE is among the 50 highest production volume chemicals (IPCS, 1998). In 1999, total worldwide annual production of MTBE was about 21 million tons or 46.3 billion pounds (ECB, 2002). MTBE is a high production volume chemical in the United States (U.S. EPA, 2007) and European Union (2004).

2.2 Use

It is anticipated that the use of MTBE will continue to increase (IPCS, 1998). North America is the largest consumer of MTBE, accounting for about two-thirds of the world's annual use (IPCS, 1998). In 1996, the US was the world's largest consumer of MTBE with a usage of 10.6 million tons (12.2 billion pounds) per year.

The major use of MTBE is as an oxygenated additive in gasoline, in which it is blended at 2 to 11.5% by volume (ECB, 2002). IPCS (1998) reports that MTBE has been added to gasoline in concentrations up to 17% by volume. Only a minor amount is used for other purposes, such as solvent instead of diethyl ether or diisopropyl ether in both the chemical and pharmaceutical industry and laboratories (ECB, 2002). Approximately 25% of gasoline in the USA is blended with MTBE (IPCS, 1998). MTBE is almost exclusively used to provide both octane enhancement and an increase in the oxygen content of gasoline. No approved uses for MTBE as a direct or indirect food additive were identified under Title 21 of the U.S. Code of Federal Regulations (U.S. FDA, 2010).

3.0 ANALYTICAL METHODS

3.1 Analysis in Water

Sorption/desorption, including purge and trap systems, and headspace procedures have been used to prepare water for analysis of MTBE (IPCS, 1998). The analytical methods for MTBE in water have been reviewed by IPCS (1998). These methods include the static headspace procedure using gas chromatography with photoionization detection (GC-PID) with a detection limit of 10.8 $\mu g/m^3$ and the purge and trap procedure using gas chromatography-mass spectrometry with detection limits ranging from 0.06 to 5 µg/L. NSF International uses U.S. EPA (1995) method 502.2 employing gas chromatography for volatile compounds to detect MTBE as an extractant from drinking water system components tested to NSF/ANSI Standard 61 (2009). The reporting limit is 0.5 µg/L.

3.2 Analysis in Biological Matrices

MTBE is analyzed in biological matrices generally by gas chromatography, using a range of capillary columns and detector systems suited to the specific matrix (IPCS, 1998).

4.0 SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

4.1 Sources of Human Exposure

MTBE does not occur naturally in the environment (IPCS, 1998). Groundwater may become contaminated with MTBE through leaking underground storage tanks or spillage from overfilling of the storage tanks (ECB, 2002). In the USA, MTBE has been detected in storm water, surface water, including streams, rivers, and reservoirs, groundwater, and drinking water (IPCS, 1998). MTBE is infrequently detected in public drinking-water systems from groundwater. In all but three out of 51 systems in which it was reported, the concentration was ≤20 µg/L. There are inadequate data to characterize the concentration of MTBE in public drinking-water systems from surface water. MTBE has been found at high levels (i.e. ≥1,000 µg/L) in a few private wells used for drinking water (IPCS, 1998). MTBE has been detected as an extractant from drinking water system components tested to NSF/ANSI 61 (2009) at normalized concentrations up to 0.2 mg/L.

Workers with potential exposure to MTBE include those involved in the production, distribution, and use of MTBE and MTBE-containing gasoline, including service station attendants and mechanics (IPCS, 1998). The sources of industrial occupational exposure to MTBE have been reviewed by ECB (2002) and include individuals involved in the production, formulation, transportation, or distribution of MTBE. These exposures include personnel employed at service stations, those involved in maintenance operations and automotive repairs, and individuals in the chemical or pharmaceutical industries in which MTBE is used as a solvent. Exposure of the public to MTBE can be principally by inhalation of fumes while refueling motor vehicles and drinking contaminated water (McGregor, 2006). Maximum internal doses resulting from such exposures are unlikely to exceed 0.05 mg/kg-day and will normally be very much lower.

4.2 Sources of Environmental Exposure

MTBE may enter the environment during all phases of the petroleum fuel cycle (IPCS, 1998). Sources include auto emissions, evaporative losses from gasoline stations and vehicles, storage tank releases, pipeline leaks, other accidental spills, and refinery stack releases. Annual estimates of MTBE mass releases to the environment from all potential sources have not been reported in the scientific literature. However, releases from storage tanks, vehicular emissions, and evaporative losses from gasoline stations and vehicles are perceived to be important sources.

Concentrations of MTBE detected in storm water ranged from 0.2 to 8.7 µg/L with a median of less than 1.0 µg/L. For streams, rivers, and reservoirs, the range of detection was from 0.2 to 30 µg/L, and the range of medians for several studies was 0.24 to 7.75

µg/L. MTBE has generally not been detected in deeper groundwater or in shallow groundwater in agricultural areas. When detected, the concentration is less than 2.0 µg/L. MTBE is more frequently found in shallow groundwater (top 5-10 feet of these aquifers) in urban areas. In this setting, the concentrations range from less than 0.2 µg/L to 23 mg/L, with a median value below 0.2 µg/L (IPCS, 1998).

5.0 COMPARATIVE KINETICS AND METABOLISM IN HUMANS AND LABORATORY ANIMALS

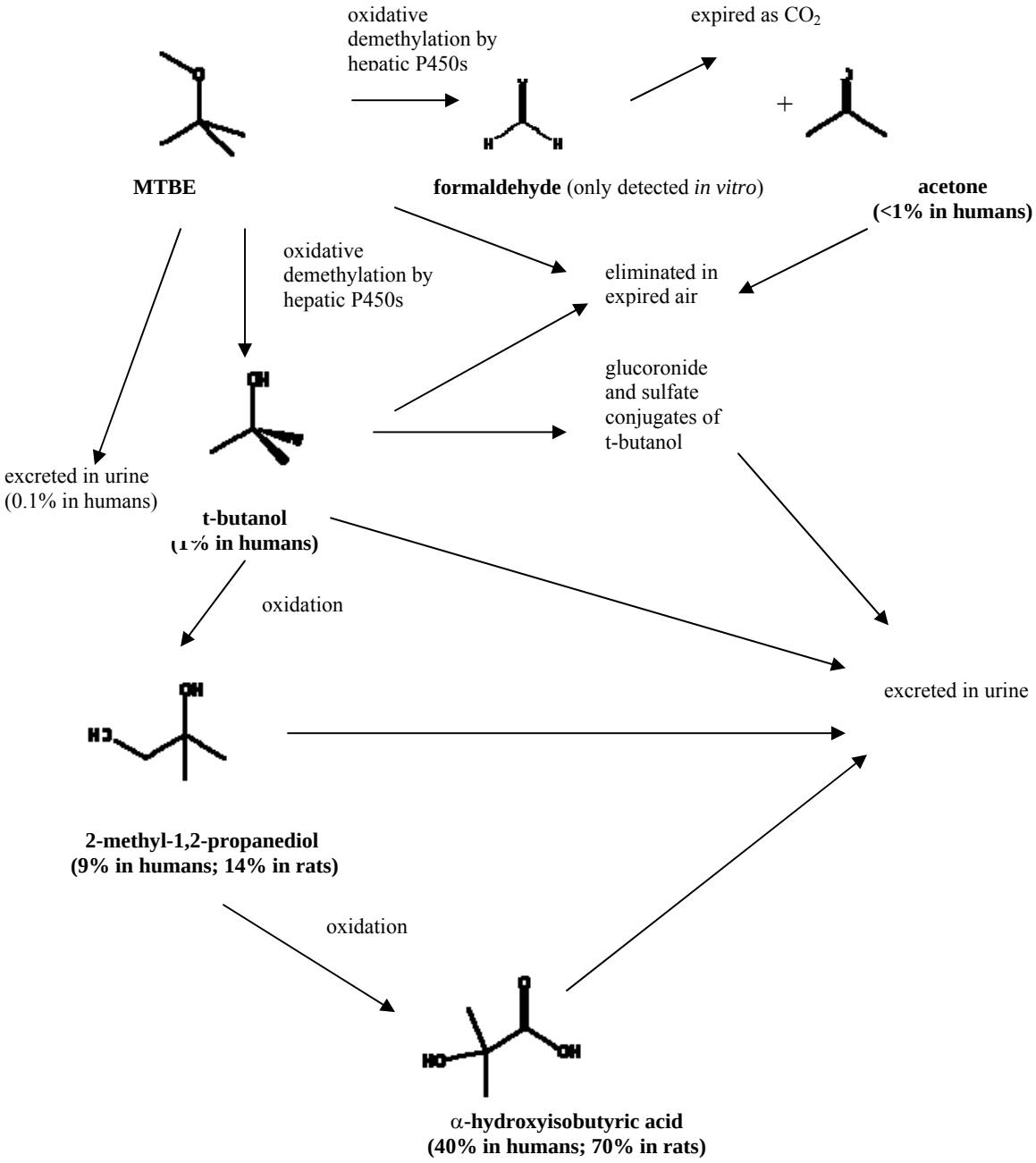
Numerous studies investigating the kinetics and metabolism of MTBE in humans and laboratory animals are available. These data have been reviewed by several regulatory organizations, including European Chemicals Bureau (ECB, 2002), Office of Environmental Health Hazard Assessment of the California EPA (OEHHA, 1999), the International Programme on Chemical Safety of the World Health Organization (IPCS, 1998), the European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC, 1997), the Agency for Toxic Substances and Disease Registry (ATSDR, 1996), and Health Canada (1992). Several review articles on these data are also available in the scientific literature.

MTBE was absorbed into the blood of human volunteers who rapidly drank 2.8 mg MTBE in 250 mL Gatorade (Prah et al., 2004). Mean blood levels of MTBE peaked at 0.17 µmol/L between 15 and 30 minutes following administration and declined to at or below the detection limit (0.05 µmol/L) at the 24-hour sampling period. In human volunteers who rapidly drank 6.7 µl MTBE in "about 5 mg" of lemon-lime solution, peak blood levels of MTBE ranged from 5 to 15 ng/ml (0.06-0.17 µmol/l) (ECB, 2002).

In rodents, MTBE is well absorbed and distributed following oral administration (IPCS, 1998). Rapid and complete absorption across the gastrointestinal tract was observed in rats administered MTBE via gavage at 40 mg/kg (ECB, 2002). At 400 mg/kg oral exposure in rats, the percentage of total absorbed dose eliminated in expired air increased with a corresponding decrease in the percentage eliminated in urine, indicating a saturation of metabolism (IPCS, 1998).

In vivo studies on the metabolism of MTBE in humans and rats indicate qualitatively similar overall metabolism (ECB, 2002). MTBE is oxidatively demethylated by microsomal enzymes to t-butanol and formaldehyde, but the latter has only been shown *in vitro*. In rodents, the biotransformation of t-butanol has been shown to yield 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid (Figure 1).

Figure 1. Proposed metabolic scheme of MTBE



The cytochrome P450-mediated biotransformation of MTBE has been explored in several *in vitro* studies with liver microsomes from humans, rats, and mice (ECB, 2002). Metabolism of MTBE by rat liver microsomes produced equivalent amounts of formaldehyde and t-butanol, and data strongly suggest that when expressed, CYP2B1 is the major enzyme involved in MTBE demethylation and that CYP2E1 may have a minor role.

Since these kinetic and metabolism data for MTBE in humans and laboratory animals have been reviewed previously, the current review focuses on only the new oral data since these reviews. Recent data confirm that MTBE is rapidly absorbed following oral administration. Approximately 30% of administered dose in humans was cleared by exhalation as unchanged MTBE and as t-butanol within 10-20 min. Less than 0.1% of the administered dose was recovered in expired air as acetone. Approximately 50% of the administered dose in humans was eliminated in the urine as unchanged MTBE (~0.1%), t-butanol (~1%), 2-methyl-1,2-propanediol (~9%), and 2-hydroxyisobutyrate (~40%).

5.1 Absorption

Previous data in humans or laboratory animals demonstrate that MTBE is rapidly absorbed following oral administration. Data by Prah et al. (2004), Amberg et al. (2001), and Dekant et al. (2001) confirm this observation. MTBE was rapidly absorbed from the gastrointestinal tract and a significant part of the administered dose was transferred into blood of human volunteers ingesting MTBE in water or Gatorade. No other recent data regarding the absorption of MTBE following oral exposure in humans or laboratory animals were identified.

5.2 Distribution

Recent data regarding the distribution of MTBE after oral exposure were limited to the measurement of MTBE and one of its metabolites, t-butanol, in blood after oral ingestion in human volunteers.

Fourteen healthy male volunteers ingested 2.8 mg MTBE (unspecified purity) in 250 mL Gatorade (Prah et al., 2004). Gatorade was used as the vehicle to mask the unpleasant taste of MTBE. Blood samples were collected after 0, 5, 15, 30, 45, 60, 75, 90, 105, 120, 180, 240, 360, and 1,440 minutes. Mean levels of MTBE and t-butanol in the blood were determined using gas chromatography/mass spectrometry. The plasma half-life of MTBE was determined. The area under the plasma concentration versus time curve was estimated for MTBE alone and for MTBE plus t-butanol.

Mean blood levels of MTBE peaked at 0.17 μmol/L between 15 and 30 minutes following administration and declined to at or below the detection limit (0.05 μmol/L) at the 24-hour sampling period. Blood levels of t-butanol peaked at 0.23 μmol/L at the 45-minute sampling period and did not return to pre-exposure levels by the 24-hour sampling period. Elimination of MTBE from the blood was best characterized by a three-compartment model. The mean half-life for MTBE elimination from the blood in the first, second, and third phases was 14.9, 102.0, and 417.3 minutes, respectively. The mean area under the plasma concentration versus time curve was estimated to be 1,682 μmol/hr/L for MTBE alone, 20,025 μmol/hr/L for t-butanol, and 10,854 μmol/hr/L for MTBE and t-butanol combined. The mean area under the curve ratio of t-butanol to MTBE was 13.1 in the blood. Since this study also included the dermal and inhalation routes of exposure, the study authors suggested that these pharmacokinetic estimates

were useful in constructing a physiologically-based pharmacokinetic model for MTBE in humans across different routes of administration.

Three human volunteers per sex and dose ingested 0, 5, or 15 mg ^{13}C-MTBE in 100 mL water (Amberg et al., 2001; Dekant et al., 2001). Blood samples were collected at 60-minute intervals for the first four hours and at 120-minute intervals thereafter until 12 hours. A final blood sample was collected 24 hours after administration.

At 5 mg, the maximum concentration in the blood averaged 0.10 μM, and these concentrations were obtained with the first blood samples, which were taken after one hour. Elimination of MTBE from the blood occurred in three phases, and the mean half-life of each phase was 0.8, 1.8, and 8.1 hours. Mean blood concentrations of t-butanol were 1.82 uM. The mean terminal half-life of t-butanol clearance from the blood was 8.1 hours. Levels of MTBE and t-butanol in blood declined to at or near the limit of detection at the 12- and 24-hour sampling times, respectively.

At 15 mg, the maximum concentration in the blood, which was reached after one hour, averaged 0.69 μM. Elimination of MTBE from the blood occurred in three phases, and the mean half-life of each phase was 0.7, 1.2, and 3.7 hours. Mean blood concentrations of t-butanol were 0.45 uM. The mean terminal half-life of t-butanol clearance from the blood was 8.5 hours.

5.3 Metabolism

5.3.1 Humans

The metabolism of MTBE was studied in three human volunteers per sex and dose after ingestion of 0, 5, or 15 mg ^{13}C-MTBE in 100 mL water (Amberg et al., 2001; Dekant et al., 2001). Mass spectrometry was used to identify urinary metabolites in urine samples collected at 6-hour intervals for 96 hours. At 5 and 15 mg, 46% and 49%, respectively, of the administered dose was eliminated in the urine as unchanged MTBE, t-butanol, 2-methyl-1,2-propanediol, and 2-hydroxyisobutyrate. At 5 mg, unchanged MTBE, t-butanol, 2-methyl-1,2-propanediol, and 2-hydroxyisobutyrate comprised 0.01, 1, 9, and 36% of the administered dose, respectively. At 15 mg, unchanged MTBE, t-butanol, 2-methyl-1,2-propanediol, and 2-hydroxyisobutyrate comprised 0.1, 1, 8, and 40% of the administered dose, respectively. Hepatic first-pass metabolism was not observed. The authors concluded that the metabolic pathway for MTBE after oral exposure was identical to concurrently conducted inhalation exposure studies.

The metabolism of MTBE was studied in a panel of 12 human liver microsomes isolated from nine male and two female donors (Le Gal et al., 2001). The human liver microsomes metabolized MTBE into t-butanol and formaldehyde. The mean Michaelis-Menten constant (Km), which describes the catalytic power of an enzyme or rate of a reaction catalyzed by an enzyme, was determined. The mean apparent Km(1) was determined to be 0.25 mM, which was considered low by the study authors, and the mean apparent Km(2) was 2.9 mM, which was considered high. The study authors concluded

that kinetic data, along with the results from correlation studies and chemical inhibition studies, support the assertion that the major enzyme involved in MTBE metabolism is CYP2A6, with a minor contribution of CYP3A4 at low substrate concentration.

5.3.2 Laboratory Animals

Williams and Borghoff (2000) investigated the hypothesis that MTBE-induced decrease in serum testosterone levels in male rats may be due in part to the ability of MTBE to induce the metabolism of endogenous testosterone and, hence, enhance its clearance. Fifteen male Sprague-Dawley rats per dose were administered 0 or 1,500 mg/kg-day MTBE (> 99.9% purity in corn oil) via gavage for 15 days. In a second experiment, fifteen male Sprague-Dawley rats per dose were administered 0, 250, 500, 1,000, or 1,500 mg/kg-day MTBE (> 99.9% purity in corn oil) via gavage for 28 days. At study termination, the rats were sacrificed, body and liver weights were determined, and hepatic microsomes were isolated for measurement of CYP450 activity. Testosterone hydroxylase activities of hepatic microsomes, which were used as markers for CYP450 enzyme activities, were also assessed. These enzymes included 2-α-, 2-β-, 6-β-, 7-α-, 16-α-, and 17- β-hydroxytestosterone. The activities of p-nitrophenol and UDP-glucuronosyltransferase were also assessed to evaluate the mechanism of centrilobular hypertrophy observed in rodents after repeated MTBE exposures. The formation of formaldehyde, a metabolite of MTBE, was also measured.

After 15 days, total hepatic microsomal cytochrome CYP450 was increased 1.3-fold in rats treated with 1,500 mg/kg-day MTBE. CYP1A1/2, CYP2A1, CYP2E1, and CYP2B1/2 activities were increased 1.5-, 2.4-, 2.3-, and 6.5-fold, respectively, at 1,500 mg/kg-day after 15 days. 7-α-hydroxytestosterone was statistically increased by 2.4-fold compared to controls.

After 28 days, total hepatic microsomal cytochrome CYP450 was not statistically different compared to control. At 1,000 mg/kg-day after 28 days, a statistical increase in mean relative liver weight (10-14%, not further specified) and a 2.0-fold increase in CYP2B1/2 were observed compared to controls.

After 28 days at 1,500 mg/kg-day, a statistical increase in mean relative liver weight (10-14%, not further specified) was observed. CYP 2B1/2, CYP2E1, CYP3A1/2, and UDP-glucuronosyltransferase activities were statistically increased by 2.9-, 2.0-, 2.1-, and 1.7-fold respectively, compared to controls. 6-β-hydroxytestosterone was statistically increased by 2.1-fold compared to controls. UDP-glucuronosyltransferase was statistically increased compared to controls. Formaldehyde production was statistically increased compared to controls at 1,500 mg/kg-day after 28 days. MTBE also induced its own metabolism 2.1-fold at 1,500 mg/kg-day after 28 days, and the authors noted that this effect was consistent with the induction of CYP2E1 and CYP2B1. It should be noted that mean body weight was reduced by 12% compared to controls at 1,500 mg/kg-day after 28 days.

The study authors concluded that MTBE induced mild increases in testosterone hydroxylase enzymes. Further, the increase in UDP-glucuronosyltransferase was consistent with the centrilobular hypertrophy observed in rodents after repeated MTBE exposures. The decrease in serum testosterone observed following MTBE administration may be the result of enhanced testosterone metabolism and subsequent clearance. However, the authors stated that the most pronounced effects were observed at the high dose of 1,500 mg/kg-day, at which clinical signs of toxicity and reduced body weight (12%) were also observed. The authors further noted that since the increases in testosterone hydroxylase enzyme activities were generally mild, the hypothalamus-pituitary hormonal feedback loop could be expected to compensate for mild reductions in circulating testosterone *in vivo*.

Eight female $B6C3F_1$ mice per dose were given MTBE (> 99.95% purity in corn oil) by gavage at 0 or 1,800 mg/kg-day for three days (Moser et al., 1996). Food and water were available *ad libitum*. Eighteen hours after the last dose, the mice were sacrificed and hepatocyte cytochromes were isolated. MTBE induced a statistical increase (37%) in total hepatic cytochrome P450 content, a 9-fold increase in hepatic 7-pentoxy-resorufin-*O*-dealkylase activity (a CYP2B marker) and a 2-fold increase in hepatic 7-ethoxy-resorufin-*O*-deethylase activity compared to controls.

5.4 Elimination/Excretion

The elimination of MTBE and t-butanol in expired air was investigated in seven healthy male volunteers who ingested 2.8 mg MTBE (unspecified purity) in 250 mL Gatorade (Prah et al., 2004). Gatorade was used as the vehicle to mask the unpleasant taste of MTBE. Exhaled air samples were collected after 0, 5, 15, 30, 45, 60, 75, 90, 105, 120, 180, 240, 360, and 1,440 minutes. Mean levels of MTBE and t-butanol in exhaled air were determined using gas chromatography/mass spectrometry.

Elimination of MTBE from expired air was best characterized by a three-compartment model. The mean half-life for MTBE in expired air in the first, second, and third phases was 13.0, 63.1, and 254.0 minutes, respectively. The mean area under the curve ratio of t-butanol to MTBE was 0.175 in exhaled air. Since this study also included the dermal and inhalation routes of exposure, the study authors suggested that these pharmacokinetic estimates were useful in constructing a physiologically-based pharmacokinetic model for MTBE in humans across different routes of administration.

The urinary elimination of MTBE was examined in three healthy human volunteers per sex administered 5 and 15 mg ^{13}C-MTBE (> 98% purity) in spiked tap water samples (Amberg et al., 2001). The different doses were administered four weeks apart. Urine samples were collected for 96 hours after administration in six hour intervals, and blood samples were taken in 60-minute intervals up to four hours, then at 120-minute intervals up to 12 hours, and ultimately at 24 hours. MTBE and t-butanol concentrations in blood were determined. Urine metabolites, including the parent compound, t-butanol, 2-methyl-1,2-propanediol, and 2-hydroxyisobutyrate were quantified.

At 5 and 15 mg/kg, 46% and 49%, respectively, of the administered dose was eliminated in the urine as unchanged MTBE, t-butanol, 2-methyl-1,2-propanediol, and 2-hydroxyisobutyrate. The authors concluded that the kinetics of excretion after oral exposure were identical to concurrently conducted inhalation exposure studies.

In the same experiment, the respiratory elimination of MTBE was examined in three healthy male volunteers administered 15 mg ^{13}C-MTBE (> 98% purity) in 100 mL tap water samples (Amberg et al., 2001). Approximately 30% of the MTBE dose was cleared by exhalation as unchanged MTBE and as t-butanol. MTBE exhalation was rapid and maximum concentrations of 100 nM in exhaled air were achieved within 10-20 minutes. Less than 0.1% of the administered dose was recovered in expired air as ^{13}C-acetone. The study authors concluded that the results indicate that the biotransformation and excretion of MTBE after oral exposure is similar to inhalation exposure and suggested the absence of a significant first-pass metabolism of MTBE in the liver after oral administration.

5.5 Physiologically-based pharmacokinetic models

Although several physiologically-based pharmacokinetic models have been constructed to model the behavior of inhaled MTBE, models describing the behavior of MTBE after oral exposure are limited and usually include multiple exposure routes. Kim et al. (2007) developed a multiple-route (oral, inhalation and dermal) nine-compartment model of MTBE and t-butanol in humans based on blood measurements of these compounds. Borghoff et al. (1996) developed a multiple-route (oral, inhalation and intravenous) seven-compartment model of MTBE and t-butanol in F344 rats. A model describing MTBE-binding to α-2μ-globulin in the kidneys of male rats that inhaled MTBE has also been developed (Leavens and Borghoff, 2009).

6.0 EFFECTS ON HUMANS

6.1 Case Reports

No recent case reports regarding oral exposure to MTBE were identified.

6.2 Epidemiological Studies

Epidemiological studies of human populations exposed under occupational as well as non-occupational conditions, and experimental studies of human volunteers exposed under controlled conditions, have not been able to identify a basis for headache, eye and nose irritation, cough, nausea, dizziness, and disorientation reported by consumers in some areas as a result of fueling with gasoline (IPCS, 1998). Although results are mixed, IPCS (1998) suggested that community studies conducted in Alaska, New Jersey, Connecticut, and Wisconsin provided limited or no evidence of an association between MTBE exposure and the prevalence of health complaints. A review of these epidemiology studies by Phillips et al. (2008) reached a similar conclusion based primarily on the limitations of the study designs.

In controlled experimental studies on adult volunteers exposed in inhalation chambers to MTBE at concentrations ranging from 5.0 mg/m^3 (1.4 ppm) to 270 mg/m^3 (75 ppm), there were no evident effects on either subjective reports of symptoms or objective indicators of irritation or other effects up to 180 mg/m^3 (50 ppm) for up to two hours (IPCS, 1998). Thus, it appears unlikely that MTBE alone induces adverse acute health effects in the general population after inhalation exposure. However, the potential effects of mixtures of gasoline and MTBE, and the manner in which most persons are exposed to MTBE in conjunction with the use of oxygenated fuels, have not been examined experimentally or through prospective epidemiological methods.

Occupational exposure to MTBE (96 Chinese petroleum factory workers aged 20 to 49, mean age 29) compared to 102 controls was investigated by Zhou and Ye (1999). Based on self-reported responses to a questionnaire, occupationally exposed workers reported health complaints (62 cases, 65%) significantly more than controls (16 cases, 17%). Data were analyzed with an Epi Info 6 and SAS statistical package and logistical regression was used to identify confounding factors. The most frequently reported symptoms in occupationally exposed workers were eye irritation (20%), dizziness (19%), burning sensation in the nose or throat (18%), insomnia (14%), nausea or vomiting (14%), headache (13%), fatigue (13%), poor memory (13%), irritability (6%) and skin irritation or redness (5%). Among these workers, 65 were male and 31 were female; 40 were smokers and 56 were nonsmokers, and among the 56 nonsmokers 22 were negative smokers; 9 workers drank and 87 did not drink. The duration of exposure was 1 to 10 years. The TWA (time weighted average) concentrations of MTBE in workplaces ranged from 10 ppm to 56 ppm (36 mg/m^3 to 202 mg/m^3). The 102 unexposed controls (aged from 20 to 49, mean age 28) were from the same factory. Of these controls, 69 were male and 33 were female; 45 were smokers and 57 were nonsmokers, and among the 57 nonsmokers 20 were negative smokers; 6 workers drank and 96 did not drink. The list of symptoms including dizziness, headache, eye irritation, burning sensation in the nose or throat, anxiety, "spaciness" or disorientation, insomnia, fever, sweats or chills, inability to concentrate, irritability, fatigue, poor memory, skin irritation or redness, muscle aches, nausea or vomiting, fatigue, fever, diarrhea, cough, difficulty in breathing, sneezing, bronchitis, rashes and others. Gemder, age, exposure duration/day, length of service, or drinking or smoking habits did not statistically influence the prevalence of symptoms. The study authors did not indicate whether they accounted for potential concurrent exposures to other chemicals in the occupationally-exposed individuals.

7.0 EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Numerous regulatory organizations, including European Chemicals Bureau (ECB, 2002), Office of Environmental Health Hazard Assessment of the California EPA (OEHHA, 1999), the World Health Organization (WHO, 2005; IPCS, 1998), the European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC, 1997), U.S. EPA (1997), the Agency for Toxic Substances and Disease Registry (ATSDR, 1996), and Health Canada (1992) have critically reviewed the studies in laboratory animals for MTBE. This section

includes only the oral studies for MTBE, due to their significance in the development of lifetime drinking water levels for MTBE, since studies by the inhalation and/or dermal routes have been critically reviewed elsewhere.

In addition to the previously reported gavage toxicity studies identified by NSF International in the February 2008 draft assessment for MTBE, recently published short-term drinking water studies in adult and juvenile CD-1 or BALB/c mice (de Peyster et al., 2008), short-term gavage studies in SD rats (Dongmei et al., 2009) as well as preliminary details for unpublished short- and long-term drinking water studies in Wistar rats (Bermudez et al., 2007, 2008, 2009) have become available.

No evidence of hepatic peroxisome proliferation was observed in male rats administered MTBE via gavage at 800 mg/kg-day for 14 days. Increased mean relative liver weight, cholesterol levels, and/or minimal-to-moderate centrilobular hypertrophy were observed in rats administered MTBE via gavage at 1,000 mg/kg-day and above for 28 days. Subchronic gavage and drinking water exposures to MTBE were associated with increased mean absolute and relative kidney weights in male rats accompanied by hyaline droplet formation, renal tubular cell regeneration, and/or α-2μ-globulin immunoreactivity in the proximal tubules. Gavage but not drinking water exposure to MTBE for 90 days was associated with increased mean liver weights, liver-associated blood effects (apartate aminotransferase, blood urea nitrogen, and/or cholesterol) and/or centrilobular hepatocyte hypertrophy in rats. Mean relative testes weights were reduced in the absence of associated histopathology in male rats that received MTBE at 384 mg/kg-day in their drinking water for one-year. Chronic gavage exposure to MTBE was associated with an increase in Leydig cell tumors in male rats and leukemias/lymphomas (combined) in female rats.

7.1 Limited-Exposure Effects

MTBE was found to be irritating to the eyes and skin of rabbits, but did not induce skin sensitization in guinea pigs.

7.1.1 Irritation and Sensitization Studies

Following the application of 0.5 mL of neat MTBE to the intact and abraded skin of six rabbits for 24 hours, a primary irritation index of 3.36 was reported, which was considered "moderately" irritating to skin (IPCS, 1998). Moderate erythema and edema were observed. Effects were slightly more pronounced on abraded skin. In mice, MTBE can induce slight to severe respiratory irritation following inhalation of 300 to 30,000 mg/m^3, respectively. A 1% induction and challenge concentration of MTBE did not induce skin sensitization in twenty guinea pigs (IPCS, 1998).

7.1.2 Ocular Exposure Studies

MTBE was irritating to the eyes of rabbits and caused mild, but reversible, changes (IPCS, 1998).

7.2 Single-Exposure Studies

The oral (gavage) LD_{50} for MTBE is approximately 3,800 mg/kg in rats (IPCS, 1998) and 4,000 in mice (OEHHA, 1999). An LD_{50} of 3,433 mg/kg in SD rats has also been reported (Dongmei et al., 2008). Signs of intoxication after a single oral lethal dose consisted of central nervous system depression, ataxia, labored respiration, and death.

7.3 Short-Term Exposure Studies

7.3.1 Three-Day Gavage Study in Female $B6C3F_1$ Mice

Eight female $B6C3F_1$ mice per dose were given MTBE (> 99.95% purity in corn oil) by gavage at 0 or 1,800 mg/kg-day for three days (Moser et al., 1996). Food and water were available *ad libitum*. Eighteen hours after the last dose, the mice were sacrificed and hepatocytes were isolated for measurement of hepatocyte proliferation *in vitro,* expressed as the amount of 5-bromo-2'-deoxyuridine incorporation into hepatocyte nuclei. The hepatic labeling index was calculated by dividing the number of labeled nuclei by the total number of nuclei and multiplying by 100. Body weight and absolute and relative liver weights were also measured. Body and liver weights were not affected by treatment, but MTBE induced a statistical increase in the hepatocyte labeling index of 6.5% compared to 2.5% in controls.

7.3.2 Fourteen-Day Drinking Water Study in Wistar Rats

Wistar rats were administered MTBE via the drinking water at 0, 3, 7, or 15 mg/mL for 14 days (Bermudez et al., 2007). The mean received doses were 0, 371, 799, or 1,624 mg/kg-day in males and 0, 363, 843, or 1,839 mg/kg in females. Body weights, clinical signs, and food and water consumption were monitored daily. Kidneys and testes weights were recorded. Hematology included hematocrit, blood urea nitrogen, serum creatinine, and blood levels of MTBE and t-butanol. Airborne concentrations of MTBE averaged ≤0.2 ppm in ambient air and control cages and ≤33 ppm in high-dose cages throughout the study. Consumption of water was significantly reduced in treated compared to control rats by approximately 20-30% and 35-39%, in males and females, respectively, in the absence of an impact on mean body weight or food consumption. MTBE blood levels averaged ≤2.1 μM, while t-butanol blood concentrations ranged from 38-116 μM. Kidney weights were increased in high-dose male rats. The study authors considered the MTBE exposure to be associated with increased blood t-butanol levels, increased kidney weights in males, and reduced blood urea nitrogen and hematocrit levels in females. Complete study details are not available at this time.

7.3.3 Fourteen-Day Gavage Study in Sprague-Dawley Rats

Ten Sprague-Dawley rats per sex and dose were administered 0, 357, 714, 1,071, or 1,428 mg/kg-day MTBE (99.95% purity in corn oil) by gavage for 14 days (Robinson et al., 1990). The high dose was selected because it was 37% of the LD_{50}. Rats were housed separately by sex and food and water were available *ad libitum*. Mortality and clinical signs were monitored daily. Food and water consumption were measured throughout the study at unspecified intervals. Body weight was measured on Days 0, 4, 6, and 14. Hematology parameters and clinical chemistry were conducted on all rats at study termination. Hematology included hematocrit, hemoglobin, mean corpuscular volume, erythrocytes, leukocytes, differential leukocytes, and reticulocytes. Clinical chemistry included glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, cholesterol, calcium, and phosphorus. Brain, liver, spleen, lung, thymus, kidney, adrenal, heart, and "gonads" weights were measured at study termination, and relative organ-to- body-weight ratios were calculated. Gross necropsies were conducted on all rats at study termination. Histological examinations were conducted on all control and high-dose rats at study termination, and included unspecified "major organs". If target histopathological organs were identified, these organs were also examined histologically in the remaining dose groups.

At 357 mg/kg-day, two males died, but the deaths were attributed to the gavage treatment. Diarrhea was observed in treated rats. Mean creatinine was statistically increased by 16% in males compared to controls. Mean absolute (15%) and relative (16%) lung weights were statistically lower in females compared to controls.

At 714 mg/kg-day, diarrhea and statistically reduced food intake (unspecified magnitude) were observed in males compared to controls. Mean hemoglobin (6%), hematocrit (4%), differential lymphocytes (6%), and creatinine (16%) were statistically increased in males compared to controls. Mean alanine aminotransferase (21%) and cholesterol (22%) were statistically increased and mean serum calcium (6%) was statistically decreased in females compared to controls. Mean absolute (11%) and relative (11%) lung weights were statistically lower in females compared to controls. Mean absolute (12%) and relative (9%) lung weights were statistically lower in males compared to controls.

At 1,071 mg/kg-day, diarrhea was observed in treated rats. Mean erythrocytes (6%), hemoglobin (6%), aspartate aminotransferase (43%), and lactate dehydrogenase (78%) were statistically increased, and mean differential monocytes (33%) were statistically decreased in males compared to controls. Mean cholesterol (34%) was statistically increased in females compared to controls. Mean absolute (14%) and relative (11%) lung weights were statistically lower in females compared to controls.

At 1,428 mg/kg-day, two males and two females died, but the deaths were attributed to gavage. Diarrhea and profound but transient (< two hours) anesthesia were observed after dosing in male and female rats. Statistically reduced food intake (unspecified magnitude) was observed in females compared to controls. Statistically reduced mean terminal body weight of 10% was observed in females compared to controls. Mean

erythrocytes (7%), blood urea nitrogen (14%), aspartate aminotransferase (38%), cholesterol (37%), and lactate dehydrogenase (63%) were statistically increased, and mean differential monocytes (33%) were statistically decreased in males compared to controls. Mean glucose (15%) was statistically increased and mean blood urea nitrogen (27%) and creatinine (20%) were statistically decreased in females compared to controls. Mean absolute (22%) and relative (15%) lung weights were statistically lower in females compared to controls. Mean absolute spleen (18%) and mean absolute (20%) and relative thymus (27%) weights were statistically lower in females compared to controls. Mean relative kidney (8%) and brain (9%) weights were statistically higher in females compared to controls. The incidence of hyaline droplet nephropathy in the renal tubules was "moderately" increased in dosed male rats, but no further details were provided, with the exception that increased hyaline droplets within the cytoplasm of proximal tubular epithelial cells were noted in 7/8 (88%) high-dose males compared with 2/5 (40%) controls.

7.3.4 Fourteen-Day Gavage Studies in Male Sprague-Dawley Rats

In a 14-day gavage study, de Peyster at al. (2003) examined whether MTBE exposure could induce hepatic peroxisome proliferation, since other chemicals that cause Leydig cell tumors in rats were also shown to induce peroxisome proliferation. Six male Sprague-Dawley rats per dose were administered MTBE (> 99.8% purity in corn oil) via gavage at 0 or 800 mg/kg-day via gavage for 14 days. Positive control rats were administered gemfibrozil via the diet. Hepatic peroxisomes were isolated from liver sections and processed for peroxisomal β-oxidation and examined with an electron microscope. Terminal blood samples were collected for measurement of cholesterol, triglyceride, alanine aminotransferase, and aspartate aminotransferease. Liver weights were measured, and relative liver-to-body- weight ratios were calculated. According to the study authors, there were no statistical differences between treated and vehicle control rats, but not all of the data were provided. It should be noted that although the methodology stated that MTBE doses of 800 mg/kg-day were administered, the results section indicated that MTBE doses were 1,000 mg/kg-day.

Ten male Sprague-Dawley rats per dose were administered MTBE (> 99.8% purity in corn oil) via gavage at 0 or 1,200 mg/kg-day for 14 days (de Peyster et al., 2003). This dose was determined in previous experiments to lower circulating testosterone levels without affecting body weight. Liver, testes, accessory sex organs (unspecified), and brain weights were measured. Total protein content and P450 content in hepatic microsomes was determined, and hepatic microsomal aromatase activity was measured.

In rats treated with 1,200 mg/kg-day MTBE, a statistical increase in mean relative liver weight of 15% was observed compared to controls. Although hepatic P450 content was comparable to controls, hepatic microsomal aromatase activity was decreased by 36% compared to controls.

7.3.5 Fifteen-Day Gavage Study in Male Sprague-Dawley Rats

Fifteen male Sprague-Dawley rats per dose were administered 0 or 1,500 mg/kg-day MTBE (> 99.9% purity in corn oil) via gavage for 15 days (Williams and Borghoff, 2000; Williams et al., 2000). At study termination, the rats were sacrificed, body, adrenal, kidney, epididymides, testes, prostate, pituitary gland, seminal vesicle, and liver weights were determined, and histopathological examination of the liver, kidneys, testes, and adrenals was conducted.

There were no treatment-related deaths. Deaths attributed to gavage, which were confirmed at necropsy, were primarily limited to the high-dose rats. Statistically increased mean absolute and relative adrenal weights of 15% and 17%, respectively, were observed at 1,500 mg/kg-day compared to controls. Minimal-to-moderate centrilobular hypertrophy was observed in 8/12 treated rats, but not in controls. The hypertrophy was characterized as increased size and cytoplasmic eosinophilia of hepatocytes that were oriented around central veins, which at times extended into the midzonal region of the lobule. The severity was dose-related and ranged from minimal to moderate, and the authors suggested that the effect was similar to that observed with phenobarbital administration. Protein droplet nephropathy of the kidney was observed in 11/12 treated rats and 1/15 controls.

7.3.6 Two- and Four-Week Gavage Studies in SD rats

Ten male SD rats per dose and exposure duration received MTBE (99.8% purity in peanut oil) via gavage at 0, 400, 800, or 1,600 mg/kg-day for two or four weeks (Dong-mei et al., 2009a). The basis of the dose selection was not specified. Mortality, body weight, and food consumption were recorded daily. Terminal hematology (total and differential leukocytes, erythrocytes, hemoglobin, hematocrit, mean corpusular volume, mean corpusular hemoglobin, mean corpusular hemoglobin concentration, red blood cell volume distribution width, and platelets) and clinical chemistry (alanine amiotransferase, aspartate aminotransferase, total protein, albumin, globulin, alkaline phosphatase, urea, creatinine, cholesterol, triglyceride, high- and low-density lipoprotein cholesterol) parameters were included for all dose groups. Brain, heart, liver, spleen, lung, kidneys, testes, epididymis, thymus, and prostate weights were recorded at study termination.

In both the two- and four-week studies, transient signs of central nervous system depression were observed in treated rats at an unspecified incidence, particularly at the high-dose.

In the two-week study, one low- and mid-dose rat each died. Mean creatinine level was reduced ($p<0.01$) at all doses compared to controls. The decrease was 22%, 28%, and 33% lower than controls at 400, 800, and 1,600 mg/kg-day, respectively. Mean relative testes to body weight ratios were statistically ($p<0.05$) decreased in a non-dose-related manner in all treated groups. The decrease was 12%, 11%, and 12% lower than controls at 400, 800, and 1,600 mg/kg-day, respectively. At the mid-dose and higher, mean alanine aminotransferase was reduced ($p<0.01$) compared to controls. The decrease was

31% and 40% lower than controls at 800 and 1,600 mg/kg-day, respectively. Mean relative thymus weight was 24% and 20% lower ($p<0.05$) than controls at 800 and 1,600 mg/kg-day, respectively. At the high-dose after four weeks, mean cholesterol was increased (9%) compared to controls and an increase ($p<0.001$) in mean leukocytes counts (55%) was accompanied by a shift in differential counts of various populations. Mean relative heart (17%) and liver (11%) weights were increased in high-dose rats compared to controls.

In the four-week study, one rat each in the control, mid- and high-dose group died. Three low-dose rats died but the cause of death was not reported. Mean creatinine level was reduced at all doses compared to controls. The decrease was 19% ($p<0.05$), 23% ($p<0.01$), and 30% ($p<0.01$) lower than controls at 400, 800, and 1,600 mg/kg-day, respectively. Mean low-density lipoprotein was reduced at the mid- and high-dose compared to controls. The decrease was 13% ($p<0.05$) and 31% ($p<0.01$) lower than controls at 800 and 1,600 mg/kg-day, respectively. Mean globulin was increased (14%, $p<0.01$) and alkaline phophatase (36%, $p<0.01$) and triglycerides (22%, $p<0.05$) were decreased at the high-dose. Other sporadic statistical differences in various clinical chemistry parameters, inlcuding alanine aminotransferase, aspartate aminotransferase, cholesterol and high-density lipoprotein, were not considered biologically-significant due to the lack of a dose response. Mean eosinophil counts were increased ($p<0.05$) in mid- (50%) but not high-dose rats and mean hemoglobin was increased ($p<0.05$) in high-dose rats. Mean relative liver (15%) and kidney (7%) weights were increased ($p<0.05$) in mid-dose rats but not high-dose rats. Mean relative prostate weights (33%) were increased ($p<0.05$) in high-dose rats. The study authors considered the possibility that MTBE may be associated with testicular atrophy or necrosis. However, the authors of the present assessment consider the decrease in mean relative testes weights in treated males after two-weeks to likely be due to an unusually high control mean relative weight since there was no dose-response and the effect was not seen after four weeks of exposure to the same doses or in a separate study conducted under the same protocol (two-week exposure with the same doses; Dongmei et al., 2008). The study authors did not identify a NOAEL.

7.3.7 Three-Week Gavage Study in CD-1 Mice

CD-1 mice were administered MTBE via gavage five days per week for three weeks (Ward et al., 1994). This study was not available, but OEHHA (1999) and ATSDR (1996) indicated that no effects on body weight or unspecified reproductive parameters were observed at doses up to 1,000 mg/kg, and thus identified the NOAEL as 1,000 mg/kg (or 714 mg/kg-day).

7.4 Long-Term and Chronic Exposure Studies

7.4.1 Subchronic Studies

7.4.1.1 Four-Week Gavage Studies In Sprague-Dawley Rats

Ten Sprague-Dawley rats per sex and dose were administered MTBE (unspecified purity unspecified in water vehicle) via gavage at 0, 90, 440, or 1,750 mg/kg for five days per week for four weeks (Johnson et al., 1992; Klan et al., 1992). These doses were approximately equivalent to 0, 64, 314, or 1,250 mg/kg-day. Rats were housed individually, and food and water were available *ad libitum*. Mortality and clinical signs were monitored daily. Body weights were measured weekly. Hematology and clinical chemistry were conducted on all rats at study termination. Hematology included erythrocytes, platelets, leukocytes, differential leukocytes, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, globulin, and albumin/globulin ratio. Clinical chemistry included glucose, creatine kinase, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood urea nitrogen, creatinine, sodium, pottasium, calcium, chloride, total protein and bilirubin, albumin, cholesterol and triglycerides. Adrenal, brain, ovary, testes, heart, kidney, liver, and spleen weights were measured, and relative organ-to-body-weight ratios were calculated. Gross necropsies were performed on all rats at study termination. Histological examinations were conducted on all control and high-dose rats at study termination, and included the adrenals, aorta, brain, cecum, colon, duodenum, epididymides, esophagus, eye, heart, ileum, jejunum, kidneys, liver, lung, mammary glands, muscle, nerve, ovaries, pancreas, pituitary, prostate, rectum, salivary gland, seminal vesicle, skin, spleen, stomach, testes, thymus, thyroid/parathyroid, trachea, urinary bladder, and uterus. If effects were noted, the same organs were examined in the lower doses as well.

No non-gavage-related deaths occurred at any dose. At 64 mg/kg-day, transitory (<one hour after dosing) salivation was observed in several rats. Mean corpuscular hemoglobin was statistically increased in females by 4% compared to controls. Mean alkaline phosphatase was statistically increased in males by 15% compared to controls. Mean relative kidney weights were increased in females by 6% compared to controls.

At 314 mg/kg-day, transitory (<one hour after dosing) salivation was observed in all rats, and hypoactivity and/or ataxia was observed in several rats. Mean erythrocytes were statistically increased in males by 6% compared to controls. Mean relative kidney weights were statistically increased in males by 8% compared to controls. Hyaline droplet formation in the proximal convoluted tubules was observed in 7/10 males.

At 1,250 mg/kg-day, transitory (<one hour after dosing) salivation was observed in all rats, and hypoactivity and/or ataxia was observed in several rats. Mean corpuscular hemoglobin was statistically increased in females by 3% compared to controls. Mean total protein was statistically increased by 8% in females compared to controls, and cholesterol was statistically increased in males by 20% and females by 26% compared to controls. Mean relative kidney weights were increased in males by 13% and females by

17% compared to controls. Mean relative liver weights were increased in males by 8% and females by 12% compared to controls. Mean relative adrenal weights were increased in males by 19% compared to controls. Hyaline droplet formation in the proximal convoluted tubules was observed in 9/10 males. Various effects in the stomach, including submucosal edema, subacute inflammation, epithelial hyperplasia, and ulceration were observed in up to 4/7 males and 5/10 females. The effects were largely confined to the forestomach.

The study authors concluded that the hyaline droplet formation in the proximal tubules in males was attributable to α-2μ-globulin nephropathy, which was not relevant to humans. Further, the stomach lesions were attributable to local irritation, which was not considered a direct result of systemic toxicity.

Fifteen male Sprague-Dawley rats per dose were administered 0, 250, 500, 1,000, or 1,500 mg/kg-day MTBE (> 99.9% purity in corn oil) via gavage for 28 days (Williams and Borghoff, 2000; Williams et al., 2000). At study termination, the rats were sacrificed, body, adrenal, kidney, epididymides, testes, prostate, pituitary gland, seminal vesicle, and liver weights were determined, and histopathological examination of the liver, kidneys, testes, and adrenals was conducted.

There were no treatment-related deaths. Deaths attributed to gavage, which were confirmed at necropsy, were primarily limited to the high-dose rats. At 250 mg/kg-day, statistically increased mean relative kidney weights of 10% were observed compared to controls. Minimal-to-moderate centrilobular hypertrophy was observed in 1/15 treated rats, but not in controls. The hypertrophy was characterized as increased size and cytoplasmic eosinophilia of hepatocytes that were oriented around central veins, which at times extended into the midzonal region of the lobule. The severity was dose-related and ranged from minimal to moderate, and the authors suggested that the effect was similar to that observed with phenobarbital administration. Protein droplet nephropathy of the kidney was observed in 12/15 treated rats, but not in controls.

At 500 mg/kg-day, statistically increased mean relative kidney weights of 9% were observed compared to controls. Minimal-to-moderate centrilobular hypertrophy was observed in 10/15 treated rats, but not in controls. Protein droplet nephropathy of the kidney was observed in 15/15 treated rats, but not in controls.

At 1,000 mg/kg-day, statistically increased mean absolute and relative kidney weights of 10% and 16%, respectively, were observed compared to controls. Statistically increased mean relative liver weights of 10% were observed compared to controls. The increased relative liver weight was accompanied by minimal-to-moderate centrilobular hypertrophy in 11/13 treated rats, but not in controls. Protein droplet nephropathy of the kidney was observed in 12/13 treated rats, but not in controls.

At 1,500 mg/kg-day, mean body weight was reduced by 12% compared to controls. Statistically increased mean relative kidney weights of 18% were observed compared to controls. Statistically increased mean relative liver weights of 14% were observed

compared to controls. Statistically increased mean relative testes weights of 15% were observed compared to controls. The increased relative liver weight was accompanied by minimal-to-moderate centrilobular hypertrophy in 11/11 treated rats, but not in controls. Increased mean relative kidney weights, accompanied by protein droplet nephropathy of the kidney, were observed in 10/11 treated rats, but not in controls.

7.4.1.2 13-Week Drinking Water Study in Wistar Rats

In the range finding study for a chronic study (Bermudez et al., 2009), Wistar rats were administered MTBE via drinking water at 0, 0.5, 3, 7.5, or 15 mg/mL for 13 wks (Bermudez et al., 2008). The mean received doses were 0, 37, 209, 514, or 972 mg/kg-day in male rats and 0, 50, 272, 650, or 1,153 mg/kg-day in females. Body weights, clinical signs, and food and water consumption were monitored weekly. Urine was collected from males and analyzed at Day 4 and 21. Cell replication in the kidney was assessed at Week 1, 4, and 13. Complete histological examinations were performed on all rats at study termination. Serum hormone levels were assayed after 28 days of exposure. Mean terminal body weights in males at 514 and 972 mg/kg-day were less than controls. MTBE exposure resulted in decreased water consumption in both sexes of all treated groups in the absence of an impact on food consumption. Males had elevated urine specific gravity and osmolality. Serum hormone levels were unchanged by treatment in either sex. Kidney wet weights were elevated in males and females that received 7.5 and 15 mg/mL. Cell replication of kidney cortical epithelial cells was unchanged in females but was elevated in males of the 15mg/mL group at Week 4. Renal tubular cell regeneration was noted in males exposed to 15 mg/mL at 13 wks of exposure. Quantitative α-2μ globulin levels in kidney were elevated in high-dose males at Week 1 and 4. The study authors considered the reduction in water consumption in male and female rats of all MTBE dose groups to be treatment-related and attributed the reduction in mean body weights and renal tubule effects in males receiving the two highest dose levels to α-2μ- nephropathy. Complete study details are not available at this time.

7.4.1.3 Thirteen-Week or Longer Gavage Studies In Sprague-Dawley Rats

Ten Sprague-Dawley rats per sex and dose were administered MTBE (≥ 99.95% purity in corn oil) via gavage at 0, 100, 300, 900, or 1,200 mg/kg-day for 90 days (Robinson et al., 1990). Rats were housed separately by sex and food, and water was available *ad libitum*. Mortality and clinical signs were monitored daily. Food consumption was measured once a week and water consumption was measured three times a week. Body weight was measured twice a week. Hematology and clinical chemistry were conducted on all rats at study termination. Hematology included hematocrit, hemoglobin, mean corpuscular volume, erythrocytes, leukocytes, differential leukocytes, and reticulocytes. Clinical chemistry included glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, cholesterol, calcium, and phosphorus. Brain, liver, spleen, lung, thymus, kidney, adrenal, heart, and "gonads" weights were recorded at study termination, and relative organ-to-body-weight ratios were calculated. Gross necropsies were conducted on all rats at study termination. Histological examinations were conducted on all control and high-dose rats at study termination, and

included unspecified "major organs". If target histopathological organs were identified, these organs were also examined histologically in the remaining dose groups.

This study was not designed to meet current U.S. EPA (2009) Health Effects Testing Guidelines, since hematology did not include a measure of clotting potential, and clinical chemistry did not include albumin, alkaline phosphatase, gamma glutamyl transferase, globulin, sorbitol dehydrogenase, bilirubin, protein, or serum chloride, magnesium, potassium, or sodium. Further, urinalysis was not conducted, and organs examined histologically were specified only as including "major organs". Although Robinson et al. (1990) noted that the weight of the "gonads" were reported, data for the testes were not reported.

At 100 mg/kg-day, one male died. Diarrhea was observed in male and female rats. Water consumption (unspecified magnitude) was statistically increased in females compared to controls. A statistical decrease in blood urea nitrogen was observed in males (15%) and females (20%).

At 300 mg/kg-day, one female died. Diarrhea was observed in male and female rats. A statistical decrease in blood urea nitrogen was observed in males (20%) and females (33%). A statistical decrease in glucose (17%) and lactate dehydrogenase (62%) and an increase in cholesterol (11%) were observed in females. A statistical decrease in creatinine (15%) and an increase in aspartate aminotransferase (34%) were observed in males. Mean absolute (4%) and relative (4%) brain weights were statistically increased in males compared to controls. Mean relative kidney weights (10%) were statistically increased in females compared to controls.

At 900 mg/kg-day, two females and one male died. Diarrhea was observed in male and female rats. Food consumption (unspecified magnitude) was statistically increased in females compared to controls. A statistical decrease in blood urea nitrogen was observed in males (18%) and females (35%). A statistical decrease in mean glucose (13%) and lactate dehydrogenase (16%) and an increase in cholesterol (31%) were observed in females compared to controls. A statistical decrease in mean creatinine (26%) and an increase in cholesterol (22%) and lactate dehydrogenase (5%) were observed in males compared to controls along with a statistical increase in mean relative liver weights (13%). Mean absolute (14%) and relative (15%) kidney weights and relative liver weights (13%) were statistically increased in males compared to controls. Mean relative heart (11%), liver (12%), kidney (13%), and thymus (33%) weights were statistically increased in females compared to controls.

At 1,200 mg/kg-day, four females and one male died. Diarrhea and a profound but transient (<two hours) anesthetic effect were observed in male and female rats. Water consumption (unspecified magnitude) was statistically increased in males and females compared to controls. A statistical decrease in blood urea nitrogen was observed in males (18%) and females (17%). A statistical decrease in mean glucose (24%) and lactate dehydrogenase (16%) and an increase in cholesterol (20%) were observed in females compared to controls. A statistical decrease in mean creatinine (19%) and an increase in

aspartate aminotransferase (33%) were observed in males compared to controls. Terminal mean body weight was statistically reduced by 9% in males compared to controls. Mean absolute (18%) and relative (21%) kidney weights, absolute (9%) and relative (13%) lung weights, and relative liver weights (13%) were statistically increased in male rats and mean relative kidney (12%) and adrenal (25%) weights were statistically increased in female rats compared to controls. Microscopic findings included chronic nephropathy in control and high-dose male rats. These changes, such as renal tubular degeneration, were more severe in treated rats than controls. Renal tubules plugged with granular casts were found in 5/10 high-dose males, and 10/10 males exhibited slight increases in cytoplasmic hyaline droplets in proximal tubular epithelial cells. No further details regarding the renal changes were provided. The study authors attributed the early deaths in treated rats to dosing error since macroscopic findings in the lungs of most rats that died included "lungs that were mottled to uniformly red, fluid-filled, and often exhibited foreign material in airways".

Ten male Sprague-Dawley rats per dose were administered 0, 200, 600, and 1,000 mg/kg MTBE (98.8% purity in soybean oil) by gavage for five days per week for 13 weeks (Zhou and Ye, 1999). These doses were equivalent to 0, 143, 428, or 857 mg/kg-day, respectively. Body weight and food and water consumption were measured weekly. Clinical chemistry was conducted at study termination and included aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total protein, albumin, globulin, albumin/globulin ratio, blood urea nitrogen, and creatinine. Liver, kidney, testes, and lung weights were measured at study termination. Gross necropsies and histopathological examinations were conducted at study termination, and included the liver, kidney, testes, and lung. Liver sections were also examined under an electron microscope.

This study was not designed to meet current U.S. EPA (2009) Health Effects Testing Guidelines, since only males were evaluated, hematology was not conducted, and clinical chemistry did not include alkaline phosphatase, gamma glutamyl transferase, glucose, sorbitol dehydrogenase, total bilirubin, total cholesterol, or serum electrolytes. Further, urinalysis was not conducted; spleen, heart, ovary, and brain weights were not measured; and histopathology included only the liver, kidney, testes, and lung.

At 143 mg/kg-day, mean absolute and relative liver weights were statistically increased by 12% and 14%, respectively, compared to controls. Lactate dehydrogenase was statistically decreased (32%) at the low, but not mid or high doses compared to controls. Aspartate aminotransferase was statistically increased by 31% compared to controls, but within historical control ranges. Histopathological examination in treated rats was comparable to controls. Electron microscopy of the liver revealed nuclear condensation, fat droplets, lysosome appearance in cells, and smooth endoplasmic reticulum disintegration, but the magnitude and number of animals affected was not specified. The study authors did, however, indicate that more severe changes were observed at higher doses.

At 428 mg/kg-day, mean absolute and relative liver weights were statistically increased by 18% and 15%, respectively, compared to controls. Mean relative kidney weight was statistically increased by 6% compared to controls, but no accompanying renal pathology was observed. Aspartate aminotransferase was statistically increased by 29% compared to controls, but within historical control ranges. Histopathological examination in treated rats was comparable to controls. Electron microscopy of the liver revealed nuclear condensation, fat droplets, lysosome appearance in cells, and smooth endoplasmic reticulum disintegration, but the magnitude and number of animals affected was not specified. However, the study authors indicated that more severe changes were observed at higher doses.

At 857 mg/kg-day, mean absolute and relative liver weights were statistically increased by 21% and 22%, respectively, compared to controls. Mean absolute and relative kidney weights were statistically increased by 12% and 13%, respectively, compared to controls, but no accompanying renal pathology was observed. Aspartate aminotransferase was statistically increased by 27% compared to controls, but within historical control ranges. Histopathological examination in treated rats was comparable to controls. Electron microscopy of the liver revealed nuclear condensation, fat droplets, lysosome appearance in cells, and smooth endoplasmic reticulum disintegration, but the magnitude and number of animals affected was not specified. However, the study authors indicated that more severe changes were observed at higher doses.

7.4.2 Chronic Studies

7.4.2.1 One-year Drinking Water Study in Wistar Rats

As part of a two-year bioassay, Wistar rats received MTBE (>99% purity) in their drinking water at 0, 0.5, 3, or 7.5 mg/mL in males and 0, 0.5, 3, or 15 mg/mL in females for 52 weeks (Bermudez et al., 2009). Dose selection was based on the results of a 90-day study (Bermudez et al., 2008). The mean received doses ranged from 30 to 384 mg/kg-day in males and 56 to 1,147 mg/kg-day in females. The mid-dose was not reported and can not be calculated due to the lack of body weight and water consumption data. Body weights, clinical signs, and food and water consumption were monitored regularly. Interim and terminal hematology, clinical chemistry, and urinalyses parameters were included at various intervals. A complete necropsy was performed at six months (males) and 12 months (males and females). Blood levels of t-butanol (TBA) were determined for males and females at 12-months. Food consumption was comparable to controls, while water consumption was less than control ($p<0.01$) in treated males and females. Mean body weight in male rats was 9%, 11%, and 7% less than controls in the low-, mid- and high-dose groups, respectively. There were no significant changes in hematology or serum chemistry parameters for males or females. Blood levels of TBA increased with dose in males and females. Urine osmolality and specific gravity were increased in males (7.5 mg/mL MTBE) and females (15 and 3 mg/mL MTBE) and urine creatinine was increased in males (3 mg/mL MTBE) and females (3 and 15 mg/mL MTBE). There was a trend in males and females of increasing urine protein with dose. Increases in osmolality and specific gravity suggest increased concentration of urine as a response to reduced

intake of water and suggest that the apparent increase in protein is due to a concentration effect. The statistical increase in mean relative kidney weights in treated male rats at 12 months of exposure was accompanied by an increase in nephropathy of minimal to mild severity. Nephropathy was observed in 3/10, 8/9, 9/10, and 9/10 male rats in the control, low-, mid-, and high-dose groups, respectively. Nephropathy was observed in 2/9, 2/10, 1/10, and 2/10 female rats in the control, low-, mid-, and high-dose groups, respectively. A non-dose-related but statistical increase in mean relative testes weights was observed in mid- (20%, right testes) and high-dose (13%, right; 15% left) male rats in the absence of testicular histopathology. The study authors considered the treatment-related effects to be limited to reduced water intake in males and females and an increase in nephropathy in males. Complete study details are not available.

7.4.2.2 Two-year Gavage Study in SD rats

Sixty Sprague-Dawley rats per sex and dose were administered 0, 250, or 1,000 mg/kg MTBE (> 99% purity in extra virgin olive oil) by gavage four times a week for 104 weeks on a weekly schedule of two days dosing, one day without dosing, two days dosing, and two days without dosing (Belpoggi et al., 1995; 1997). These doses were approximately equivalent to daily doses of 0, 143, or 571 mg/kg-day. The animals were housed five per cage and kept under observation until natural death. Food and water were available *ad libitum*. Mortality and clinical signs were monitored daily. Food and water consumption and body weight were measured weekly for the first 13 weeks and twice monthly thereafter until 112 weeks. Thereafter, body weights were measured every eight weeks until death. Gross necropsies were performed on all rats after natural death. Histopathological examinations, which were performed on all rats after natural death, included the aorta, adrenals, bone, bone marrow, brain, bronchi, cecum, colon, diaphragm, duodenum, esophagus, eye, Harderian gland, heart, ileum, jejunum, kidneys, liver, lung, lymph nodes (mediastinal, subcutaneous, mesenteric), mammary glands, muscles, nerve, ovaries, pancreas, pharynx, larynx, pituitary, prostate, salivary gland, seminal vesicle, subcutaneous tissue, skin, subcutaneous tissue, spinal cord, spleen, stomach, testes, thymus, thyroid/parathyroid, tongue, trachea, urinary bladder, uterus, Zymbal gland, and gross lesions.

This study was not designed to meet current U.S. EPA (2009) Health Effects Testing Guidelines, since the dosing occurred on a four-day per week schedule, with two days dosing, one day without dosing, two days dosing, and two days without dosing. Further, since no results for hematology, clinical chemistry, urinalysis, or organ weights were reported, it was presumed that these parameters were not examined. Histology did not include the aorta, bone, bone marrow, eye, mammary glands, muscles, nerve, seminal vesicle, or spinal cord. The tumor incidences reported in this study were reviewed by Belpoggi et al. (1998) after a re-evaluation of the histopathology slides.

At the low dose, survival at the end of the treatment period (104 weeks) was 35% in treated females compared to 48% in controls. Survival at the end of the treatment period (104 weeks) was 30% in low-dose males compared to 30% in controls. There was a statistical increase in lymphomas and leukemias combined (7/51) in female rats

compared to controls (2/58). The individual incidence of lymphomas or leukemias was not indicated. The lymphatic tumors were accompanied by an increase in dysplastic proliferation of lymphoreticular tissue, which was characterized as hyperplastic lymphoid tissues at various sites, in which atypical lymphoid cells, usually lymphoimmunoblasts, isolated and/or aggregated in small clusters, were observed. An increased incidence of uterine sarcomas was observed in low-dose females, but not high-dose females, compared to controls.

At the high-dose, survival at the end of the treatment period (104 weeks) was 28% in treated females compared to 48% in controls. Survival at the end of the treatment period (104 weeks) was 42% in high-dose males compared to 30% in controls. There was a statistical increase in the incidence of testicular Leydig cell (interstitial cell) tumors in male rats compared to controls. The incidence was 3/26, 5/25, and 11/32 in control, low-, and high-dose males (based on the number of rats surviving at the occurrence of the first Leydig tumor, which was 96 weeks). In female rats, there was a dose-related statistical increase in lymphomas and leukemias combined (12/47) compared to controls (2/58), and an increase in dysplastic proliferation of lymphoreticular tissue. The study authors reported that the range of the lymphatic tumors in females in this study was within the historical control incidence for these tumors in female Sprague-Dawley rats from studies in their laboratory (below 10%).

The study authors reported that "no treatment-related non-oncological pathological changes were detected by gross inspection and histological examination", but the data were not provided.

7.5 Reproductive and Developmental Toxicity Studies

No *in vivo* oral two-generation reproduction or developmental studies were identified for MTBE. One- and two-generation inhalation reproductive studies in rats and four inhalation developmental studies in rats, mice, and rabbits are available for MTBE. These studies have been reviewed by ECB (2002), OEHHA (1999), IPCS (1998), ECETOC (1997), and ATSDR (1996). Specific reproductive effects were not observed in rats at concentrations up to 28,800 mg/m^3. MTBE was not associated with developmental effects at concentrations below those associated with maternal toxicity. Decreases in uterine weight and increases in estrogen metabolism in mice have been observed at 28,800 mg/m^3 (IPCS, 1998). Since the reproductive and developmental studies for MTBE have been extensively reviewed by several other regulatory agencies, this section includes only the oral reproductive and developmental studies for MTBE, including those published since the various regulatory reviews. None of the oral studies identified were standardized two-generation reproduction or developmental studies.

7.5.1 Reproduction Studies

No oral one- or two-generation reproduction studies were identified for MTBE, but effects on reproductive hormone levels, reproductive organ weights and/or histology has been investigated following oral exposure to MTBE in non-standardized reproduction studies.

***In vivo* studies**

Since MTBE exposure has previously been linked to some limited evidence of seminiferous tubule degeneration in CD-1 or BALB/c mice (Billiti et al., 1999; Almeida et al., 2004), de Peyster et al. (2008) conducted a series of experiments to replicate or further characterize these effects. Six adult male CD-1 mice per dose received 0, 400, 1,000, or 2,000 mg/kg MTBE (unspecified purity in corn oil) via gavage on Days 1, 3, and 5 (de Peyster et al., 2008). After an intraperitoneal injection of human Chorionic Gonadotropin on Day 6 to stimulate testosterone production, rats were sacrificed on Day 7. Body, testes, epididymides, seminal vesicle, liver and brain weights were recoded along with testicular histology and testosterone levels. No examined parameter was in treated mice was statistically different than controls. Mild unilateral seminiferous tubule degeneration was observed in one control mouse and an abscess of the preputial gland was observed in one mid-dose mouse.

In a second experiment, six male BALB/c mice per dose received MTBE in their drinking water at 0, 80, 800, or 8,000 μg/L for 28 days (de Peyster et al., 2008). Mean received doses were calculated by the study authors to be 0, 305, 3,180, or 31,920 mg/mouse/day. Based on mean terminal body weight for each respective group, the approximate received doses can be considered 0, 11, 111, or 1,178 mg/kg-day. Dose selection was based on a two-week palatability study which found no difference in water intake in treated mice compared to controls. Mean terminal serum testosterone or number of sperm/ mg cauda in treated mice was not statistically different than controls. Mild or minimal unilateral seminiferous tubule degeneration was observed in 2/6, 1/6, 1/6, and 2/6 mice in the control, low-, mid-, and high-dose groups, respectively. All mice had a Grade 1 (minimal) severity score with exception of one control male that had a Grade 2 (mild) severity score.

In a third experiment, ten male juvenile (22-day old) BALB/c mice per dose received MTBE in their drinking water at 0, 80, 800, or 8,000 μg/L for 51 days through PND 77 (de Peyster et al., 2008). Mean received doses were calculated by the study authors to be 0, 381, 3,900, or 39,170 mg/mouse/day. Based on mean terminal body weight for each respective group, the approximate received doses can be considered 0, 15, 155, or 1,536 mg/kg-day. Mean relative (but not absolute) seminal vesicle (low-dose) and lung weights (mid-dose) were statistically increased compared to controls. The increase in mean lung weight was attributed to one mid-dose mouse that had a large lung mass. However, since bloody lungs were noted upon necropsy in several treated mice (incidence/group unspecified but including the one with the mass) and one control mouse, the possibility that the effect was treatment-related could not be discounted by the study authors,

particularly considering the increasing trend (non-statistical) in lung weights. Mean serum estradiol or testosterone concentrations or mean seminiferous tubule diameter in treated mice were not statistically different from controls.

No evidence of oxidative stress in liver homogenates from juvenile mice was observed based on malondialdehyde, Trolox equivalent antioxidant capacity (TEAC) and 8-hydroxy-2'-deoxyguanosine adduct formation as endpoints. Collectively, the study authors concluded that drinking water exposure to MTBE at up to 8,000 µg/L for up to 51 days was not associated with adverse effects on reproductive hormones, organ weights, or histology under the conditions of their studies.

Ten male SD rats per dose and exposure duration received MTBE (99.8% purity in peanut oil) via gavage at 0, 400, 800, or 1,600 mg/kg-day for two or four weeks (Dongmei et al., 2009b). The basis of the dose selection was not specified. Mortality, body weight, and food consumption were recorded daily. Serum testosterone, leutenizing hormone, and follicle stimulating hormone were measured at study termination along with serum total antioxidant ability and peroxide levels (serum maleic dialdehyde levels), and the mRNA expressions of androgen binding protein, 8-oxoguanine DNA glycosidase, and extracellular superoxide dismutase. Epididymides sperm counts and abnormal sperm were recorded by one technician blinded to the treatment group. Liver, kidneys, testes, and epididymis weights were recorded at study termination and testicular histology was included on all rats.

Although the authors indicated that liver, kidneys, and testes weights were recorded at study termination, these data were not reported. After two weeks of exposure, mean serum leutenizing hormone was statistically increased in a non-dose-related manner in all dosed groups (~25-30% estimated from graph). Mean serum follicle stimulating hormone was statistically increased in mid- (~30%) and high-dose rats (~40%). Mean serum testosterone was reduced in mid- (~70%) and high-dose rats (~60%). High-dose rats had "less compact cells" in the testes upon histological examination compared to controls. The mRNA level of androgen binding protein was decreased at the high-dose (33%).

After four weeks of exposure, no effects on reproductive organ weights were observed. The percent of abnormal sperm was statistically increased in treated rats in a dose-related fashion. The mean "semina deformity ratio" estimated from the graph was ~12%, 18% ($p<0.05$), 19% ($p<0.05$), and 28% ($p<0.01$) in rats from the control, 400, 800, or 1,600 mg/kg-day groups, respectively. Mid-dose rats had increased (as opposed to reduced after two weeks) serum testosterone levels (~35%, estimated). Mid- and high-dose rats had "irregular and disordered arrangement, with the shedding of cellular material from the seminiferous epithelium" in the testes upon histological examination compared to controls. The mRNA level of androgen binding protein was decreased at the mid- (~20%) and high-dose (~22%).

Some other parameters (serum maleic dialdehyde total serum antioxidant ability, 8-oxoguanine DNA glycosidase and extracellular superoxide dismutase) were statistically significant compared to controls but due to the lack of a dose- or temporally-related

pattern, they were not considered biologically-significant by the authors of the present assessment. The study authors concluded that high-doses of MTBE could disrupt spermatogenesis but did not identify a NOAEL. The authors of the present assessment consider the four-week NOAEL to be 400 mg/kg-day since the non-dose related reduction in serum leutenizing hormone observed after two weeks was not seen after four weeks as well and the minimal magnitude and lack of dose-response of the increase in sperm deformity ratio at the low- and mid-dose after four weeks. The LOAEL can be considered 800 mg/kg-day based on the alterations in serum testosterone and histopathology in the testes.

Potential testicular toxicity associated with MTBE was assessed in five male CD-1 mice per dose that received MTBE (unspecified purity in canola oil) via gavage on Days 1, 3, and 5 at 0, 400, 1,000 or 2,000 mg/kg (Billitti et al., 2005). Testosterone levels were measured on Day 6 fecal samples collected from all mice. Thereafter, mice were injected with human chorionic gonadotrophin to stimulate maximum testosterone production and fecal samples were collected after one day. Body weight and serum testosterone were measured and histological examination of the testes was included at study termination. Two high-dose mice died as a result of dosing error. All examined parameters in the treated mice that survived were comparable and/or not statistically different compared to controls.

Eight female B6C3F$_1$ mice per dose were given MTBE (> 99.95% purity in corn oil) by gavage at 0 or 1,800 mg/kg-day for three days (Moser et al., 1996). Food and water were available *ad libitum*. Twenty-four hours after the last dose, the mice were sacrificed and hepatocytes were isolated for measurement of estrogen metabolism *in vitro*, which was expressed as the amount (nM) of 17-β–estradiol metabolized/ mg protein/ minute. MTBE induced a two-fold statistical increase in the rate of estrogen metabolism *in vitro* compared to controls.

Six to eleven female CD-1 mice per dose were administered MTBE via gavage at 0, 600, or 1,500 mg/kg-day for five days either with or without subcutaneous administration of 1 ug estradiol on Days 3-5 (Okahara et al., 1998). The authors reported that MTBE had some mild, but in some cases, seemingly opposite, activity under these conditions, but no further details were provided. At 1,500 mg/kg-day, delayed vaginal opening by Postnatal Day 26 was observed in half of the treated females. Mean relative uterine weights were statistically increased in the MTBE/estradiol group compared to the estradiol alone control group, but the dose level or magnitude was not specified. According to the authors, no clear or consistent effect was observed in uterine peroxidase activity or in ovarian, liver, or kidney weights compared to controls. No further details were available in this abstract, and a full publication was not located.

Twelve male Sprague-Dawley rats per dose were administered MTBE (> 99.8% purity in corn oil) via gavage at 0, 1,000, or 1,500 mg/kg every other day for a total of 14 doses over 28 days (de Peyster et al., 2003). The 1,000 mg/kg dose was selected since it was the highest dose in the Belpoggi et al. (1995) chronic gavage study, and since this dose induced a statistical increase in Leydig cell tumors in male rats compared to controls.

The 1,500 mg/kg dose was chosen since it was approximately the highest dose from a 90-day gavage study for MTBE by Robinson et al. (1990). The experiment originally included an untreated and a vehicle-treated control group, but the results were ultimately combined into one control group. Due to excess weight loss and one death, the 1,000 and 1,500 mg/kg doses were reduced to 500 and 750 mg/kg, respectively, starting on Day 13. The terminal doses were approximately equivalent to 0, 357, or 536 mg/kg-day. This study was conducted to investigate the mechanism of Leydig cell tumors induced in male rats after chronic gavage exposure to MTBE in a study by Belpoggi et al. (1995). It has been suggested that increased hepatic metabolism through P450 enzymes results in increased steroid catabolism, resulting in reduced testosterone circulation.

Testosterone concentrations were measured on Day 1 and 14 (tail blood) and 28 (cardiac puncture). If the serum sample volume was sufficient, terminal corticosterone was also measured to determine whether the Leydig tumors were induced through an increased stimulation of testicular glucocorticoid receptors, which can impair testosterone production. Liver, kidney, testes, seminal vesicles, and epididymides weights were measured, and mean organ-to-body weight ratios were calculated. Total protein and total P450 were measured from isolated liver microsomes.

At study termination, mean body weight gain was 8, 3, 1, and 0% in the negative control, vehicle control, 357 mg/kg-day, and 536 mg/kg-day groups, respectively. The Day 1 testosterone concentration in rats administered 537 mg/kg-day MTBE was statistically reduced by approximately 70% compared to pooled controls (vehicle and negative, n=4 only). The Day 14 and 28 testosterone concentrations in treated rats were not statistically different compared to controls. At study termination, mean absolute liver weight and total microsomal protein in treated rats were comparable to controls, but mean liver P450 content (mmol/mg protein and nmol/g liver weight) was slightly, but statistically, increased in rats administered 537 mg/kg-day compared to controls. There was a 24% increase in mmol/mg P450 protein and a 35% increase in nmol P450/g liver weight compared to pooled controls. Mean corticosterone levels on Day 1, 14, and 28 were not statistically different compared to pooled controls, but the sample size was only about 4-5 rats per dose. The authors concluded that high gavage doses of MTBE result in reduced circulating testosterone in rats during the hours immediately following dosing (4-5 hours). However, the increase in hepatic P450 content did not result in reduced circulating testosterone, as originally hypothesized by the study authors, but the authors could not rule out other hormonal or metabolic compensatory mechanisms.

Twelve male Sprague-Dawley rats per dose were administered MTBE (> 99.8% purity in corn oil) via gavage at 0, 40, 400, or 800 mg/kg-day for 28 days (de Peyster et al., 2003; Day et al., 1998). This study was conducted to further investigate the mechanism of Leydig cell tumors induced in male rats after chronic gavage exposure to MTBE in a study by Belpoggi et al. (1995). Luteinizing hormone, prolactin, testosterone, and corticosterone concentrations were measured on Day 1 and 14 (tail blood) and 28 (trunk). Liver, pituitary, testes, epididymides, thyroid, adrenal, prostate, and brain weights were measured, and mean organ-to-body and brain weight ratios were calculated.

At 40 mg/kg-day, mean plasma corticosterone was statistically reduced by 28% compared to controls on Day 14, but the corticosterone was not statistically different from controls at study termination.

At 400 mg/kg-day, terminal mean body weight was statistically reduced by 7% compared to controls. Mean plasma corticosterone was statistically reduced by 42% compared to controls on Day 14, but the corticosterone was not statistically different from controls at study termination. Mean pituitary weight was statistically reduced by 23% compared to controls.

At 800 mg/kg-day, terminal mean body weight was statistically reduced by 13% compared to controls. Mean plasma corticosterone was statistically reduced by 43% compared to controls on Day 14. At study termination, mean plasma testosterone was statistically reduced by 35% and mean plasma corticosterone was statistically reduced by 44% compared to controls. The mean adrenal-to-body-weight ratio was statistically reduced by 20% compared to controls. The mean thyroid-to-body-weight ratio was statistically reduced by 29% compared to controls.

Six male Sprague-Dawley rats per dose were administered MTBE (> 99.8% purity in corn oil) via gavage at 0 or 800 mg/kg-day for five days (de Peyster et al., 2003). This study was conducted to further investigate the mechanism of Leydig cell tumors induced in male rats after chronic gavage exposure to MTBE in a study by Belpoggi et al. (1995). The effect of castration on the hypothalamic-pituitary axis was investigated using testosterone implants in phosphate buffered saline (PBS) and four experimental groups of male rats. The four groups consisted of sham implant (PBS) and 800 mg/kg-day MTBE via gavage, sham implant (PBS) and corn oil vehicle gavage, testosterone implant and 800 mg/kg-day MTBE via gavage, and testosterone implant and corn oil vehicle gavage. The amount of testosterone in each implant was intended to result in average circulating testosterone as in normal non-castrated rats. Lutenizing hormone, prolactin, and testosterone concentrations from the tail vein were measured four hours after the initial dose (Day 1) and two hours after the final dose (Day 5). Terminal prostate and seminal vesicle weights were measured. The experiment was repeated with a younger set of animals, reportedly to reduce the amount of body weight variation, since each testosterone implant contained a standard amount of testosterone.

In the first experiment, the authors found that circulating testosterone was higher and lutenizing hormone was lower in rats with testosterone implants compared to controls, but the differences were not statistically significant. Since each testosterone implant contained a standard amount of testosterone, the authors suggested that the results were confounded by the difference in body weights between the rats after the 3-day recovery period from the surgical implant, even though prior to surgery, the rats were of comparable body weights. Thus, the experiment was repeated with a younger set of animals, but the results of the first experiment could not be duplicated and may have been confounded by a small sample size, since one control rat gained a large amount of body weight. Recognizing confounding factors, the authors concluded that there was no clear evidence of an effect on the hypothalamic-pituitary axis in either experiment.

Ten male Sprague-Dawley rats per dose were administered MTBE (> 99.8% purity in corn oil) via gavage at 0 or 1,200 mg/kg-day for 14 days (de Peyster et al., 2003). This dose was determined in previous experiments to lower circulating testosterone levels without affecting body weight. Terminal plasma estradiol, luteinizing hormone, and testosterone concentrations were measured from trunk blood samples. Testes and accessory sex organs (unspecified) weights were measured. Total protein content in testicular microsomes was determined, and testicular microsomal aromatase activity was also measured.

In rats treated with 1,200 mg/kg-day MTBE, a statistical decrease in mean testosterone and luteinizing hormone of 51% and 10%, respectively, was observed compared to controls, and a statistical increase in mean estradiol of 26% was observed compared to controls. Testicular microsomal aromatase activity was decreased by 55% compared to controls.

Williams and Borghoff (2000) and Williams et al. (2000) investigated the hypothesis that MTBE-induced decrease in serum testosterone levels in male rats may be due in part to the ability of MTBE to induce the metabolism of endogenous testosterone and, hence, enhance its clearance. Male Sprague-Dawley rats were administered 0, 250, 500, 1,000, or 1,500 mg/kg-day MTBE (> 99.9% purity in corn oil) via gavage for 15 or 28 days. Rats were sacrificed one hour following the last dose, and serum and interstitial fluid testosterone, and serum dihydrotestosterone, 17-β-estradiol, prolactin, triiodothyronine (T3), thyroxin (T4), thyroid stimulating hormone, follicle stimulating hormone, and luteinizing hormone levels were measured. Histopathology of the testes was performed in all rats.

After 15 days at 1,500 mg/kg-day, interstitial fluid and serum testosterone levels (approximately 60% each, estimated from graph) and serum prolactin levels (56%) were statistically decreased compared to controls.

After 28 days at 1,000 mg/kg-day, serum triiodothyronine (T3) was statistically decreased by 19% compared to controls.

After 28 days at 1,500 mg/kg-day, serum triiodothyronine (T3; 19%), luteinizing hormone (approximately 20%, estimated from graph), and dihydrotestosterone (45%) were statistically decreased compared to controls.

No testicular lesions were observed at any dose level. The authors concluded that MTBE causes mild perturbations in T3 and prolactin; however, the short-term (15-day), but not longer-term (28-day), decrease in testosterone and the mild increase in luteinizing hormone levels did not fit the pattern caused by known Leydig cell tumorigens, since larger increases in luteinizing hormone have been caused by chemicals known to cause Leydig cell tumors.

Ten CD-1 mice per sex and dose were given 0, 1, 10, 100 or 1,000 mg/kg MTBE (purity unspecified in corn oil) by gavage for five days per week for three weeks (Ward et al., 1994). As this study was not available, this summary was based on IPCS (1998). These doses were approximately equivalent to 0, 0.7, 7, 71, or 714 mg/kg-day. At study termination, the mice were sacrificed and one testis from each male and both ovaries from each female were sectioned for cytological evaluation. In males, sperm number, Sertoli cells, spermatogonia, spermatocytes, and capped spermatids were evaluated. In females, oocyte quality was assessed. There were no effects of MTBE on any of the cell types examined, but no further details were provided. OEHHA (1999) and ATSDR (1996) indicated that the reproductive NOAEL for this study was 1,000 mg/kg-day, but no further details were available. It should be noted that OEHHA (1999) and ATSDR (1996) likely did not adjust for the less than daily dosing regimen, and likely should have indicated the reproductive NOAEL as 714 mg/kg-day.

***In vitro* assays**

High concentrations of MTBE were cytotoxic to cultured Sertoli seminiferous epithelium cells possibly through an oxidative stress-mediated pathway (Dongmei et al., 2008). Cytotoxicity and oxidative stress were measured in cultured SD rat Sertoli cells exposed to MTBE (99.8% purity) concentrations at 0, 0.005, 0.5 or 50 mM (Dongmei et al., 2008). The production of reactive oxygen species, maleic dialdehyde content and the level of superoxide dismutase activity in cell supernatants were measured along with the expression of 8-oxoguanine DNA glycosidase and extracellular superoxide dismutase in Sertoli cells. Effects at the low-dose (0.005 mM) were limited to an increase in reactive oxygen species after three and 48 hours of exposure but not after two, six or 24 hours. High concentrations (0.5 mM and higher) were associated with cytotoxicity, induced lactate dehydrogenase leakage, and increased plasma membrane damage in Sertoli cells. The relevance of these effects at lower, more environmentally-relevant exposure concentrations was not discussed.

The effect of MTBE on the testosterone production of Leydig cells in culture was examined *in vitro* by de Peyster et al. (2003). Leydig cells were isolated from adult male Sprague-Dawley rats and incubated for three hours with 0, 50, or 100 mM MTBE (> 99.8% purity) or t-butanol, a major metabolite of MTBE. The same concentrations were also tested with human Chorionic Gonadotropin (hCG), added to stimulate testosterone production. Cell viability at the tested concentrations was at least 85%. Testosterone production after the three-hour exposure was measured by radioimmunoassay. Aminoglutethimide was used as a positive control, and the experiment was conducted in triplicate.

A statistical reduction in basal testosterone production of 56% and 76%, compared to controls, was observed at 50 and 100 mM MTBE, respectively. A statistical reduction in human Chorionic Gonadotropin-stimulated testosterone production of 51% and 60%, compared to controls, was observed at 50 and 100 mM MTBE, respectively. T-butanol induced a statistical reduction in basal testosterone production of 72% and 66% at 50 mM and 100 mM compared to controls, respectively. T-butanol induced a statistical

reduction in human Chorionic Gonadotropin-stimulated testosterone production of 73% and 83% at 50 mM and 100 mM compared to controls, respectively. The positive control, aminoglutethimide (5 mM) induced a statistical reduction of basal and human Chorionic Gonadotropin-stimulated testosterone production of 80% and 75% compared to controls, respectively.

In a 14- and 90-day systemic gavage study in Sprague-Dawley rats by Robinson et al. (1990), effects on ovary weight and histology and testes weight and histology were examined, and no effects were reported.

7.5.2 Developmental Toxicity Studies

No oral developmental studies were identified for MTBE.

7.6 Studies of Immunological and Neurological Effects

No standardized immunological or neurological assays were identified for MTBE, but some immunological or neurological effects have been reported in systemic studies for MTBE. Reported immunological effects were limited to reduced circulating corticosterone levels and thyroid weights in rats after short-term gavage exposures. Reported neurological effects were limited to transitory post-dosing salivation after gavage doses of 64 mg/kg-day and higher and transitory hypoactivity and/or ataxia at higher doses in rats. However, the transient salivation may reflect the irritating properties of methyl *tert*-butyl ether rather than a neurological effect.

7.6.1 Immunological Effects

Twelve male Sprague-Dawley rats per dose were administered MTBE (> 99.8% purity in corn oil) via gavage at 0, 1,000, or 1,500 mg/kg every other day for a total of 14 doses over 28 days (de Peyster et al., 2003). After an adjustment of doses due to excess weight loss, the terminal doses were approximately equivalent to 0, 357, or 536 mg/kg-day. Terminal corticosterone was measured on Day 1, 14, and 28. Mean corticosterone levels on Day 1, 14, and 28 were not statistically different compared to controls, but the sample size was only about 4-5 rats per dose, due to other analyses concurrently requiring blood volume.

Twelve male Sprague-Dawley rats per dose were administered MTBE (> 99.8% purity in corn oil) via gavage at 0, 40, 400, or 800 mg/kg-day for 28 days (de Peyster et al., 2003). Corticosterone concentrations were measured on Day 1 and 14 (tail blood) and 28 (trunk). Thyroid weights were measured, and mean organ-to-body and brain weight ratios were calculated.

At 40 mg/kg-day, mean plasma corticosterone was statistically reduced by 28% compared to controls on Day 14, but the corticosterone was not statistically different from controls at study termination.

At 400 mg/kg-day, mean plasma corticosterone was statistically reduced by 42% compared to controls on Day 14, but the corticosterone was not statistically different from controls at study termination.

At 800 mg/kg-day, mean plasma corticosterone was statistically reduced by 43% compared to controls on Day 14. At study termination, mean plasma corticosterone was statistically reduced by 44% compared to controls. The mean thyroid-to-body- weight ratio was statistically reduced by 29% compared to controls.

In a 14-day and 90-day systemic gavage study in Sprague-Dawley rats by Robinson et al. (1990), effects on spleen and thymus weight and histology were examined, and no effects were reported. Although some statistical reductions in monocyte differential counts were observed, the effect was not dose- or duration-related and did not occur in both sexes.

In a 28-day gavage study by Lee et al. (1998), MTBE (unspecified purity in corn oil) was administered to male Sprague-Dawley rats at 0, 40, 400, or 800 mg/kg-day via gavage. At 800 mg/kg-day, high corticosterone levels were observed, but the magnitude and statistical significance were not specified. Limited details were available in this published abstract and a full publication was not located.

7.6.2 Neurological Effects

Neurological effects in rats were limited to transitory salivation reported after a single gavage dose of 90 mg/kg-day and higher and transitory hypoactivity and/or ataxia at higher doses (Johnson et al., 1992).

Intraventricular injection of high doses of MTBE impaired the performance of rats in a Morris water maze task, significantly increased the expression of GABA(A) receptor alpha1 subunit in the hippocampus, and reduced phosphorylation of ERK1/2 (Zheng et al., 2009). The biological significance of this effect in humans was not proposed by the authors.

Martin et al. (2002) studied the effect of 200 and 400 mM MTBE (unspecified purity) on binding at the gamma-aminobutyric acid receptor site in cerebral cortex membrane preparations isolated from male Sprague-Dawley rats. The gamma-aminobutyric acid receptor was probed using the ^{3}H-t-butylbicycloorthobenzoate, which binds to the convulsant recognition site of the receptor. The experiment was conducted in triplicate.

The 50% inhibitory concentration (IC_{50}) of MTBE and its metabolite, t-butanol, on the binding of ^{3}H-t-butylbicycloorthobenzoate at the gamma-aminobutyric acid(A) receptor site was 120 and 69 mM, respectively. In additional saturation binding assays, 200 and 400 mM MTBE statistically reduced apparent density of convulsant binding, or B_{max}, to 36 and 17% of the control value, respectively. The study authors suggested that their results indicate that direct effects on the gamma-aminobutyric acid(A) receptor site by MTBE or its metabolite t-butanol could explain some of the neurotoxicological or

neurobehavioral effects observed after MTBE exposures in humans and laboratory animals.

8.0 RISK CHARACTERIZATION

8.1 Hazard Identification

8.1.1 Major Non-Cancer Effects

The scientific literature for MTBE in humans and laboratory animals has been reviewed extensively by several national and international regulatory agencies, including the World Health Organization (WHO, 2005; IPCS, 1998), the Netherlands (Baars et al. 2004); European Chemicals Bureau (ECB, 2002), California EPA (OEHHA, 1999), International Agency for Research on Cancer (IARC, 1999), U.S. EPA (1997), European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC, 1997), Agency for Toxic Substances and Disease Registry (ATSDR, 1996), and Health Canada (1996; 1992). Thus, this risk assessment to determine a non-cancer RfD for MTBE focuses mainly on the oral exposure studies included in these reviews or that have been published since these reviews. Oral LOEL and NOEL values from the animal studies reviewed are shown in the Appendix. Although inhalation toxicity studies are available for MTBE, oral studies were preferred due to the lack of a physiologically-based pharmacokinetic model to reliably extrapolate inhaled doses in rodents to human equivalent oral doses.

Drinking water exposure to MTBE for up to one year was associated with reduced water intake likely secondary to palatability (Bermudez et al., 2007; 2008, 2009). As a result, the increases in urine osmolality, specific gravity, and creatinine levels were attributed to a "concentration effect" secondary to reduced water intake (Bermudez et al., 2009). Statistical increases in mean relative kidney weights in treated male rats at 12 months were accompanied by nephropathy of minimal to mild severity. A statistical increase in mean relative testes weights was also observed in treated male rats in the absence of testicular histopathology. The LOAEL for one-year drinking water exposure to MTBE can be considered 384 mg/kg-day based on the increase in mean relative testes weights at the high-dose. However, the received mg/kg-day dose at the mid-dose was not reported and thus the NOAEL is not known for this effect (Bermudez et al., 2009). Interpretation of this effect in high-dose males may be impacted by concurrent reductions in mean body weight (7%). Full details of these unpublished drinking water studies are not available.

Gavage (Dongmei et al., 2009a; Johnson et al., 1992; Robinson et al., 1990; Williams and Borghoff, 2000; Williams et al., 2000) but not drinking water exposure (Bermudez et al., 2008, 2009) to MTBE was associated with increased mean liver weights, liver-associated blood effects (apartate aminotransferase, blood urea nitrogen, and/or cholesterol) and minimal-to-moderate centrilobular hepatocyte hypertrophy in SD rats. "No treatment-related nononcological pathological changes were detected by gross inspection and histological examination" after two-years of gavage exposure to MTBE at adjusted doses

up to 571 mg/kg-day (1,000 mg/kg-day adjusted for daily dosing; Belpoggi et al., 1995), but the data were not reported. Similar to drinking water exposure, gavage exposure to MTBE was associated with increased mean absolute and relative kidney weights in male rats accompanied by hyaline droplet formation in the renal proximal tubules (Johnson et al., 1992; Robinson et al., 1990; Williams and Borghoff, 2000; Williams et al., 2000).

8.1.2 Mode of Action (Non-Cancer Effects)

The effects seen in the kidneys of male rats that received MTBE via drinking water or gavage exposures for up to one year (Bermudez et al., 2007, 2008, 2009; Johnson et al., 1992; Klan et al., 1992; Williams and Borghoff, 2000; Williams et al., 2000) were consistent with α-2μ-globulin nephropathy. These effects are specific to male rats and of questionable relevance to humans (Meek et al., 2003).

The liver effects associated with four or 13 weeks of gavage exposure to MTBE are likely due to an adaptive mechanism to metabolize bolus doses of MTBE at 250 mg/kg-day and above (Johnson et al., 1992; Robinson et al., 1990; Williams and Borghoff, 2000; Williams et al., 2000) since they were not observed after drinking water exposure to doses up to 972 mg/kg-day in male rats and 1,153 mg/kg-day in females for the equivalent exposure duration or longer (Bermudez et al., 2008, 2009). Limited *in vivo* metabolism data suggest that oral exposure to MTBE induces various CYP450 isozymes (Le Gal et al., 2001; Williams and Borghoff, 2000), and MTBE has been shown to induce its own metabolism by 2.1-fold beginning after 15 days of gavage exposure to 1,500 mg/kg-day MTBE (> 99.9% purity in corn oil; Williams and Borghoff, 2000). The lack of multiple examined doses in the study precludes an assessment of dose-response. These adaptive mechanisms likely lead to the centrilobular hepatocyte hypertrophy observed after gavage exposure but that appear to be lacking after drinking water exposure (Bermudez et al., 2008), recognizing that the latter study is not available for review. The lack of hepatic tumors from the Belpoggi et al. (1995) chronic gavage study is reassuring.

The lack of reported thyroid or liver tumors in rats from the Belopoggi et al. (1995) study at adjusted doses of 571 mg/kg-day (1,000 mg/kg-day adjusted for less than seven day dosing) supports a mode of action independent of a disruption of the thyroid/pituitary axis (as seen with phenobarbital), a mode of action that has unclear relevance to humans (Meek et al., 2003). Studies examining the activation of the constitutive androstane receptor (CAR) or thyroid stimulating hormone (TSH) levels after oral exposure to MTBE were not identified in the public literature.

The potential for MTBE to induce peroxisome proliferation, which is mediated through a series of evens that are unlikely to be relevant to humans (Cohen et al., 2003; Klaunig et al., 2003), has been examined in one study (de Peyster et al., 2003). There were no statistical differences in liver weights, liver-associated blood effects (cholesterol, triglyceride, alanine aminotransferase, and aspartate aminotransferease), or peroxisomal β-oxidation in hepatic peroxisomes from male rats that received MTBE via gavage at 800 mg/kg-day for 14 days compared to controls (de Peyster et al., 2003). In addition to liver

tumors, a peroxisome proliferation-mediated mode of action may also result in Leydig cell tumors and/or pancreatic cell tumors (Klaunig et al., 2003). An increase in Leydig cell tumors were observed in male rats that received MTBE for two years (Belpoggi et al., 1995). The mode of action of the Leydig cell tumors observed in male rats after chronic gavage dosing (Belpoggi et al., 1995) is unclear and may be mediated through mechanisms considered to have a threshold (ie. may be potentially relevant to the derivation of a RfD for MTBE). Reproductive hormone levels and reproductive organ weights and histology have been examined after single and repeated gavage or drinking water exposure in rats and mice. Single or repeated gavage dosing (up to 28 days) of MTBE in corn oil at ≥800 mg/kg-day was associated with reductions in mean serum testosterone (de Peyster et al., 2003). Increased mean relative testes weights (15%) and estradiol levels along with reduced serum luteinizing hormone and testicular microsomal aromatase levels were observed in SD rats after high gavage doses of MTBE (≥1,200 mg/kg-day) for 28 days (de Peyster et al., 2003; Williams and Borghoff, 2000; Williams et al., 2000). The decrease in mean relative testes weights in male SD rats that received MTBE via gavage in peanut oil at 400 mg/kg-day and higher for two weeks was likely due to an unusually high control mean relative testes weight since there was no dose-response and the effect was not seen after four weeks of exposure to the same doses or in a separate study conducted under the same protocol (two-week exposure with the same doses; Dongmei et al., 2008). In this latter study, the NOAEL was considered 400 mg/kg-day based on the alterations in serum testosterone and histopathology in the testes observed at 800 mg/kg-day after four weeks of gavage exposure (Dongmei et al., 2008). No effects on testes weights were reported in SD rats that received MTBE in soybean oil via gavage at adjusted doses up to 857 mg/kg-day (1,000 mg/kg-day adjusted for less than daily dosing) for 13 weeks (Zhou and Ye, 1999). Although Robinson et al. (1990) noted that the weight of the "gonads" were reported, data for the testes were not reported. A statistical increase in mean relative testes weights was observed in the absence of testicular histopathology after one year of drinking water exposure to MTBE at 384 mg/kg-day (Bermudez et al., 2009), but the received mg/kg-day dose at the mid-dose was not reported and thus the NOAEL is not known for this effect. High concentrations (> 50 mM) of MTBE were also found to reduce basal and human Chorionic Gonadotropin (hCG)-stimulated testosterone production in cultured rat Leydig cells (de Peyster et al., 2003). All investigations in male mice failed to find a clear or consistent effect on reproductive hormone levels, organ weights or histology at gavage doses up to 2,000 mg/kg-day for three days (Billitti et al., 2005); gavage doses of 714 mg/kg-day (adjusted for less than daily dosing) for three weeks (Ward et al., 1994), or drinking water exposure at up to ~1,500 mg/kg-day for up to 51 days (de Peyster et al., 2008).

Collectively, studies examining reproductive hormone levels or reproductive tissue responses in male rats or mice after oral exposure to MTBE failed to find a clear or consistent pattern. Some studies reported effects on testes weights or histology in rats at high gavage doses (800 mg/kg-day) for 28 days de Peyster et al., 2003; Dongmei et al., 2008) while other studies reported no effects in rats at higher exposure doses (≥857 mg/kg-day) for longer (13 weeks) exposure periods (Robinson et al., 1990; Zhou and Ye, 1999). Nonetheless, in studies reporting an effect, the gavage NOAEL and LOAEL for alterations in serum testosterone accompanied by testicular histopathology in male SD

rats may be ~400 mg/kg-day and 800 mg/kg-day, respectively (de Peyster et al., 2003; Dongmei et al., 2008). The drinking water NOAEL is unknown for the increase in relative testes weights observed in the absence of testicular histopathology in Wistar rats after one year of drinking water exposure to MTBE at 384 mg/kg-day (Bermudez et al., 2009).

8.1.3 Key Study and Critical Effect for RfD

The liver effects associated with subchronic gavage exposure to MTBE in rats (Robinson et al., 1990) were attributed to adaptive mechanisms responding to bolus dosing since they do not appear to have been observed after drinking water exposure to higher doses for longer exposure periods (Bermudez et al., 2008, 2009), recognizing that these latter studies are not available. The highest dose administered in the 13-week gavage study was 1,200 mg/kg-day (Robinson et al., 1990) and the highest dose received in the 13-week drinking water study was 972 mg/kg-day in male rats and 1,153 mg/kg-day in females. (Bermudez et al., 2008)

Since full study details are not available for the unpublished 13-week or one-year drinking water studies, the key study for the RfD is therefore considered the subchronic gavage study in rats (Robinson et al., 1990). No critical effects could be identified since the liver effects, which include increased mean liver weights and liver-associated blood effects (aspartate aminotransferase, blood urea nitrogen, and cholesterol) were attributed to bolus dosing and the kidney effects were attributed to α-2μ-gloobulin nephropathy.

Although the two-year gavage study (Belpoggi et al., 1995) was perhaps conducted for a more appropriate exposure duration to serve as the basis of a lifetime drinking water level, the non-neoplastic data were not available for review. Recognizing that standardized chronic inhalation studies in rats and mice are available (Bird et al., 1997), insufficient kinetics data are available to reliably extrapolate an inhalation concentration in rats to human equivalent oral doses.

8.1.4 Identification of Susceptible Populations

Individuals with reduced ability to metabolize MTBE may potentially be more sensitive to adverse health outcomes resulting from MTBE exposure. Some human variants of CYP2A6, obtained from people who claimed to be sensitive to MTBE had 33% less activity than the wild type in oxidizing MTBE (Hong et al., 2001; as cited by McGregor, 2006). There are no other data by which to identify any subpopulations (e.g., the elderly, pregnant women, children, or people with allergies or asthma) that might be at special risk to MTBE exposure (IPCS, 1998).

8.1.5 Dose-Response Assessment

The liver effects observed after gavage dosing in the Robinson et al. (1990) study include increased mean liver weights and liver-associated blood effects (aspartate aminotransferase, blood urea nitrogen, and cholesterol), with the most sensitive effect

being the statistical reduction in mean blood urea that occurred at all doses (250 mg/kg-day and above) in both sexes (Table 2). While centrilobular hepatocyte hypertrophy was not specifically reported in the Robinson et al. (1990) study, there is dose-related evidence of this observation in another study administering lower doses (250 mg/kg-day) for a shorter exposure duration (28 days; Williams and Borghoff, 2000). While adaptive mechanisms to metabolizing bolus or high-dose chemical exposures are usually reversible upon cessation of treatment, these mechanisms, if provoked for a sufficiently prolonged duration, may result in irreversible changes that are considered adverse and potentially relevant to humans.

Table 2. Decreased mean blood urea nitrogen in SD rats that received MTBE via gavage (Robinson et al., 1990)

Dose (mg/kg-day)	Mean blood urea nitrogen (mg/dL)		Mean terminal relative liver weight (g) [1]		Mean terminal body weight (g)	
	Males	Females	Males	Females	Males	Females
0	22.5	24.8	3.13	3.83	477.1	330.2
100	17.9 (15%)**	21.1 (20%)**	3.12 (0%)	3.78 (↓1%)	427.7 (↓1%)	330.1 (0%)
300	18.1 (20%)*	16.7 (33%)**	3.08 (↓2%)	4.03 (↑5%)	475.5 (0%)	312.5 (↓5%)
900	18.4 (18%)*	16.2 (35%)**	3.60 (↑13%)**	4.39 (↑13%)*	470.1 (↓2%)	311.3 (↓6%)
1,200	18.5 (18%)*	20.6 (17%)*	3.54 (↑13%)**	4.07 (↑6%)	458.8 (↓4%)	302.1 (↓9%)*

* $p<0.05$ compared to controls
** $p<0.001$
[1] Relative to mean terminal body weight; mean terminal absolute liver weights were not statistically different from controls at any dose

The plateau in the reduction of blood urea nitrogen and the increase in mean relative liver weights in male rats observed at 900 mg/kg-day and above after gavage dosing (Robinson et al., 1990) suggests that the threshold for inducing adaptive metabolic pathways after bolus dosing may be around 900 mg/kg-day (Table 1). Although environmentally-relevant exposure concentrations of MTBE are unknown, they are likely to be much lower than those associated with an adaptive response. Williams and Borghoff (2000) demonstrated that MTBE induced its own metabolism 2.1-fold beginning after 15 days of gavage exposure to 1,500 mg/kg-day MTBE. The effect of long-term drinking water exposure to MTBE at levels below the threshold that would elicit such adaptive responses is unknown since data from the two-year drinking water study are not available (Bermudez et al., 2009). Therefore, the NOAEL can be considered 300 mg/kg-day based on the induction of adaptive responses observed at 900 mg/kg-day. The lack of a critical effect precludes dose response assessment for MTBE and thus, the NOAEL/uncertainty factor approach can be used to calculate the RfD for MTBE.

There are insufficient details available from the drinking water studies to compare to the results of gavage dosing (Bermudez et al., 2008). Other than reduced water intake and $\alpha 2\mu$-globulin associated renal effects, mean body weight was reduced by an unspecified magnitude in males that received 514 mg/kg-day for 13 weeks (Bermudez et al., 2008). Mean relative testes weights were reduced in the absence of associated histopathology in male rats that received MTBE at 384 mg/kg-day in their drinking water for one-year (Bermudez et al., 2009).

8.1.6 Uncertainty Factor Selection

- **Interspecies Extrapolation = 10x**

Chemical-specific adjustment of either portion of the interspecies uncertainty factor can be made using chemical-specific data if the conditions described in WHO/IPCS (2005) can be satisfied. For the toxicokinetic portion of the factor, these conditions include:

1. Identification of the active chemical moiety.

   There are insufficient data to clearly establish a mode of action or identify the active chemical moiety since a critical effect could not be identified for MTBE based on the available studies.

2. Determination of whether the toxicity depends on the area under the concentration-time curve (AUC) or the maximum concentration (C_{max}).

   The liver changes likely depend on the maximum concentration (C_{max}) since they are observed after bolus dosing but not drinking water exposure to comparable doses.

3. The availability of a physiologically based pharmacokinetic (PBPK) model to describe target organ dosimetry, or comparable animal and human data.

   A physiologically-based model extrapolating from oral dosing in rats to humans was not identified. Preliminary details from the unpublished drinking water studies (Bermudez et al., 2007, 2008, 2009) indicate that blood levels of MTBE and t-butanol were included. These data may be useful in constructing such a model.

4. The route of administration to laboratory animals must be relevant to human exposure. The animal doses must approximate to the expected human exposure, and an adequate number of subjects and samples should be included.

   Although the drinking water route of exposure is preferred, these studies are not finalized and not available at this time (Bermudez et al., 2007, 2008, 2009).

There is insufficient information for chemical-specific adjustment of the interspecies uncertainty factor based on WHO/IPCS (2005) criteria. Thus, the default 3x factor was considered appropriate to address these toxicokinetic differences between humans and rats.

With respect to the toxicodynamic portion of the interspecies uncertainty factor, the adjustment factor for interspecies toxicodynamics will usually be based on results of *in*

vitro studies comparing animal and human tissue (WHO/IPCS, 2005). The active chemical moiety should be identified and *in vitro* data examining the critical effects or key events should serve as the basis for quantitatively defining interspecies toxicodynamic differences. The default 3x factor was considered appropriate to address potential toxicodynamic differences between humans and rats, since the active chemical moiety is unclear and there are no *in vitro* studies comparing animal and human tissue responses at target tissues. Thus, the interspecies uncertainty factor for MTBE is 10x.

- **Intraspecies Extrapolation = 10x**

Individuals with reduced ability to metabolize MTBE may potentially be more sensitive to adverse health outcomes resulting from MTBE exposure. Some human variants of CYP2A6, obtained from people who claimed to be sensitive to MTBE had 33% less activity than the wild type in oxidizing MTBE (Hong et al., 2001). Therefore, the 10x default intraspecies uncertainty factor is appropriate.

- **LOAEL to NOAEL Extrapolation = 1x**

The NOAEL from the key Robinson et al. (1990) study was considered 300 mg/kg-day. This study is supported by a 13-week drinking water study that administered comparable doses (Bermudez et al., 2008).

- **Extrapolation from Subchronic to Chronic Exposure = 10x**

Details for the two-year drinking water study currently in progress are not available (Bermudez et al., 2009). "No treatment-related nononcological pathological changes were detected by gross inspection and histological examination" after two-years of gavage exposure to MTBE at adjusted doses up to 571 mg/kg-day (1,000 mg/kg-day adjusted for daily dosing; Belpoggi et al., 1995), but the non-neoplastic data were not available for review. The LOAEL for one-year drinking water exposure to MTBE can be considered 384 mg/kg-day based on the increase in mean relative testes weights. However, the received mg/kg-day dose at the mid-dose was not reported and thus the NOAEL is not known for this effect (Bermudez et al., 2009). Although Robinson et al. (1990) reported that "gonads" were weighed, testes weights were not reported. Since the NOAEL of 900 mg/kg-day from the key Robinson et al. (1990) study used as the point of departure is higher than the one-year LOAEL (Bermudez et al., 2009), a departure from the default subchronic to chronic uncertainty factor can not be justified. The lack of associated testicular histopathology after one-year is reassuring (Bermudez et al., 2009), recognizing that chronic gavage exposure to MTBE at 571 mg/kg-day (1,000 mg/kg-day adjusted for daily dosing) was associated with a statistical increase in Leydig cell tumors (Belpoggi et al., 1995).

- **Incomplete Database = 3x**

When considering only the oral toxicity data for MTBE, data are available to satisfy only one of the five core areas due to the lack of a second-species systemic bioassay of at least

13 weeks in duration as well as the lack of a two-generation reproduction study. A second-species chronic bioassay in CD-1 mice (Bird et al., 1997), a two-generation reproduction study in SD rats (Bevan et al., 1997a), and developmental toxicity data in New Zealand white rabbits and CD-1 mice (Bevan et al., 1997b) are available when the inhalation data are also considered. Thus, based on both routes of exposure, standardized studies are available in all five core areas. Complete study details are not available for the unpublished drinking water studies in rats (Bermudez et al., 2007, 2008, 2009)

The Total Uncertainty Factor is therefore, 3000x (10 x 10 x 1 x 10 x 3).

8.1.7 RfD Calculation

The NOAEL of 300 mg/kg-day from the Robninson et al. (1990) subchronic gavage study can be used as the point of departure for the RfD.

$$\textbf{RfD} = \frac{\text{NOAEL}}{\text{Total UF}}$$

$$= \frac{300 \text{ mg/kg-day}}{3000}$$

$$= \mathbf{0.1 \text{ mg/kg-day}}$$

8.2 TAC Derivation

The Total Allowable Concentration (TAC) is used to evaluate the results of extraction testing normalized to static at-the-tap conditions and is defined as the RfD multiplied by the 70 kg weight of an average adult assumed to drink two liters of water per day. A relative source contribution (RSC), applied when calculating a TAC for non-carcinogens, is used to ensure that the RfD is not exceeded when food and other non-water sources of exposure to the chemical are considered. In the absence of data to estimate the contribution from food or other non-water sources of exposure to the chemical of concern, a default of 20% can be used (EPA, 1991).

The RfD of 0.1 mg/kg-day can be used to calculate the TAC for MTBE. Due to the lack of data estimating potential environmental exposure levels for MTBE, a default of 20% RSC was used to calculate the TAC.

$$\textbf{TAC} = \frac{\text{RfD x 70 kg}}{\text{2 L/day}} \text{ x 20\% RSC}$$

$$= 3.5 \text{ mg/L x } 0.2$$

$$= \mathbf{0.7 \text{ mg/L (or 700 } \mu\text{g/L)}}$$

Taste and odor thresholds for MTBE in water have been reported to be between 2.5 and 680 μg/L (IPCS, 1998; OEHHA, 1999; Suffet et al., 2007; U.S. EPA, 1997).

8.3 SPAC Derivation

The SPAC (single product allowable level) is the TAC action level divided by the estimated number of drinking water sources for MTBE. Since there were insufficient data to quantify the number of drinking water sources of MTBE, a default standard multiple source factor of 10 was used.

$$\textbf{SPAC} = \frac{\text{TAC}}{10} = \frac{0.7\ \text{mg/L}}{10}$$

$$= \textbf{0.07 mg/L (or 70 μg/L)}$$

9.0 RISK COMPARISONS AND CONCLUSIONS

One of the primary uncertainties associated with the present assessment is the lack of complete study details for the drinking water studies (Bermudez et al., 2007, 2008, 2009) thus necessitating the use of a gavage study as the key study (Robinson et al., 199). Health Canada (1992) and the Netherlands (Baars et al., 2004) have derived non-cancer oral risk levels for MTBE. Health Canada (1991) derived a tolerable daily intake (TDI) of 0.01 mg/kg-day based on a NOAEL of 100 mg/kg-day from Robinson et al. (1990). An uncertainty factor of 10,000 was applied (10 for intraspecies variation, 10 for interspecies variation, and 100 for a less-than-chronic study, lack of data on carcinogenicity and minimal effects observed at the NOAEL). Using the same study as Health Canada (1992), the Netherlands (Baars et al., 2004) derived a tolerable daily intake (TDI) of 0.3 mg/kg-day based on a NOAEL of 300 mg/kg-day for liver and kidney toxicity in rats from the Robinson et al. (1990) study. The Netherlands (Baars et al., 2004) applied an uncertainty factor of 1000 (10 each for intra- and interspecies differences, and an additional 10 for limited duration of the study and database deficiencies). The RfD of 0.1 mg/kg-day derived herein is based on the same key Robinson et al. (1990) study and NOAEL of 300 mg/kg-day as the Netherlands (Baars et al., 2004). However, NSF International did not depart from the default study duration extrapolation factor.

The effect of long-term drinking water exposure to MTBE at levels below the threshold that would elicit an adaptive liver response is unknown since data from the two-year drinking water study are not available (Bermudez et al., 2009). While adaptive mechanisms to metabolizing high-dose chemical exposures are usually reversible upon cessation of treatment, these mechanisms, if provoked for a sufficiently prolonged duration, may result in irreversible changes that are considered adverse and potentially relevant to humans. A physiologically-based pharmacokinetic model extrapolating oral rat doses to humans and additional studies examining potential modes of action would increase the confidence and reduce the uncertainty associated with the non-cancer risk levels derived herein. The relevance of the drinking water levels derived herein should be

re-evaluated when the results of the two-year drinking water study are available (Bermudez et al., 2009).

10.0 ADDENDUM REFERENCES:

Almeida, L., C. Pascale, andE. Hall. 2004. The effects of methyl tertiary-butyl ether on mouse testis, Abstract #914. Toxicol. 78(S-1):188.

Amberg, A., E. Rosner, and W. Dekant. 2001. Toxicokinetics of methyl tert-butyl ether and its metabolites in humans after oral exposure. Toxicol Sci. 61(1):62-7.

ATSDR (Agency for Toxic Substances and Disease Registry). 1996. Toxicological Profile for MTBE. U.S. Department of Health and Human Sevices. Public Health Service. Agency on Toxic Substances and Disease Registry. August.

Baars, A.J., P.J.C.M. Janssen, and W.C. Mennes. 2004. Human-Toxicological Maximum Permissible Risk Levels for Methyl-tertiary-butylether (MTBE). Unpublished report. National Institute of Public Health and the Environment, Bilthoven, The Netherlands. June. Available at http://www.tera.org/iter/rivm/mtbereport.htm.

Barnes, D.G., and M. Dourson. 1988. Reference Dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

Belpoggi, F., M. Soffritti, and C. Maltoni. 1998. Pathological characterization of testicular tumors and lymphomas-leukaemias and of their precursors observed in Sprague-Dawley rats exposed to methyl tertiary-butyl ether (MTBE) Eur. J. Oncol. 3(3):201-206.

Belpoggi, F., M. Soffritti, and C. Maltoni. 1995. Methyl-tertiary-butyl ether (MTBE) - a gasoline additive - causes testicular and lympho-haematopoietic cancers in rats. Toxicol. Ind. Health. 11(2):119-149.

Belpoggi, F., M. Soffritti, F. Filippini, and C. Maltoni. 1997. Results of long-term experimental studies on the carcinogenicity of methyl tert-butyl ether. Ann. N.Y. Acad. Sci. 837:77-95.

Bermudez, E., H. Parkinson, and S.J. Borghoff. 2007. Methyl Tertiary Butyl Ether (MTBE) 14-Day Drinking Water Study In Wistar Rats. Abstract #1515. Toxicol Sci. 96(S-1):313.

Bermudez, E., H. Parkinson and D.E. Dodd. 2008. Methyl Tertiary Butyl Ether (MTBE) 13-Week Drinking Water Study In Wistar Rats. Abstract #508. Toxicol Sci. 102(S-1):104.

Bermudez, E., H. Parkinson and D.E. Dodd. 2009. Methyl Tertiary Butyl Ether (MTBE): One-year Toxicity Drinking Water Study In Wistar Rats. Abstract #1481. Toxicol Sci. 108(S-1):307.

Bevan, C., T.L. Neeper-Bradley, R.W. Tyl, L.C. Fisher, R.D. Panson, J.J. Kneiss and L.S. Andrews. 1997a. Two-generation reproductive toxicity study of methyl tertiary-butyl ether (MTBE) in rats. J Appl Toxicol. 17(Suppl 1):S13-9.

Bevan, C., R.W. Tyl, T.L. Neeper-Bradley, L.C. Fisher, R.D. Panson, J.F. Douglas and L.C. Andrews. 1997b. Developmental toxicity evaluation of methyl tertiary-butyl ether (MTBE) by inhalation in mice and rabbits. J Appl Toxicol. 17:S21-9.

Billitti, J.E., B.C. Faulkner, and B.W. Wilson. 1999. Acute testicular toxicity of MTBE and breakdown products in lab mice, Abstract #1255. Toxicol. 48(S-1).

Billitti, J.E., B.C. Faulkner, and B.W. Wilson. 2005. Absence of acute testicular toxicity of methyl-tert butyl ether and breakdown products in mice. Bull Environ Contam Toxicol. 75(2):228-35.

Bird, M.G., H.D. Burleigh-Flayer, J.S. Chun, J.F. Douglas, J.J. Kneiss and L.S. Andrews. 1997. Oncogenicity studies of inhaled methyl tertiary-butyl ether (MTBE) in CD-1 mice and F-344 rats. J Appl Toxicol. 17(Suppl 1):S45-55.

Borghoff, S.J., J.E. Murphy, and M.A. Medinsky. 1996. Development of physiologically based pharmacokinetic model for methyl tertiarybutyl ether and tertiary-butanol in male Fisher-344 rats. Fundam Appl. Toxicol. 30:264–275.

Cohen, S.M., M.E. Meek, J.E. Klaunig, D.E. Patton, and P.A. Fenner-Crisp. 2003. The human relevance of information on carcinogenic modes of action: overview. Crit Rev Toxicol. 33(6):581-9.

Day, K.J., A. de Peyster, B.S. Allgaier, A. Luong, J.A. MacGregor. 1998. MTBE (MTBE) effects on the male rat reproductive endocrine axis [abstract]. Toxicol. 42(1-S):174.

Dekant, W., U. Bernauer, E. Rosner, and A. Amberg. 2001. Biotransformation of MTBE, ETBE, and TAME after inhalation or ingestion in rats and humans. Res. Rep. Health Eff. Inst. 102:29-71; discussion 95-109.

de Peyster, A., K.J. MacLean, B.A. Stephens, L.D. Ahern, C.M. Westover, and D. Rozenshteyn. 2003. Subchronic studies in Sprague-Dawley rats to investigate mechanisms of MTBE-induced Leydig cell cancer. Toxicol Sci. 72(1):31-42.

de Peyster, A., Y. Rodriguez, R. Shuto, B. Goldberg, F. Gonzales, X. Pu, and J.E. Klaunig. 2008. Effect of oral methyl-t-butyl ether (MTBE) on the male mouse reproductive tract and oxidative stress in liver. Reprod Toxicol. 26(3-4):246-53.

Dongmei, L., Y. Chuntao, G. Yi, H. Yufeng, and H. Xiaodong. 2008. The effects of methyl tert-butyl ether (MTBE) on the male rat reproductive system. Food Chem Toxicol. 46(7):2402-8.

Dong-mei, L., G. Yi, Y. Chun-Tao, H. Yu-feng, and H. Xiao-dong. 2009a. Effects of subchronic methyl tert-butyl ether exposure on male Sprague-Dawley rats. Toxicol Ind Health. 25(1):15-23.

Dongmei, L., L. Quin, G. Yi, H. Yufeng, and H. Xiaodong. 2009b. Cytotoxicity and oxidative stress study in cultured rat Sertoli cells with methyl tert-butyl ether (MTBE) exposure. Reprod Toxicol. 27(2):170-6.

European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC). 1997. Technical Report No. 72. Methyl tert-Butyl Ether (MTBE) Health Risk Characterisation CAS No.1634-4-4 (EINECS No. 216.653.1). ISSN-0773-8072-72. June.

European Chemicals Bureau (ECB). 2002. European Union Risk Assessment Report. Tert-Butyl Methyl Ether. CAS No. 1634-04-4. EINECS No. 216-653-1. 3rd Priority List. Volume 19. Institute for Health and Consumer Protection, European Chemicals Bureau, Europena Commission. EUR 20417 EN. September 9.

Health Canada. 1992. Canadian Environmental Protection Act. Priority Substances List Assessment Report No. 5. Methyl tertiary-butyl ether. Government Canada, Environment Canada, Health and Welfare Canada, Health Canada. ISBN 0-662-19941-3.

Health Canada. 1996. Health-Based Tolerable Daily Intakes/Concentrations and Tumorigenic Doses/Concentrations for Priority Substances. Environmental Health Directorate, Health Protection Branch, Health Canada. ISBN 0-662-24858-9.

Hong, J.Y., Y.Y. Wang, S.N. Mohr, F.Y. Bondoc, and C. Deng. 2001. Human cytochrome P450 isozymes in metabolism and health effects of gasoline ethers. Health Effects Institute Research Report. 102:7–27. As cited by McGregor, 2006.

IARC (International Agency for Research on Cancer). 1999. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Vol. 73, pp 339. September 30.

IPCS (International Programme On Chemical Safety). 1998. Environmental Health Criteria 206. Methyl Tertiary-Butyl Ether. United Nations Environment Programme. International Labour Organisation. World Health Organization. Available from: http://www.inchem.org/documents/ehc/ehc/ehc206.htm#PartNumber:1.

Johnson, W.D., J. Findlay, and R.A. Boyne. 1992. 28-day oral (gavage) toxicity study of MTBE in rats. Prepared for Amoco. Illinois Institute of Technology Research. ITT Research Institute Project No. L08100. Chicago, Illinois, 48 pp.

Kim, D., M. E. Andersen, J.D. Pleil, L.A. Nylander-French, and J.D. Prah. 2007. Refined PBPK model of aggregate exposure to methyl tertiary-butyl ether. Toxicol Lett. 169(3):222-35.

Klan, M.J. W. Johnson, N.S. Hatoum, and J.K. Yermakoff. 1992. 28-day oral (gavage) toxicity study of MTBE in rats [abstract]. Toxicol. 12(1):117.

Klaunig, J.E., M.A. Babich, K.P. Baetcke, J.C. Cook, J.C. Corton, R.M. David, J.G. DeLuca, D.Y. Lai, R.H. McKee, J.M. Peters, R.A. Roberts, P.A. Fenner-Crisp. 2003. PPARalpha agonist-induced rodent tumors: modes of action and human relevance. Crit. Rev. Toxicol. 33(6):655-780.

Leavens TL and S.J. Borghoff. 2009. Physiologically based pharmacokinetic model of methyl tertiary butyl ether and tertiary butyl alcohol dosimetry in male rats based on binding to alpha2u-globulin. Toxicol Sci. 109(2):321-35.

Le Gal, A., Y. Dreano, P.G. Gervasi, and F. Berthou. 2001. Human cytochrome P450 2A6 is the major enzyme involved in the metabolism of three alkoxyethers used as oxyfuels. Toxicol Lett. 124(1-3):47-58.

Martin, J.V., N.M. Bilgin, and M.M. Iba. 2002. Influence of oxygenated fuel additives and their metabolites on the binding of a convulsant ligand of the gamma-aminobutyric acid(A) (GABA(A)) receptor in rat brain membrane preparations. Toxicol Lett. 129(3):219-26.

McGregor, D. 2006. Methyl *tertiary*-Butyl Ether: Studies for Potential Human Health Hazards. Crit Rev Toxicol. 36(4):319-358.

Meek, M.E., J.R. Bucher, S.M. Cohen, V. Dellarco, R.N. Hill, L.D. Lehman-McKeeman, D.G. Longfellow, T. Pastoor, J. Seed, and D.E. Patton. 2003. A framework for human relevance analysis of information on carcinogenic modes of action. Crit Rev Toxicol. 33(6):591-653.

Moser, G.J., B.A. Wong, D.C. Wolf, O.R. Moss, and T.L. Goldsworthy. 1996. Comparative short-term effects of methyl tertiary butyl ether and unleaded gasoline vapor in female B6C3P1 mice. Fundam Appl Toxicol. 31:173-183.

NSF/ANSI 61. 2009. Drinking Water System Components - Health Effects. NSF International, Ann Arbor, MI.

OECD (Organisation for Economic Co-Operation and Development). 2004. The 2004 OECD list of high production volume chemicals. OECD. Paris, 2004. Available at : http://www.oecd.org/dataoecd/55/38/33883530.pdf.

OEHHA (Office of Environmental Health Hazard Assessment). 1999. Public Health Goal for Methyl Tertiary-Butyl Ether (MTBE) in Drinking Water. Pesticide and Environmental Toxicology Section. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. March.

Okahara, N. A. de Peyster, S.E. McPherson, and J.A. MacGregor. 1998. Effect of MTBE on estrogen-sensitive tissues of immature female CD-1 mice [abstract]. Toxicol. 42(1-S):174-175.

Phillips, S., R.B. Palmer, and A. Brody. 2008. Epidemiology, toxicokinetics, and health effects of methyl tert-butyl ether (MTBE). J Med Toxicol. 4(2):115-26.

Prah, J., D. Ashley, B. Blount, M. Case, T. Leavens, J. Pleil, and F. Cardinali. 2004. Dermal, Oral, and Inhaltion Pharmacokinetics of Methyl Tertiary Butyl Ether (MTBE) in Human Volunteers. Toxicol. Sci. 77:195-205.

Robinson, M., R.H. Bruner, and G.R. Olson. 1990. Fourteen- and ninety-day oral toxicity studies of methyl tertiary-butyl ether in Sprague-Dawley rats. J. Am. Coll. Toxicol. 9(5):525-540.

Suffet, I.H. 2007. A re-evaluation of the taste and odour of methyl tertiary butyl ether (MTBE) in drinking water. Water Sci Technol. 55(5):265-73.

U.S. Environmental Protection Agency. 1991. National primary drinking water regulations: Final Rule. Federal Register 56(20):3526-3614.

U.S. Environmental Protection Agency. 1993. Reference Dose (RfD): Description and use in health risk assessment. Integrated Risk Information System (IRIS) background document 1A. http://www.epa.gov/ngispgm3/iris/rfd.htm

U.S. Environmental Protection Agency. 1995. Methods for the Determination of Organic Compounds in Drinking Water-Supplement III. Method 502.2. VOCs by Purge and Trap Capillary GC with Photoionization and Electrolytic Conductivity Detectors in Series. EPA/600/R-95-131, NTIS Pub. No. PB95-261616.

U.S. Environmental Protection Agency. 1997. Drinking Water Advisory: Consumer Acceptability Advice and Health Effects Analysis on Methyl tertiary-Butyl Ether (MtBE). EPA 822-F-97-008. December.

U.S. Environmental Protection Agency. 2002. A Review of the Reference Dose and Reference Concentration Process. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, EPA/630/P-02/002F. December 2002. Available at: http://www.epa.gov/iris/backgrd.html.

U.S. Environmental Protection Agency. 2007. ChemRTK HPV Challenge Program. U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. Available at: http://www.epa.gov/chemrtk/pubs/general/sponsorship.htm. Last Updated November 27, 2007.

U.S. EPA (U.S. Environmental Protection Agency). 2009. Health effects testing guidelines. U.S. Code of Federal Regulations, Title 40, Part 798. U.S. Environmental Protection Agency. Last Updated July 1, 2009.

U.S. Environmental Protection Agency. 2010. Glossary of IRIS terms. Integrated Risk Information System (IRIS). Last Updated March 16, 2010. Available at: http://www.epa.gov/iris/help_gloss.htm.

U.S. FDA (U.S. Food and Drug Administration). 2010. U.S. Code of Federal Regulations, Title 21 (Food and Drugs). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=176.170. Last updated April 1, 2010.

Ward Jr., J.B., W.W. Au, E.B. Whorton, et al. 1994. Genetic toxicity of methyl tertiary-butyl ether. Division of Environmental Toxicology, Department of Preventive Medicine and Community Health. Galveston, Texas: University of Texas Medical Branch. As cited in IPCS (1998).

Ward Jr., J.B., D.H. Daiker, D.A. Hastings, M.M. Ammenheuser, and M.S. Legator. 1995. Assessment of the mutagenicity of methyl tertiary-butyl ether at the HPRT gene in CD-1 mice [abstract]. Toxicol. 15:79.

WHO (World Health Organization). 2005. Methyl tertiary-Butyl Ether (MTBE) in Drinking-water, Background document for development of WHO Guidelines for Drinking-water Quality. WHO/SDE/WSH/05.08/122. Available at: http://www.who.int/water_sanitation_health/dwq/chemicals/MTBE200605.pdf. Accessed on April 5, 2010.

Williams, T.M. and S.J. Borghoff. 2000. Induction of testosterone biotransformation enzymes following oral administration of methyl tert-butyl ether to male Sprague-Dawley rats. Toxicol. Sci. 57(1):147-55.

Williams, T.M., R.C. Cattley, and S.J. Borghoff. 2000. Alterations in endocrine responses in male Sprague-Dawley rats following oral administration of methyl tert-butyl ether. Toxicol. Sci. 54(1):168-76.

Zheng, G., W. Zhang, Y. Zhang, Y. Chen, M. Liu, T. Yao, Y. Yang, F. Zhao, J. Li, C. Huang, W. Luo, and J. Chen. 2009. gamma-Aminobutyric acid(A) (GABA(A)) receptor regulates ERK1/2 phosphorylation in rat hippocampus in high doses of methyl tert-butyl ether (MTBE)-induced impairment of spatial memory. Toxicol Appl Pharmacol. 236(2):239-45.

Zhou,W. and S. Ye. 1999. Subchronic oral methyl tertiary-butyl ether exposure (MTBE) in male Sprague-Dawley rats and effects on health of MTBE exposed workers. J. Occup. Health. 41:33-38.

APPENDIX

Summary of non-cancer LOEL and NOEL values from repeated-dose oral studies with MTBE [a]

Study Type (Species)	Route of Exposure	NOEL mg/kg-day [a]	LOEL mg/kg-day [a]	Non-Cancer Biological Effect(s)	Reference
Two-Week (Wistar rat)	Drinking Water	Insufficient details to determine		↑ kidney weights in males, ↓ blood urea nitrogen and hematocrit in females. Study not available.	Bermudez et al., 2007
Two-Week (SD Rat)	Gavage	None (♀) 357 (♂)	357 (♀) 714 (♂)	↓ mean absolute and relative lung weights in male and female rats and altered clinical parameters in male rats. Limited endpoints evaluated.	Robinson et al., 1990
Two-Week (SD Rat)	Gavage	800 (♂ only)	None (♂ only)	No effect on hepatic clinical chemistry or peroxisomal proliferation. Limited endpoints evaluated.	DePeyster et al., 2003
Up to Four-Week (SD rat)	Gavage	None	400 (♂ only)	Reduced serum creatinine. Limited endpoints evaluated.	Dongmei et al., 2009a
Three-Week (CD-1 Mouse)	Gavage	714[b]	None	No effects on body weight or reproductive parameters (sperm number, Sertoli cells, spermatogonia, spermatocytes, and capped spermatids in males and oocyte quality in females). Limited endpoints evaluated.	Ward et al., 1994[c]; 1995[c]
Four-Week (CD-1 mouse)	Drinking Water	1,178 (♂ only)	None	No effects on testosterone level, testes weight or histology. Limited endpoints evaluated	De Peyster et al., 2008
Four-Week (SD Rat)	Gavage	250 (♂ only)	500 (♂ only)	↑ mean relative liver weight and minimal-to-moderate centrilobular hypertrophy. ↑ mean relative kidney weight and protein droplet nephropathy in renal tubules. Limited endpoints evaluated.	Williams and Borghoff, 2000; Williams et al., 2000
Four-Week (SD Rat)	Gavage	314 (♂ and ♀)[b]	1,250 (♂ and ♀)[b]	↑ mean cholesterol and relative liver weight. Gastric inflammation, edema, hyperplasia, and ulcers. ↑ mean relative kidney weight and hyaline droplet formation in renal tubules of males. Limited endpoints evaluated.	Johnson et al., 1992; Klan et al., 1992
Four-Week (SD Rat)	Gavage	357 (♂ only)	536 (♂ only)	↓ circulating testosterone concentration immediately following dosing; ↑ mean liver P450 content. Limited endpoints evaluated.	DePeyster et al., 2003
Four-Week (SD Rat)	Gavage	400 (♂ only)	800 (♂ only)	↓ body weight and ↓ plasma testosterone and corticosterone. Limited endpoints evaluated.	DePeyster et al., 2003; Day et al., 1998

Study Type (Species)	Route of Exposure	NOEL mg/kg-day [a]	LOEL mg/kg-day [a]	Non-Cancer Biological Effect(s)	Reference
Four-Week (SD Rat)	Gavage	None (♂ only)	1,200 (♂ only)	↑ mean relative liver weight, ↓ mean testosterone and luteinizing hormone, ↑ mean estradiol, ↓ hepatic and testicular microsomal aromatase activity. Limited endpoints evaluated.	DePeyster et al., 2003
Up to Four-Week (SD Rat)	Gavage	400 (♂ only)	800 (♂ only)	Alterations in serum testosterone and histopathology in the testes Limited endpoints evaluated.	Dongmei et al., 2008
Seven-Week (CD-1 mouse)	Drinking Water	1,536 (juvenile ♂ only)	None	No effect on serum estradiol or testosterone concentrations or mean seminiferous tubule diameter or reproductive organ histology. No evidence of oxidative stress in liver homogenates. Limited endpoints evaluated.	De Peyster et al., 2008
13-week (Wistar rat)	Drinking Water	Insufficient details to determine		↓ mean body weights (unspecified magnitude) and α-2μ-globulin-associated renal effects in males at 514 and 972 mg/kg-day. Study not available.	Bermudez et al., 2008
13-Week (SD Rat)	Gavage	None (♂only)	143 (♂ only)[b]	↑ liver weights and aspartate aminotransferase, hepatic nuclear condensation, fat droplets, lysosome appearance in cells, and smooth endoplasmic reticulum disintegration. Limited endpoints evaluated.	Zhou and Ye, 1999
13-Week (SD Rat)	Gavage	None (♂ and ♂)	100 (♂ and ♂)	↓ blood urea nitrogen in males and females. Limited endpoints evaluated.	Robinson et al., 1990
One-year (Wistar rat)	Drinking Water	Insufficient details to determine		Study not available. Part of a two-year study.	Bermudez et al., 2009
104-Week (SD Rat)	Gavage	Not determined		Although study authors reported "no treatment-related nononcological pathological changes were detected by gross inspection and histological examination," data were not provided. Limited endpoints evaluated (no hematology, clinical chemistry, or urinalysis).	Belpoggi et al., 1995; 1997; 1998

[a] Biologically-observed effects not necessarily considered adverse (see text)
[b] Doses were adjusted to account for a less than 7-day dosing regimen.
[c] Study not available, and thus as cited in OEHHA (1999) and ATSDR (1996).

Appendix D

Public Health Goal for MTBE in Drinking Water—California Office of Environmental Health Hazard Assessment (OEHHA)

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

Prepared by

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Pesticide and Environmental Toxicology Section
Anna M. Fan, Ph.D., Chief

Deputy Director for Scientific Affairs
George V. Alexeeff, Ph.D.

March 1999

LIST OF CONTRIBUTORS

PHG PROJECT MANAGEMENT	REPORT PREPARATION	SUPPORT
Project Director Anna Fan, Ph.D. ***Workgroup Leaders*** Joseph Brown, Ph.D. Robert Howd, Ph.D. Lubow Jowa, Ph.D. David Morry, Ph.D. Rajpal Tomar, Ph.D. ***Public Workshop*** Yi Wang, Ph.D. Coordinator Juliet Rafol Genevieve Vivar ***Report Template/Reference Guide*** Hanafi Russell Yi Wang, Ph.D. ***Revisions/Responses*** Joseph Brown, Ph.D. Yi Wang, Ph.D. Michael DiBartolomeis, Ph.D.	***Authors*** Yi Y. Wang, Ph.D. Lead/Editor Joseph P. Brown, Ph.D. Martha S. Sandy, Ph.D. Andrew G. Salmon, M.A.,D. Phil. Mari Golub, Ph.D. James Morgan, Ph.D. ***Primary Reviewers*** John Budroe, Ph.D. Michael DiBartolomeis, Ph.D. ***Secondary Reviewers*** Jim Donald, Ph.D. Frank Mycroft, Ph.D. ***External Reviewers*** Eddie T. Wei, Ph.D. Ann dePeyster, Ph.D. ***Final Reviewers*** Anna Fan, Ph.D. George Alexeeff, Ph.D. ***Education and Outreach/Summary Documents*** David Morry, Ph.D. Hanafi Russell Yi Wang, Ph.D. ***Format/Production*** Edna Hernandez	***Administrative Support*** Edna Hernandez Coordinator Juliet Rafol Genevieve Vivar ***Library Support*** Charlene Kubota, M.L.S. Mary Ann Mahoney, M.L.I.S. Valerie Walter ***Website Posting*** Edna Hernandez Laurie Monserrat

We thank the U.S. EPA (Office of Water), Cal/EPA (Air Resources Board, State Water Resources Control Board, Regional Water Quality Control Boards), and the University of California, Berkeley, as well as San Diego State University for their peer review of the PHG document, and appreciate the comments received from all interested parties.

LIST OF AUTHORS AND CORRESPONDING SECTIONS

SUMMARY	Drs. Yi Wang, Martha Sandy
INTRODUCTION	Dr. Yi Wang
CHEMICAL PROFILE	Dr. Yi Wang
ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE	Dr. Yi Wang
METABOLISM AND PHARMACOKINETICS	Drs. Joe Brown, Andy Salmon, Yi Wang
TOXICOLOGY	
Toxicological Effects in Animals	
Acute Toxicity, Subacute Toxicity, Subchronic Toxicity	Dr. Yi Wang
Genetic Toxicity	Dr. Yi Wang
Developmental and Reproductive Toxicity	Drs. Mari Golub, Jim Morgan, Yi Wang
Immunotoxicity, Neurotoxicity, Chronic Toxicity	Dr. Yi Wang
Carcinogenicity	Drs. Martha Sandy, Andy Salmon, Joe Brown, Yi Wang
Ecotoxicity	Dr. Yi Wang
Toxicological Effects in Humans	Dr. Yi Wang
Acute Toxicity, Immunotoxicity, Neurotoxicity	
DOSE-RESPONSE ASSESSMENT	Drs. Joe Brown, Yi Wang, Martha Sandy, Andy Salmon
CALCULATION OF PHG	Drs. Joe Brown, Yi Wang
RISK CHARACTERIZATION	Drs. Joe Brown, Yi Wang
OTHER REGULATORY STANDARDS	Dr. Yi Wang

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

TABLE OF CONTENTS

LIST OF CONTRIBUTORS ..... **II**

LIST OF AUTHORS AND CORRESPONDING SECTIONS ..... **III**

PREFACE ..... **IV**

LIST OF ABBREVIATIONS ..... **VI**

TABLE OF CONTENTS ..... **XI**

PUBLIC HEALTH GOAL FOR METHYL TERTIARY BUTYL ETHER (MTBE) IN DRINKING WATER **1**

SUMMARY 1

INTRODUCTION 2

Background – Prior and Current Evaluations 3

CHEMICAL PROFILE 8

Chemical Identity 8

Physical and Chemical Properties 8

Organoleptic Properties 9

Production and Uses 14

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE 15

Air, Soil, Food, and Other Sources 16

Water 18

METABOLISM AND PHARMACOKINETICS 22

Absorption 22

Distribution 23

Metabolism 23

Excretion 24

Pharmacokinetics 25

Physiologically-Based Pharmacokinetic (PBPK) Models 26

TOXICOLOGY 26

Toxicological Effects in Animals 27

Acute Toxicity 33

Subacute Toxicity 34

Subchronic Toxicity 34
Genetic Toxicity 35
Developmental and Reproductive Toxicity 36
Immunotoxicity 50
Neurotoxicity 51
Chronic Toxicity 51
Carcinogenicity 52
Ecotoxicity 65
Toxicological Effects in Humans 65
Acute Toxicity 66
Immunotoxicity 69
Neurotoxicity 70
DOSE-RESPONSE ASSESSMENT 70
Internal Dose Estimation 70
Noncarcinogenic Effects 76
Carcinogenic Effects 76
Possible Modes of Action 76
Estimation of Carcinogenic Potency 76
CALCULATION OF PHG 82
Noncarcinogenic Effects 82
Exposure Factors 83
Carcinogenic Effects 87
RISK CHARACTERIZATION 88
Acute Health Effects 88
Carcinogenic Effects 88
OTHER REGULATORY STANDARDS 92
REFERENCES 96

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-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)

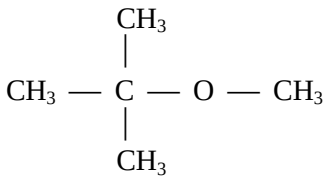
Characteristic	Information	Reference
Chemical Name	Methyl tertiary butyl ether	Merck 1989
Synonyms	Methyl tertiary-butyl ether; methyl tert-butyl ether; tert-butyl methyl ether; tertiary-butyl methyl ether; methyl-1,1-dimethylethyl ether; 2-methoxy-2-methylpropane; 2-methyl-2-methoxypropane; methyl t-butyl 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	ACGIH 1996
		(~90 - 130 ppb)	
		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) 100	1,200 (Male) (hyaline droplets, granular casts) 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	1,000		Belpoggi et al. 1995
		Cardiovascular	1,000		
		Gastrointestinal	1,000		
		Muscle/skeleton	1,000		
		Hepatic	1,000		
		Renal	1,000		
		Endocrine	1,000		
		Dermal	1,000		
		Body weight	1,000		
		Immunological/ Lymphoreticular	1,000 (Male)	250 (Female) (dysplastic proliferation of lympho-reticular tissues, possibly preneoplastic)	
		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
	Fe-male	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-day)$^{-1}$	LED_{10} mg/kg/day	CSF (mg/kg-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):

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

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-day)$^{-1}$. Individual tumor endpoint CSFs ranged from 1.55×10^{-3} (mg/kg-day)$^{-1}$ to 8.7×10^{-3} (mg/kg-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-day)$^{-1}$ to 9.2×10^{-3} (mg/kg-day)$^{-1}$, also a range of six-fold. A time-to-tumor analysis gave much higher values of 0.076 (mg/kg-day)$^{-1}$ and 0.072 (mg/kg-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-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-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.

REFERENCES

Aarstad K, Zahlsen K, Nilsen OG (1985). Inhalation of butanols: Changes in the cytochrome P_{450} enzyme system. Arch. Toxicol. Suppl 8: 418-421.

Abel EL, Bilitzke PJ (1992). Effects of prenatal exposure to methanol and t-butanol in Long Evans rats. Am. J. Obstet. Gynecol. 166(1, pt 2): 433.

ACGIH (1996). Methyl Tert-Butyl Ether. In: Documentation of the Threshold Limit Values and Biological Exposure Indices. Supplements to the Sixth Edition: Methyl Tert-Butyl Ether. pp. 1 - 12. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists, Inc. (ACGIH).

Allen MJ, Borody TJ, Bugliosi TF, May GR, Thistle JL, Etzel AL (1985). Rapid dissolution of gallstones by methyl tertiary-butyl ether: Preliminary observations. New Engl. J. Med. 312(4): 217-220. January 24.

Anderson HA, Hanrahan L, Goldring J, Delaney B (1995). An Investigation of Health Concerns Attributed to Reformulated Gasoline (RFG) Use in Southeastern Wisconsin. Final Report. May 30. Addendum. September 18. 99 pp. Milwaukee, Wisconsin: Section of Environmental Epidemiology and Prevention, Bureau of Public Health, Division of Health, Wisconsin Department of Health and Social Services.

Anderson RAJ, Reddy JM, Joyce C, Willis BR, Van der Ven H, Zaneveld LJ (1982). Inhibition of mouse sperm capacitation by ethanol. Biol. Reprod. 27(4): 833-40.

Angle CR (1991). If the tap water smells foul, think MTBE. Letter to the Editor. JAMA 266(21): 2985-2986. December 4.

Anonymous (1995). USGS reports MTBE in groundwater. Oil & Gas J. 93(16): 21-22. April 17. PennWell Publishing Company.

API (1994). Odor threshold studies performed with gasoline and gasoline combined with MTBE, ETBE and TAME. Prepared by TRC Environmental Corporation, Windsor, Connecticut, for American Petroleum Institute (API). January. API # 4592. Submitted to the U.S. Environmental Protection Agency with cover letter dated February 22, 1995. EPA/OTS DOC#86950000131. Washington, D.C.: API. API MTBE website: http://www.api.org/ehs/othrmtbe.htm

Arashidani K, Katoh T, Yoshikawa M, Kikuchi M, Kawamoto T, Kodama Y (1993). LD_{50} and weight change in organs of mice following intraperitoneal administration of methyl tertiary-butyl ether. Sangyo Igaku (Japan) 35(5): 404-405. September.

ARB (1996). Preliminary Ambient Oxygenates Data of the California ARB Laboratory Information System, and San Francisco Bay Area Air Quality Management District (BAAQMD) Ambient Air Toxics Data on MTBE. Laboratory and Monitoring Division, California Air Resources Board (ARB), California Environmental Protection Agency (Cal/EPA). Sacramento, California: ARB, Cal/EPA.

ARCO (1995a). MTBE Use and Possible Occurrences in Water Supplies. Prepared by William J. Piel. May 10. 4 pp. Newton Square, Pennsylvania: ARCO Chemical Company.

ARCO (1995b). Methyl t-Butyl Ether (MtBE): A status report of its presence and significance in U.S. drinking water. Presented by ARCO Chemical Company to the Office of Water, U.S. Environmental Protection Agency on June 8. Glenolden, Pennsylvania: ARCO Chemical Company.

ARCO (1980). Methyl tertiary-butyl ether: acute toxicological studies. Unpublished study for ARCO Research and Development for ARCO Chemical Company. Glenolden, Pennsylvania: ARCO Chemical Company.

ATSDR (1996). Toxicological profile for methyl tert-butyl ether. August. Prepared by Research Triangle Institute for the Agency for Toxic Substances and Disease Registry (ATSDR), Centers for Disease Control (CDC), Public Health Service (PHS), United States Department of Health and Human Services (USDHHS). Atlanta, Georgia: ATSDR, CDC.

Baehr AL, Baker RJ, Lahvis MA (1997). Transport of methyl tert-butyl ether across the water table to the unsaturated zone at a gasoline-spill site in Beaufort, South Carolina. Paper ENVR 230. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 417-418.

Balter NJ (1997). Casualty assessment of the acute health complaints reported in association with oxygenated fuels. Risk Anal. 17(6): 705-715. December.

Barker JF, Hubbard CE, Lemon LA (1990). The influence of methanol and MTBE on the fate and persistence of monoaromatic hydrocarbons I ground water. Ground Water Manag. 113-117.

Begley R (1994). MTBE high demand time looms as health questions linger. Chemical Week 155: 13. August 31 - September 7.

Begley R, Rotman D (1993). Health complaints fuel federal concern over MTBE. Chemical Week 152(10): 7. March 17.

Beller M, Schloss M, Middaugh J (1992). Potential Illness Due to Exposure to Oxyfuels. Evaluation of Health Effects from Exposure to Oxygenated Fuel in Fairbanks, Alaska. December 11. Bulletin Number 26. Anchorage, Alaska: Alaska Department of Health and Social Services.

Belpoggi F, Soffritti M, Maltoni C (1998). Pathological characterization of testicular tumours and lymphomas-leukaemias, and of their precursors observed in Sprague-Dawlay rats exposed to methyl tertiary-butyl ether (MTBE). Eur. J. Oncol. 3(3): 201-206.

Belpoggi F, Soffritti M, Maltoni C (1995). Methyl tertiary-butyl ether (MtBE) - a gasoline additive - causes testicular and lymphohaematopoietic cancers in rats. Toxicol. Ind. Hlth. 11(2): 119-149. March.

Belpoggi F, Soffritti M, Filippini F, Maltoni C (1997). Results of long-term experimental studies on the carcinogenicity of methyl tert-butyl ether. Annals N. Y. Acad. Sci. 837: 77-95. December 26.

Bernauer U, Amberg A, Scheutzow D, Dekant W (1998). Biotransformation of ^{12}C- and 2-^{13}C-labeled methyl tert-butyl ether, ethyl tert-butyl ether, and tert-butyl alcohol in rats: Identification of metabolites in urine by ^{13}C nuclear magnetic resonance and gas chromatography/mass spectrometry. Chem. Res. Toxicol. 11(6): 651-658. June.

Bevan C, Neeper-Bradley TL, Tyl RW, Fischer LC, Panson RD, Kneiss JJ, Andrews LS (1997a). Two-generation reproductive study of methyl tertiary-butyl ether (MTBE) in rats. J. Appl. Toxicol. 17(S1): S13-S19. May.

Bevan C, Tyl RW, Neeper-Bradley TL, Fischer LC, Panson RD, Douglas JF, Andrews LS (1997b). Developmental toxicity evaluation of methyl tertiary-butyl ether (MTBE) by inhalation in mice and rabbits. J. Appl. Toxicol. 17(S1): S21-S29. May.

BIBRA (1990). Methyl t-butyl ether (MTBE) toxicology profile. The British Industrial Biological Research Association (BIBRA) Working Group. 6 pp. London, Great Britain: BIBRA Toxicology International.

Biles RW, Schroeder RE, Holdsworth CE (1987). Methyl tert-butyl ether inhalation in rats: a single generation reproduction study. Toxicol. Ind. Hlth. 3(4): 519-534. December.

Bio/dynamics, Inc. (1984a). An inhalation teratology study in rats with methyl tertiary-butyl ether (MtBE). Project No. 80-2515. Unpublished report submitted to API, Washington, D.C. East Millstone, New Jersey: Bio/dynamics, Inc.

Bio/dynamics, Inc. (1984b). An inhalation teratology study in mice with methyl tertiary-butyl ether (MtBE). Project No. 80-2516. Unpublished report submitted to API, Washington, D.C. East Millstone, New Jersey: Bio/dynamics, Inc.

Bio/dynamics, Inc. (1984c). The metabolic fate of methyl tertiary-butyl ether (MtBE) following acute intraperitoneal injection. Project No. 80089. Unpublished report submitted to API, Washington, D.C. 150 pp. East Millstone, New Jersey: Bio/dynamics, Inc.

Bio/dynamics, Inc. (1981). A nine day inhalation toxicity study of MTBE in the rat. Project No. 40-1452. Unpublished report submitted to API, Washington, D.C. 352 pp. East Millstone, New Jersey: Bio/dynamics, Inc.

Bioresearch Laboratories (1990a). Pharmacokinetics of methyl tertiary-butyl ether (MtBE) and tert-butyl alcohol (TBA) in male and female Fischer-344 rats after administration of ^{14}C-MtBE by intravenous, oral, and dermal routes. Report #38842. Senneville, Quebec, Canada: Bioresearch Laboratories.

Bioresearch Laboratories (1990b). Mass balance of radioactivity and metabolism of methyl tert-butyl ether (MtBE) in male and female Fischer-344 rats after administration of ^{14}C MtBE by intravenous, oral, and dermal routes. Report #38843. Senneville, Quebec, Canada: Bioresearch Laboratories.

Bioresearch Laboratories (1990c). Pharmacokinetics of methyl tert-butyl ether (MtBE) and tert-butyl alcohol (TBA) in male and female Fischer-344 rats after single and repeat inhalation nose-only exposure to ^{14}C-MtBE. Report #38844. Senneville, Quebec, Canada: Bioresearch Laboratories.

Bioresearch Laboratories (1990d). Disposition of radioactivity of methyl tertiary- butyl ether (MtBE) in male and female Fischer-344 rats after nose-only inhalation exposure to ^{14}C-MtBE. Report #38845. Senneville, Quebec, Canada: Bioresearch Laboratories.

Bird MG, Burleigh-Flayer HD, Chun JS, Douglas JF, Kneiss JJ, Andrews LS (1997). Oncogenicity studies of inhaled methyl tertiary-butyl ether (MTBE) in CD-1 mice and F-344 rats. J. Appl. Toxicol. 17 (S1): S45-S55. May.

Bonin MA, Ashly DL, Cardinali FL, Mccraw JM, Wooten JV (1995). Measurement of methyl tert-butyl ether and tert-butyl alcohol in human blood by purge-and-trap gas chromatography-mass spectrometry using an isotope-dilution method. J. Analyt. Toxicol. 19(3): 187-191. May - June.

Borak J, Pastides H, Van Ert M, Russi M, Herastein J (1998). Exposure to MTBE and acute human health effects: A critical literature review. Human and Ecological Risk Assess. 4(1): 177-200. February.

Borden RC, Daniel RA, LeBrun LE IV, Davis CW (1997). Intrinsic biodegradation of MTBE and BTEX in a gasoline-contaminated aquifer. Water Resources Res. 33(5): 1105-1115. May.

Borghoff SJ, Murphy JE, Medinsky MA (1996a). Development of a physiologically based pharmacokinetic model for methyl tertiary-butyl ether and tertiary-butanol in male Fischer-344 rats. Fundam. Appl. Toxicol. 30(2): 264-275. April.

Borghoff SJ, Prescott-Mathews JS, Poet TS (1996b). The mechanism of male rat kidney tumors induced by methyl tert-butyl ether (MTBE) and its relevance in assessing human risk. CIIT Activities. 16(10): 1-10. October. Research Triangle Park, North Carolina: Chemical Industry Institute of Toxicology (CIIT).

Boughton CJ, Lico MS (1998). Volatile Organic Compounds in Lake Tahoe, Nevada and California, July - September 1997. USGS Fact Sheet FS-055-98. June. 2 pp. Carson City, Nevada: USGS.

Brady JF, Xiao F, Ning WJ, Yang CS (1990). Metabolism of methyl tertiary-butyl ether by rat hepatic microsomes. Arch. Toxicol. 64(2): 157-160.

Brown A, Devinny JS, Davis MK, Browne TE, Rodriguez RA (1997). A review of potential technologies for the treatment of methyl tertiary-butyl ether (MTBE) in drinking water. In: Proceedings of the NGWA-API Conference on Petroleum Hydrocarbons and Organic Chemicals in Ground Water: Prevention, Detection, and Remediation. 16 pp. November 12 - 14. Houston, Texas. Dublin, Ohio: National Ground Water Association (NGWA).

Brown SL (1997). Atmospheric and potable water exposures to methyl tertiary-butyl ether (MTBE). Reg. Toxicol. Pharmacol. 25(3): 256-276. June.

Bruce BW, McMahon PB (1996). Shallow groundwater quality beneath a major urban center: Denver, Colorado, USA. J. Hydrology (Amsterdam, Netherlands) 186(1-4): 129-151.

Buckley TJ, Prah JD, Ashley D, Zweidinger RA, Wallace LA (1997). Body burden measurements and models to assess inhalation exposure to methyl tertiary-butyl ether (MTBE). J. Air Waste Manag. Assoc. 47(7): 739-752. July.

Burbacher TM (1993). Neurotoxic effects of gasoline and gasoline constituents. Environ. Hlth. Perspect. 101(S6): 133-141. December.

Burleigh-Flayer HD, Chun JS, Kintigh WJ (1992). Methyl tertiary butyl ether: vapor inhalation oncogenicity study in CD-1 mice. Bushy Run Research Center Report No. 91N0013A. October 15. Union Carbide Chemicals and Plastics Company, Inc. submitted to the U.S. EPA under TSCA Section 4 Testing Consent Order 40 CFR 799.5000 with cover letter dated October 29, 1992. EPA/OPTS#42098. Export, Pennsylvania: Bushy Run Research Center.

Burleigh-Flayer HD, Doss DE, Bird MG, Ridlon SA (1991). Oncogenicity study of inhaled methyl tertiary butyl ether (MTBE) in CD-1 mouse. MTBE Task Force. Washington, D.C.: Oxygenated Fuels Association (OFA).

Burleigh-Flayer HD, Garman R, Neptun K, Bevan C, Gardiner T, Kapp R, Tyler T, Wright G (1997). Isopropanol vapor inhalation oncogenicity study in Fischer 344 rats and CD-1 mice. Fund. Appl. Toxicol. 36:95-111.

Buxton HT, Landmeyer JE, Baehr AL, Church CD, Tratnyek PG (1997). Interdisciplinary investigation of subsurface contaminant transport and fate at point-source releases of gasoline containing methyl tert-butyl ether (MTBE). In: Proceedings of the Petroleum Hydrocarbons and Organic Chemicals in Ground Water: Prevention, Detection, and Remediation Conference. pp. 15. November 11 - 14. Houston, Texas. Dublin, Ohio: NGWA.

Cain WS, Leaderer BP, Ginsberg GL, Andrews LS, Cometto-Muniz JE, Gent JF, Buck M, Berglund LG, Mohsenin V, Monahan E, Kjaergaard S (1996). Acute exposure to low-level methyl tertiary-butyl ether (MTBE): Human reactions and pharmacokinetic responses. Inhalation Toxicol. 8(1): 21-49. January.

Cal/EPA (1998). MTBE (methyl tertiary butyl ether) briefing paper by the California Environmental Protection Agency (Cal/EPA). April 24, 1997, updated September 3, 1998. 33 pp. Sacramento, California: Cal/EPA. Available at: http:/www.arb.ca.gov/cbg/pub/pub.htm

Caprino L, Togna GI (1998). Potential health effects of gasoline and its constituents: a review of current literature (1990-1997) on toxicological data. Environ. Hlth. Perspect. 106:115-125.

Casanova M, Heck HA (1997). Lack of evidence for the involvement of formaldehyde in the hepatocarcinogenicity of methyl tertiary-butyl ether in CD-1 mice. Chem. Biol. Interact. 105(2): 131-143. July 11.

CDC (1993a). An investigation of exposure to methyl tertiary-butyl ether (MTBE) in oxygenated fuel in Fairbanks, Alaska. October 22. National Center for Environmental Health (NCEH), Centers for Disease Control and Prevention (CDC), PHS, USDHHS. Atlanta, Georgia: CDC.

CDC (1993b). An investigation of exposure to MTBE among motorists and exposed workers in Stamford, Connecticut. September 14. NCEH, CDC, PHS, USDHHS. Atlanta, Georgia: CDC.

CDC (1993c). An investigation of exposure to MTBE and gasoline among motorists and exposed workers in Albany, New York. August 4. NCEH, CDC, PHS, USDHHS. Atlanta, Georgia: CDC.

Cederbaum AI, Cohen G (1980). Oxidative demethylation of t-butyl alcohol by rat liver microsomes. Biochem. Biophys. Res. Comm. 97: 730-736.

Chandler B, Middaugh J (1992). Potential illness due to exposure to oxyfuels: Anchorage, Alaska. Bulletin Number 1. Middaugh J ed. Anchorage, Alaska: Alaska Department of Health and Social Services.

Chun JS, Burleigh-Flayer HD, Kintigh WJ (1992). Methyl tertiary ether: vapor inhalation oncogenicity study in Fisher 344 rats. Bushy Run Research Center Report No. 91N0013B. November 13. Union Carbide Chemicals and Plastics Company, Inc. submitted to the U.S. EPA under TSCA Section 4 Testing Consent Order 40 CFR 799.5000 with cover letter dated November 19, 1992. EPA/OPTS#42098. Export, Pennsylvania: Bushy Run Research Center.

Church CD, Isabelle LM, Pankow JF, Rose DL, Tratnyek PG (1997). Method for determination of methyl tert-butyl ether and its degradation products in water. Environ. Sci. Technol. 31(12): 3723-3726.

Cinelli S, Ciliutti P, Falezza A, Meli C, Caserta L, Marchetti S, Seeberg AH, Vericat JA (1992). Absence of mutagenicity of methyl-tertiary-butyl ether [abstract No. P36/P10]. Toxicol. Lett. Suppl. 1-356: 300.

Cirvello JD, Radovsky JE, Heath DR, Farnell DR, Lindamood, III C (1995). Toxicity and carcinogenicity of t-butyl alcohol in rats and mice following chronic exposure in drinking water. Toxicol. Ind. Hlth. 11(2): 151-165.

Clary JJ (1997). Methyl tertiary butyl ether systemic toxicity. Risk Anal. 17(6): 661-672. December.

Clegg ED, Cook JC, Chapin RE, Foster PMD, Daston GP (1997). Leydig cell hyperplasia and adenoma formation: Mechanisms and relevance to humans. Reproductive Toxicol. 11(1): 107-121.

Clerici C, Gentili G, Zakko SF, Balo S, Miglietti M, Giansanti M, Modesto R, Guttermuth CF, Morelli A (1997). Local and systemic effects of intraduodenal exposure to topical gallstone solvents ethyl propionate and methyl tert-butyl ether in the rabbit. Digest. Dis. Sci. 42(3): 497-502.

Cohen Y (1998). Multimedia distribution of oxygenated fuel additives. Presented at the MTBE Workshop, co-sponsored by the UCLA Center for Environmental Risk Reduction, UC Toxic Substances Research and Teaching Program, and Southern California Society for Risk Analysis. February 28. 29 pp. UCLA, Los Angeles, California.

Cohen Y, Allen DT, Clay R, Tsai WT, Rosselot K, Klee H, Blewitt D (1991). Multimedia assessment of refinery emissions. Paper No. 91-84.6 presented at the 84th Annual Meeting of the Air and Waste Management Association. June 16 - 21. Vancouver, British Columbia, Canada.

Conaway CC, Schroeder RE, Snyder NK (1985). Teratology evaluation of methyl tertiary-butyl ether in rats and mice. J. Toxicol. Environ. Hlth. 16(6): 797-809.

Cooney CM (1997). California struggles with presence of MTBE in public drinking water wells. Environ. Sci. Technol. 31(6): A269. June.

Cornitius T (1996). California air rules foster MTBE demand. Chemical Week 158(27): 33. July 17.

Cox DR (1972). Regression models and life-tables (with discussion). J. R. Stat. Soc. B. 24: 187-220.

Crump KS, Howe RB, van Landingham C, Fuller WG (1993). TOX_RISK, a Toxicology Risk Assessment Program. Version 3.5. October. Ruston, Louisiana: K.S. Crump Division, Clement International Corp.

Cullen PG (1998). MTBE: A remediation headache. Environ. Protect. 6: 32-35. June.

Dale MS, Losee RF, Crofts EW, Davis MK (1997a). MTBE: Occurrence and fate in source-water supplies. Paper ENVR 101. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 376-377.

Dale MS, Moylan MS, Koch B, Davis MK (1997b). MTBE: Taste and odor threshold determinations using the flavor profile method. Presented at the Water Quality Technology Conference. November 9 - 13. Denver, Colorado. American Water Works Association (AWWA).

Daly MH, Lindsey BD (1996). Occurrence and concentrations of volatile organic compounds in shallow groundwater in the Lower Susquehanna River basin, Pennsylvania and Maryland. USGS Water Resources Investigation Report. WRIR 96-4141. 8 pp. USGS.

Daniel MA, Evans MA (1982). Quantitative comparison of maternal ethanol and maternal tertiary butanol diet on postnatal development. J. Pharmacol. Exp. Ther. 222(2): 294-300.

Daniel RA (1995). Intrinsic Bioremediation of BTEX and MTBE: Field, Laboratory and Computer Modeling Studies. Graduate Thesis, Department of Civil Engineering, North Carolina State University (NCU). Raleigh, North Carolina: NCU.

Daughtrey WC, Gill MW, Pritts IM, Douglas JF, Kneiss JJ, Andrews LS (1997). Neurotoxicological evaluation of methyl tertiary-butyl ether in rats. J. Appl. Toxicol. 17(S1): S57-S64. May.

Davidson JM (1995). Fate and transport of MTBE - The latest data. In: Proceedings of the Petroleum Hydrocarbons and Organic Chemicals in Ground Water: Prevention, Detection, and Remediation Conference. pp. 285-301. November 29 - December 1. Houston, Texas. Dublin, Ohio: NGWA.

Davidson JM, Parsons R (1996). Remediating MTBE with current and emerging technologies. In: Proceedings of the Petroleum Hydrocarbons and Organic Chemicals in Ground Water: Prevention, Detection, and Remediation Conference. pp. 15-29. November 13 - 25. Houston, Texas. Dublin, Ohio: NGWA.

Day KJ, de Peyster A, Allgaier BS, Luong A, MacGregor JA (1998). Methyl t-butyl ether (MTBE) effects on the male rat reproductive endocrine axis [Abstract No. 861 presented at the 1998 Society of Toxicology Annual Meeting]. The Toxicologist 42(1-S): 174. March.

Delzer GC, Zogorski JS, Lopes TJ (1997). Occurrence of the gasoline oxygenate MTBE and BTEX compounds in municipal stormwater in the United States, 1991-1995. Paper ENVR 100. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 374-376.

Denton J, Masur L (1996). California's cleaner burning gasoline and methyl tertiary-butyl ether [Abstract]. In: the Proceedings of the Society of Environmental Toxicology and Chemistry (SETAC) 17th Annual Meeting. p. 115. November 17 - 21. Washington, D.C.

DHS (1998). Notice of Proposed Rulemaking. Revision of the Secondary Maximum Contaminant Level List, the Unregulated Chemical Monitoring Lists, and Associated Requirements for Drinking Water (R-44-97). California Department of Health Services (DHS). July 3. Sacramento, California: DHS, Health and Welfare Agency, State of California.

DHS (1997). Proposed Regulation for a Revision to the Secondary MCL List and Revisions to Unregulated Chemical Monitoring List and Associated Requirements for Drinking Water. Division of Drinking Water Environmental Management. October and December. Sacramento, California: DHS, Health and Welfare Agency, State of California.

DHS (1985). Guidelines for Chemical Carcinogen Risk Assessments and Their Scientific Rationale. Sacramento, California: DHS, Health and Welfare Agency, State of California.

Diaz, D, Bories P, Ampelas M, Larrey D, Michel H (1992). Methyl tert-butyl ether in the endoscopic treatment of common bile duct radiolucent stones in elderly patients with nasobiliary tube. Digest. Dis. Sci. 37: 97-100.

Dodd DE, Kintigh WJ (1989). Methyl tertiary butyl ether (MTBE) repeated 13-week vapor inhalation study in rats with neurotoxicity evaluation. Bushy Run Research Center Project Report 52-507. Final Report submitted to the U.S. EPA with cover letter dated September 27, 1989 with draft submitted dated August 11, 1989. TSCATS/403186. EPA/OTS #40-8913440. No. FYI-OTS-0889-0689. WPA/PTS # FYI-OTS-0889-0689. Export, Pennsylvania: Bushy Run Research Center.

Dourson ML, Felter SP (1997). Route-to-route extrapolation of the toxic potency of MTBE. Risk Anal. 17(6): 717-725. December.

Drew RT (1995). Misunderstand MTBE. Letter to the Editor. Environ. Hlth. Perspect. 103(5): 420. May.

DTSC (1994). CalTox™, A Multimedia Total Exposure Model for Hazardous Waste Sites. Spreadsheet User's Guide. Version 1.5. Prepared by the University of California, Davis, in corporation with Lawrence Livermore National Laboratory for the Department of Toxic Substances Control, California Environmental Protection Agency. Sacramento, California: DTSC, Cal/EPA.

Du JT, Abernathy CO, Donohue J, Mahfouz A, Khanna K (1998). Provisional health and consumer acceptability advisory for methyl t-butyl ether (MTBE) [Abstract no. 1123 presented at the 1998 Society of Toxicology Annual Meeting]. The Toxicologist 42(1-S): 228. March.

Duffy JS, Del Pup JA, Kneiss JJ (1992). Toxicological evaluation of methyl tertiary-butyl ether (MTBE): Testing performed under TSCA consent agreement. J. Soil Contam. 1(1): 29-37. and Hydrocarbon Contam. Soils 2: 757-765. Washington, D.C.: American Chemical Society.

Duffy LK (1994). Oxyfuel in Alaska: Use of interleukins to monitor effects on the immune system. Sci. Total Environ. 151(3): 253-256. July 18.

ECETOC (1997). Methyl tert-Butyl Ether (MTBE) Health Risk Characterization. CAS No. 1634-04-4 (EINECS No. 216.653.1). June. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 72. Brussels, Belgium: ECETOC.

EDF (1998). Methyl tert-butyl ether. In: The Environmental Defense Fund (EDF) Chemical Scorecard. It is protected by copyright. Available at: www.scorecard.org

Edison SA, Maier M, Kohler B, Schlauch D, Buttmann A, Gauer E, Riemann JF (1993). Direct dissolution of gallstones with MTBE by endoscopic cannulation of the gallbladder. Am. J. Gastroenterol. 88(8): 1242-1248.

Environmental Canada (1993). Canadian Environmental Protection Act Priority Substances List Supporting Document, Methyl Tertiary Butyl Ether (MTBE). January. 28 pp. Ottawa, Canada: Canada Communication Group Publisher, Government of Canada.

Environmental Canada (1992). Canadian Environmental Protection Act Priority Substances List Assessment Report No. 5, Methyl Tertiary Butyl Ether (MTBE). 19 pp. Ottawa, Canada: Canada Communication Group Publisher, Government of Canada.

Erdal S, Gong H Jr., Linn WS, Rykowski R (1997). Projection of health benefits from ambient ozone reduction related to the use of methyl tertiary butyl ether (MTBE) in the reformulated gasoline program. Risk Anal. 17(6): 693-704. December.

Ershow AG, Cantor KP (1989). Total Water and Tap Water Intake in the United States: Population Based Estimates of Quantities and Sources. Life Sciences Research Office, Federation of American Societies for Experimental Biology (FASEB). Baltimore, Maryland: FASEB.

Experimental Pathology Laboratories, Inc. (1993). Histopathologic Evaluation of Kidneys from Male and Female Rats Utilized on a Vapor Inhalation Oncogenicity Study of Methyl Tertiary Butyl Ether. Pathology Slide Peer-Review Report.. MTBE Task Force Study Number 91N0013B. Submitted to Methyl Tertiary Butyl Ether Task Force organized by the Oxygenated Fuels Association, Inc. Washington, D.C.:MTBE Task Force, OFA.

Farland WH (1990). Memorandum on Drinking Water Quantification of Toxicologic Effects (QTE) for MTBE. Final Draft. ECAO-CIN-DO23. Office of Health and Environmental Assessment, U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

Farr J, Apostolakis G, Collins M, Crouch III RC, Fogg G, Reinhard M, Scow K (1996). Senate Bill 1764 Advisory Committee Recommendations Report Regarding California's Underground Storage Tank (UST) Program. May 31. Submitted to the California State Water Resources Control Board (SWRCB). Sacramento, California: SWRCB.

Faulkner TP, Wiechart JD, Hartman DM, Hussain AS (1989). The effects of prenatal tertiary butanol administration in CBA/J and C57BL/6J mice. Life Sci. 45(21): 1989-95.

Fenelon JM, Moore RC (1996). Occurrence of volatile organic compounds in groundwater in the White River basin, Indiana, 1994 - 1995. USGS Fact Sheet FS 138-96. 4 pp. USGS.

Fiedler N, Mohr SN, Kelly-McNeil K, Kipen HM (1994). Response of sensitive groups to methyl tertiary-butyl ether (MTBE). In: Proceedings of the 1993 Conference on MTBE and Other Oxygenates, pp. D65-D84. EPA/600-R95-134. Inhalation Toxicol. 6 (6): 539-552. November - December.

Freed CN (1997). EPA fuel programs. Paper ENVR 95. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 366-368.

Froines JR, Collins M, Fanning E, McConnell R, Robbins W, Silver K, Kun H, Mutialu R, Okoji R, Taber R, Tareen N, Zandonella C (1998). An evaluation of the scientific peer-reviewed research and literature on the human health effects of MTBE, its metabolites, combustion products and substitute compounds. In: Health and Environmental Assessment of MTBE. Report to the Governor and Legislature of the State of California as Sponsored by SB 521. Volume II: Human Health Effects. 267 pp. Submitted through the University of California Toxic Substances Research and Teaching Program SB521 MTBE Research Program. November 12. Davis, California. Available at: http://tsrtp.ucdavis.edu/mtberpt/

Froines JR (1998). SB521 MTBE research by UCLA: An evaluation of the peer-reviewed research literature on the human health, including asthma, and environmental effects of MTBE. Abstract presented at the University of California Toxic Substances Research and Teaching Program SB521 MTBE Research Workshop. June 16. Davis, California. Available at: http://tsrtp.ucdavis.edu/mtbe/

Fueta Y, Arashidani K, Katoh T, Fukata K, Kodama Y (1994). Effects of methyl tertiary-butyl ether on the central nervous system. Sangyo Igaku 36(1): 26-27.

Fujita EM, Bowen JL, Green MC, Moosmuller H (1997). Southern California Ozone Study (SCOS97) Quality Assurance Plan. Report prepared for California Air Resources Board, Desert Research Institute, Reno, Nevada. April 4, 1997. Sacramento, California: ARB, Cal/EPA.

Fujiwara U, Kinoshita T, Sato H, Kojima I (1984). Biodegradation and bioconcentration of alkyl ethers. Yukagaken 33: 111-114.

Garnier AC, Harper JG, Angelosanto FA, Blackburn GR, Schreiner CA, Mackerer CR (1993). The metabolite formaldehyde is responsible for the mutagenicity of methyl tertiary butyl ether (MTBE) in the activated mouse lymphoma assay. 4 pp. Presented at the Annual Meeting of the Genetic Toxicology Association. October 21. Princeton, New Jersey: Mobil Oil Corp.

Garrett P, Moreau M, Lowry JD (1986). MTBE as a groundwater contaminant. In: Proceedings of the NWWA-API Conference on Petroleum Hydrocarbons and Organic Chemicals in Ground Water - Prevention, Detection and Restoration. pp. 227-238. November 12 - 14. Houston, Texas. Dublin, Ohio: National Water Well Association (NWWA).

Gilbert CE, Calabrese EJ (1992). Developing a standard for methyl tertiary-butyl ether in drinking water. In: Regulating Drinking Water Quality. pp. 231-252. Gilbert CE, Calabrese EJ eds. Ann Arbor, Michigan: Lewis Publishers, Inc.

Goldsmith JR (1998). Vapor recovery systems can reduce risks from MTBE. Letter to the Editor. Environ. Hlth. Perspect. 106 (5): A220. May.

Gomez-Taylor MM, Abernathy CO, Du JT (1997). Drinking water health advisory for methyl tertiary-butyl ether. Paper ENVR 98. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 370-372.

Gordian ME, Huelsman MD, Brecht ML, Fisher DG (1995). Health effects of MTBE in gasoline in Alaska. Alaska Med. 37(3): 101-103, 119. July - September.

Grady SJ (1997). Distribution of MTBE in groundwater in New England by aquifer and land use. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 392-394.

Grant KA, Samson HH (1982). Ethanol and tertiary butanol induced microcephaly in the neonatal rat: Comparison of brain growth parameters. Neurobehav. Toxicol. Teratol. 4(3): 315-321.

Greenough RJ, McDonald P, Robinson P, Cowie J, Maule W, Macnaughtan F, Rushton A (1980). MTBE (Driveron) three month inhalation toxicity in rats. Project No. 413038. Inveresk Research International. Unpublished report to Chemise Werke Hols AG, Marl, West Germany. Report No. 1596. 230 pp. Edinburgh. As cited in the U.S. EPA's IRIS, MTBE, 1991. NTIS Publication No. NTIS/OTS 0513483.

Grosjean E, Grosjean D, Gunawardena R, Rasmussen RA (1998). Ambient concentrations of ethanol and methyl tert-butyl ether (MTBE) in Porto Alegre, Brazil, March 1996 - April 1997. Environ. Sci. Technol. 32(6): 736-742. March 15.

Gupta G, Lin YJ (1995). Toxicity of methyl tertiary butyl ether to Daphnia magna and Photobacterium phosphoreum. Bull. Environ. Contam. Toxicol. 55(4): 618-620. October.

Hakkola M, Honkasalo ML, Pulkkinen P (1997). Changes in neuropsychological symptoms and moods among tanker drivers exposed to gasoline during a work week. Occup. Med. (Oxford, London, England) 47(6): 344-348. August.

Hakkola M, Honkasalo ML, Pulkkinen P (1996). Neuropsychological symptoms among tanker drivers exposed to gasoline. Occup. Med. (Oxford) 46(2): 125-130. April.

Hakkola M, Saarinen L (1996). Exposure of tanker drivers to gasoline and some of its components. Annals Occup. Hyg. 40(1): 1-10. February.

Hakkola M (1994). Neuropsychological symptoms among tanker drivers with exposure to solvents. Occup. Med. (Oxford) 44(5): 243-246. December.

Hall AH, Rumack BH, eds. (1998). TOMES PLUS System. Micromedex, Inc., Englewood, Colorado.

Happel AM, Beckenbach EH, Halden RU (1998). An Evaluation of MTBE Impacts to California Groundwater Resources. UCRL-AR-130897. Report submitted to the California State Water Resources Control Board, Underground Storage Tank Program, Department of Energy, Office of Fossil Fuels, and Western States Petroleum Association. Livermore, California: Environmental Restoration Division, Environmental Protection Department, Lawrence Livermore National Laboratory (LLNL), University of California (UC).

Hartle R (1993). Exposure to methyl tertiary-butyl ether and benzene among service station attendants and operators. Environ. Hlth. Perspect. 101(S6): 23-26. December.

Hartley WR, Englande SJ Jr. (1992). Health risk assessment of the migration of unleaded gasoline - a model for petroleum products. Water Sci. Technol. 25(3): 65-72.

Haseman JK, Arnold J. (1990). Tumor incidence in Fischer 344 rats: NTP historical data. In: Pathology of the Fischer Rat. Boorman GA, Eustis SL, Elwell MR, Montgomery CA Jr, MacKenzie WF eds. pp. 555-564. San Diego, California: Academic Press.

Hattis D, Tuler S, Finkelstein L, Luo Z-Q (1986). A Pharmacokinetic/Mechanism-based Analysis of the Carcinogenic Risk of Perchloroethylene. Center for Technology, Policy and Industrial Development, Massachusetts Institute of Technology (MIT). Cambridge, Massachusetts: MIT.

Hellstern A, Leuschner U, Benjaminov A, Ackermann H, Heine T, Festi D, Orsini M, Roda E, Northfield TC, Jazrawi R, Kurtz W, Schmeck-Lindenau HJ, Stumpf J, Eidsvoll BE, Asdland E, Lux G, Boehnke E, Wurbs D, Delhaye M, Cremer M, Sinn I, Horing E, vonGaisberg U, Neubrand M, Paul F (1998). Dissolution of gallbladder stones with methyl tert-butyl ether and stone recurrence: A European survey. Digest. Dis. Sci. 43(5): 911-920. May.

HEI (1996). The Potential Health Effects of Oxygenates Added to Gasoline: A Review of the Current Literature. April. A special report of the Health Effect Institute's Oxygenates Evaluation Committee. Cambridge, Massachusetts: Health Effects Institute (HEI). Available at: http://www.healtheffects.org/oxysum.htm

Hiremath CB, Parker JC (1994). Methyl tertiary butyl ether: cancer risk assessment issues (U.S. EPA, Office of Research and Development, Office of Health and Environmental Assessment). 25 pp. [Abstract No. 540 presented at the 1994 Society of Toxicology Annual Meeting]. The Toxicologist 14(1): 152. March.

Hoel DG, Walburg HE (1972). Statistical analysis of survival experiments. J. Natl. Cancer Inst. 49: 361-372.

Hoffert SP (1998). Haze of uncertainty surrounds gas additive, lawmakers look to scientists for answers. The Scientist 12(13): 1 and 7.

Hofmann AF, Amelsberg A, Esch O, Schteingart CD, Lyche K, Jinich H, Vansonnenberg E, D'Agostino HB (1997). Successful topical dissolution of cholesterol gallbladder stones using ethyl propionate. Digest. Dis. Sci. 42(6): 1274-1282. June.

Hong JY, Wang YY, Bondoc FY, Yang CS, Lee M, Huang WQ (1997a). Rat olfactory mucosa displays a high activity in metabolizing methyl tert-butyl ether and other gasoline ethers. Fund. Appl. Toxicol. 40(2): 205-210. December.

Hong JY, Yang CS, Lee M, Wang YY, Huang WQ, Tan Y, Patten CJ, Bondoc FY (1997b). Role of cytochrome P_{450} in the metabolism of methyl tert-butyl ether in human livers. Arch. Toxicol. 71(4): 266-269.

Howard PH ed. (1993). Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Volume IV. pp. 71-75. Ann Arbor, Michigan: Lewis Publishers, Inc.

Howard PH, Boethling RS, Jarvis WF, Meylan WM, Michalenko EM (1991). Handbook of Environmental Degradation Rates. pp. 653-654. Chelsea, Michigan: Lewis Publishers, Inc.

HSDB (1997). Hazardous Substances Data Bank (HSDB): t-Butyl Methyl Ether. Last revised on April 23, 1997. Bethesda, Maryland: National Library of Medicine (NLM), National Toxicology Program (NTP).

Hubbard, CE, Barker JF, O'Hannesin SF, Vandegriendt M, Gillham RW (1994). Transport and fate of dissolved methanol, MTBE, and monoaromatic hydrocarbons in a shallow sand aquifer. API Publication 4601, Appendix H. Ontario, Canada: Institute for Groundwater Research, University of Waterloo.

Hutcheon DE, Arnold JD, ten Hove W, Boyle J III (1996). Disposition, metabolism and toxicity of methyl tertiary-butyl ether, an oxygenate for reformulated gasoline. J. Toxicol. Environ. Hlth. 47(5): 453-464. April 5.

IARC (1998a). IARC Monographs Working Group – Volume 73: Evaluation or Re-evaluation of Some Agents Which Target Specific Organs in Rodent Bioassays. Workshop, October 28, 1998, Lyon, France. Monograph in preparation, summary table available on IARC web site. Lyons, France: IARC, WHO. IARC website address: http://www.IARC.FR

IARC (1998b). Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis. Consensus Report. Final Draft. In: Consensus Document. Proceedings of the IARC Workshop, November 3 - 7, 1997, Lyon, France. January 8. Lyons, France: IARC, WHO.

IARC (1995). Formaldehyde. In: International Agency for Research on Cancer (IARC) monographs on the evaluation of carcinogenic risks to humans: wood dust and formaldehyde. 62: 217-362. Lyon, France: IARC, World Health Organization (WHO).

IARC (1993). International Classification of Rodent Tumours. Part 1 – The Rat. 4. Hematopoietic system. Editor U. Mohr. IARC Scientific Publications No. 122, Lyon, France: IARC, World Health Organization (WHO).

IARC (1987). Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: An Updating of IARC Monographs Volumes 1 to 42, Supplement 7. Lyons, France: IARC, WHO.

Imbriani M, Ghittori S, Pezzagno G (1997). Partition coefficients of methyl tert-butyl ether (MTBE). G. Ital. Med. Lav. Ergon. (Occupational Medicine, Pisa, Italy) 19(3): 63-65. July - September.

IPCS (1997). International Programme on Chemical Safety (IPCS), Environmental Health Criteria (EHC), Methyl Tertiary-Butyl Ether. Task Group Draft. PCS/EHC/97. January. Final expected in December 1998 as EHC Series No. 206 Geneva, Switzerland: United Nations Environmental Programme (UNEP), International Labour Organization, WHO.

Jeffrey D (1997). Physical-chemical properties of MTBE and preferred environmental fate and compartmentalization. Paper ENVR 209. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 397-399.

Jensen HM, Arvin E (1990). Solubility and degradability of the gasoline additive MTBE and gasoline compounds in water. In: Contaminated Soils, 90: 445-448. Netherlands: Kluwer Academic Publishers.

Jo WK, Park KH (1998). Exposure to carbon monoxide, methyl-tertiary butyl ether (MTBE), and benzene levels inside vehicles traveling on an urban area in Korea. J. Expo. Anal. Environ. Epidemiol. 8(2): 159-171.

Johanson G, Nihlen A, Lof A (1995). Toxicokinetics and acute effects of MTBE and ETBE in male volunteers. Toxicol. Lett. (Shannon, Ireland) 82/83: 713-718. December.

Johnson ML (1998). Exposure of humans to MTBE from drinking water. In: Health and Environmental Assessment of MTBE. Report to the Governor and Legislature of the State of California as Sponsored by SB 521. Volume V: Risk assessment, Exposure Assessment, Water Treatment and Cost-Benefit Analysis, Chapter 1. 11 pp. Submitted through the University of California Toxic Substances Research and Teaching Program SB521 MTBE Research Program. November 12. Davis, California. Available at: http://tsrtp.ucdavis.edu/mtberpt/

Johnson WD, Findlay J, Boyne RA (1992). 28-day oral (gavage) toxicity study of methyl tert-butyl ether in rats. Prepared for Amoco. ITT Research Institute Project No. L08100. Chicago, Illinois: ITT Research Institute.

Joseph P (1995). Illness due to methyl tertiary butyl ether. Letter to the Editor. Arch. Environ. Hlth. 50(5): 395-396. Available at: http://www.oxybusters.com/oxybustr.htm

Juliani G, Gandini G, Gabasio S, Bonardi L, Fascetti E, Gremo L (1985). Colelitolisi chimica transcutanea con metil-ter-butil etere (MtBE). La Radiol. Med. 71: 569-574.

Kado NY, Kuzmicky PA, Loarca-Pina G, Mumtaz MM (1998). Genotoxicity testing of methyl tertiary-butyl ether (MTBE) in the Salmonella microsuspension assay and mouse bone marrow micronucleus test. Mutation Res. 412 (2): 131-138. January.

Katoh T, Arashidani K, Kikuchi M, Yoshikawa M, Kodama Y (1993). Effects of methyl tertiary-butyl ether on hepatic lipid peroxidation in mice. Nippon Eiseigaku Zasshi (Japan) 48(4): 873-878. October.

Kerns KD, Pavkov KL, Donofrio DJ, Gralla EJ, Swenberg JA (1983). Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. Cancer Res. 43: 4382-4392.

Killian W (1998). Oxyfuel advertisement offends readers. Letter to the Editor. J. Am. Water Works Assoc. 90(2): 4-4. February.

Kirschner EM (1996). Growth of top 50 chemicals slowed in 1995 from very high 1994 rate. C&EN (Chemical and Engineering News) 74(15): 16-22. April 8.

Klan MJ, Carpenter MJ (1994). A risk-based drinking water concentration for methyl tertiary-butyl ether (MTBE). U.S. EPA. In: Proceedings of the Petroleum Hydrocarbons and Organic Chemicals in Ground Water: Prevention, Detection and Remediation Conference. pp. 107-115. November 2 - 4. Houston, Texas. Dublin, Ohio: National Water Well Association.

Klan MJ, Johnson W, Hatoum NS, Yermakoff JK (1992). 28-day oral (gavage) toxicity study of methyl tert-butyl ether (MTBE) in rats [Abstract No. 382 presented at the 1992 Society of Toxicology Annual Meeting]. The Toxicologist 12(1): 117. February.

Kneiss J (1995). MTBE - the headache of clean air. Environ. Hlth. Perspect. 103(7-8): 666-670. July - August.

Koenigsberg S (1997). MTBE: Wild card in groundwater cleanup. Environ. Protection 8(11): 26-28. November.

Landmeyer JE, Chapelle FH, Bradley PM, Pankow JF, Church CD, Tratnyek PG (1998). Fate of MTBE relative to benzene in a gasoline-contaminated aquifer (1993–98). 37 pp. In: Ground Water Monitoring & Remediation. Accepted April 17. In press.

Landmeyer JE, Pankow JF, Church CD (1997). Occurrence of MTBE and tert-butyl alcohol in a gasoline-contaminated aquifer. Paper ENVR 228. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 413-415.

Lapham WW, Neitzert KM, Moran MM, Zogorski JS (1997). USGS compiles data set for national assessment of VOCs in groundwater. Ground Water Monitoring & Remediation. XVII(4): 147-157. Fall.

Lee LC, Quintana PJE, de Peyster A (1998). Comet assay evaluation of the effect of methyl t-butyl ether (MTBE) on rat lymphocytes [Abstract No. 923 presented at the 1998 Society of Toxicology Annual Meeting]. The Toxicologist 42(1-S): 187. March.

Lee CW, Weisel CP (1998). Determination of methyl tert-butyl ether and tert-butyl alcohol in human urine by high-temperature purge-and-trap gas chromatography-mass spectrometry. J. Analyt. Toxicol. 22(1): 1-5. January/February.

Leuschner U, Hellstern A, Ansell A, Gatzen M, Guldutuna S, Leuschner M (1994). Manual and automatic gallstone dissolution with methyl tert-butyl ether. Digest. Dis. Sci. 39(6): 1302-1308. June.

Life Science Research Roma Toxicology Centre S.P.A. (1989a). Reverse mutation in Salmonella typhimurium, test substance: MtBE. Report No. 216001-M-03489. Rome, Italy: Roma Toxicology Centre S.P.A.

Life Science Research Roma Toxicology Centre S.P.A. (1989b). Gene mutation in Chinese hamster V79 cells, test substance: MtBE. Report No. 216002-M-03589. Rome, Italy: Roma Toxicology Centre S.P.A.

Life Science Research Roma Toxicology Centre S.P.A. (1989c). Unscheduled DNA synthesis (UDS) in primary rat hepatocytes (autoradiographic method), test substance: MtBE. Report No. 216003-M-03689. Rome, Italy: Roma Toxicology Centre S.P.A.

Lin XZ, Chou TC, Lin PW, Chow YL, Li CC, Chen SK (1994). Chemical dissolution of gallstones in Taiwan: An in vitro study. J. Gastroenterol. Hepatol. 9(2): 143-147.

Lince DP, Wilson LR, Carlson GA (1998). Methyl tert-butyl ether (MTBE) contamination in private wells near gasoline stations in upstate New York. Bull. Environ. Contam. Toxicol. 61(4): 484-488.

Lindsey BD, Breen KJ, Daly MH (1997). MTBE in water from fractured-bedrock aquifers, southcentral Pennsylvania. Paper ENVR 210. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 399-400.

Lindstrom SB Pleil JD (1996). Alveolar breath sampling and analysis to exposures to methyl tertiary-butyl ether (MTBE) during motor vehicle refueling. J. Air Waste Manag. Assoc. 46: 676-682. July.

Lington AW, Dodd DE, Ridlon SA, Douglas JF, Kneiss JJ, Andrew LS (1997). Evaluation of 13-week inhalation toxicity study on methyl t-butyl ether (MTBE) in Fischer 344 rats. J. Appl. Toxicol. 17(S1): S37-S44. May.

Little CJ, Dale AD, Whatley JA (1979). Methyl tert-butyl ether: A new chromatographic effluent. J. Chromatogr. 169: 381-385.

Livo KB (1995). Overview of public's perspective of health effects from oxyfuels in Colorado. Presented at the HEI Workshop on Acute Health Effects on Oxygenates and Oxygenated Gasolines. July 27. Chicago, Illinois.

Long G, Meek ME, Savard S (1994). Methyl tertiary-butyl ether (MTBE): Evaluation of risks to health from environmental exposure in Canada. J. Environ. Sci. Hlth., Part C, Environ. Carcinog. Ecotoxicol. Rev. C12(2): 389-395.

Lucier G, Genter MB, Lao YJ, Stopford W, Starr T (1995). Summary of the carcinogenicity assessment of MTBE conducted by the Secretary's Scientific Advisory Board on Toxic Air Pollutants. Report to the North Carolina Department of Environment, Health, and Natural Resources. Environ. Hlth. Perspect. 103(5): 420-422. May.

MacGregor JA, Richter WR, Magaw RI (1993). Uterine changes in female mice following lifetime inhalation of wholly vaporized unleaded gasoline: A possible relationship to liver tumors? Am. Coll. Toxicol. 12: 119-126.

Mackay D, Shiu WY, Ma KC (1993). Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals. V. III. Volatile Organic Chemicals. p. 756. Chelsea, Michigan: Lewis Publishers.

Mackerer CR, Angelosanto FA, Blackburn GR, Schreiner CA (1996). Identification of formaldehyde as the metabolite responsible for the mutagenicity of methyl tertiary-butyl ether in the activated mouse lymphoma assay. Proc. Soc. Exp. Biol. Med. 212(4): 338-341. September.

Mancini ER (1997). Aquatic toxicity data for methyl tertiary-butyl ether (MTBE): Current status, future research. Paper ENVR 245. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 427-429.

Mantel N (1966). Evaluation of survival data on two new rank order statistics arising in its consideration. Cancer Chemother. Rep. 50: 163-170.

MCCHD (1993). Oxygenated Fuel Data Collection: Missoula Physician Screening. Missoula, Montana: Missoula City-County Health Department (MCCHD).

McClurg S (1998). The challenge of MTBE: clean air vs. clean water? Western Water July/August: 4-13.

McConnell R, Taber R (1998). Acute effects of exposure to methyl tert-butyl ether in gasoline. West. J. Med. 169(6): 375. December.

McCoy M Jr, Abernethy J, Johnson T (1995). Anecdotal Health-Related Complaint Data Pertaining to Possible Exposures to MTBE: 1993 and 1994 Follow-up Survey (1984 - 1994). API Publication 4623. Washington D.C.: API.

McGregor DB, Brown A, Cattanach P, Edwards I, McBride D, Caspony WJ (1988). Responses of the LS178y tk^+/tk^- mouse lymphoma cell forward mutation assay. II: 18 coded chemicals. Environ. Mol. Mutagen. 11: 91-118.

McKee RH, Vergnes JS, Galvin JB, Douglas JF, Kneiss JJ, Andrews LS (1997). Assessment of the in vivo mutagenic potential of methyl tertiary-butyl ether. J. Appl. Toxicol. 17(S1): S31-S36. May.

McKinnon RJ, Dyksen JE (1984). Removing organics from groundwater through aeration plus GAC. J. Am. Water Works Assoc. 76: 42-47. May.

Medlin J (1995). MTBE: The headache of clean air. Environ. Hlth. Perspect. 103: 666-670. July - August.

Mehlman MA (1998a). Human health effects from exposure to gasoline containing methyl tertiary butyl ether (MTBE). Eur. J. Oncol. 3(3): 171-189.

Mehlman MA (1998b). Concluding remarks on the hazards of MTBE in gasoline. Eur. J. Oncol. 3(3): 207-208.

Mehlman MA (1998c). Pollution by gasoline containing hazardous methyl tertiary butyl ether (MTBE). [Editorial] Arch. Environ. Hlth. 53(4): 245-246.

Mehlman MA (1998d). Dangerous and cancer-causing properties of products and chemicals in the oil-refining and petrochemical industry: Part XXV, neurotoxic, allergic, and respiratory effects in humans from water and air contaminated by methyl tertiary butyl ether in gasoline. J. Clean Technol., Environ. Toxicol. & Occup. Med. 7(1): 65-87.

Mehlman MA (1996). Dangerous and cancer-causing properties of products and chemicals in the oil-refining and petrochemical industry: Part XXII, health hazards from exposure to gasoline containing methyl tertiary butyl ether, study of New Jersey residents. Toxicol. Ind. Hlth. 12(5): 613-627. September - October.

Mehlman MA (1995). Dangerous and cancer-causing properties of products and chemicals in the oil-refining and petrochemical industry: Part XV, health hazards and health risks from oxygenated automobile fuels (MTBE), lessons not heeded. Int. J. Occup. Med. Toxicol. 4(2): 219-236.

Mennear JH (1997a). Carcinogenicity studies on Methyl tertiary butyl ether (MTBE): Critical review and interpretation. Risk Anal. 17(6): 673-681. December.

Mennear JH (1997b). Methyl tertiary butyl ether (MTBE) carcinogenesis: Hazard identification and safety assessment. Toxicol. Ecotoxicol. News (TEN) 4(5): 139-147.

Mennear JH (1995). MTBE: Not carcinogenic. Letter to the Editor. Environ. Hlth. Perspect. 103(11): 985-986. November.

Merck (1989). The Merck Index: An encyclopedia of Chemicals, Drugs, and Biologicals. 11th ed. Budavari S, O'Neil MJ, Smith A, Heckelman PE eds. Rahway, New Jersey: Merck & Co., Inc.

Miller MJ, Ferdinandi ES, Klan M, Andrews LS, Douglas JF, Kneiss JJ (1997). Pharmacokinetics and disposition of methyl t-butyl ether in Fischer-344 rats. J. Appl. Toxicol. 17(S1): S3-S12. May.

Mohr S, Fiedler N, Weisel C, Kelly-McNeil K (1994). Health effects of MTBE among New Jersey garage workers. Inhalation Toxicol. 6(6): 553-562. November - December.

Moolenaar RL, Hefflin BJ, Ashley DL, Middaugh JP, Etzel RA (1997). Blood benzene concentrations in workers exposed to oxygenated fuel in Fairbanks, Alaska. Int. Arch. Occup. Environ. Hlth. 69(2): 139-143.

Moolenaar RL, Hefflin BJ, Ashley DL, Middaugh JP, Etzel RA (1994). MTBE in human blood after exposure to oxygenated fuel in Fairbanks, Alaska. Arch. Environ. Hlth. 49(5): 402-409. September - October.

Mordechai E, Vojdani A, Magtoto L, Choppa PC, Brautbar N (1997). Induction of apoptosis in individuals exposed to methyl tertiary butyl ether (MTBE) [Abstract No. 1727 presented at the 1997 Society of Toxicology Annual Meeting]. The Toxicologist 36(1, Pt. 2): 340. March.

Mormile MR, Liu S, Suflita JM (1994). Anaerobic biodegradation of gasoline oxygenates: Extrapolation of information to multiple sites and redox conditions. Environ. Sci. Technol. 28(9): 1727-1732. September.

MORS (1995). Justification for Decreasing the ORS Guideline for MTBE in Drinking Water from 0.7 mg/L to 0.07 mg/L. Office of Research and Standards (ORS), Department of Environmental Protection, the Commonwealth of Massachusetts. Boston, Massachusetts: MORS.

Moser GJ, Wolf DC, Sar M, Gaido KW, Janszen D, Goldsworthy TL (1998). Methyl tertiary butyl ether-induced endocrine alterations in mice are not mediated through the estrogen receptor. Toxicol. Sci. (formerly Fund. Appl. Toxicol.) 41(1): 77-87. January.

Moser GJ, Wong BA, Wolf DC, Fransson-Steen RL, Goldsworthy TL (1996a). Methyl tertiary butyl ether lacks tumor-promoting activity in N-nitrosodiethylamine-initiated B6C3F1 female mouse liver. Carcinogenesis 17(12): 2753-2761. December.

Moser GJ, Wong BA, Wolf DC, Moss OR, Goldsworthy TL (1996b). Comparative short-term effects of methyl tertiary-butyl ether and unleaded gasoline vapor in female B6C3F1 mice. Fundam. Appl. Toxicol. 31(2): 173-183. June.

Neeper-Bradley TL (1991). Two-generation reproduction study of inhaled methyl tert-butyl ether (MTBE) in CD Sprague-Dawley rats. Final Report. August 13. Bushy Run Research Center Project ID 53-594. Submitted to the U.S. EPA with cover letter dated August 16, 1991. EPA/OTS #40-9113465. Export, Pennsylvania: Bushy Run Research Center.

Nelson BK, Brightwell WS, Khan A, Burg JR, Goa PT (1989a). Lack of selective developmental toxicity of three Butanol isomers administered by inhalation to rats. Fundam. Appl. Toxicol. 12(3): 469-79.

Nelson BK, Brightwell WS, Khan A, Kreig EFJ, Massari VJ (1989b). Behavioral teratology investigation of tertiary-butanol administered by inhalation to rats. Teratology 39(5): 504.

Nihlen A, Lof A, Johanson G (1998a). Experimental exposure to methyl tertiary-butyl ether I. Toxicokinetics in humans. Toxicol. Appl. Pharmacol. 148(2): 274-280. February.

Nihlen A, Walinder R, Lof A., Johanson G (1998b). Experimental exposure to methyl tertiary-butyl ether II. Acute effects in humans. Toxicol. Appl. Pharmacol. 148(2): 281-287. February.

Nihlen A, Lof A, Johanson G (1997). Liquid/air partition coefficients of methyl and ethyl t-butyl ethers, t-amyl methyl ether, and t-butyl alcohol. J. Clean Technol., Environ. Toxicol., Occup. Med. 6(2): 205-213.

Nihlen A, Lof A, Johanson G (1995). Liquid/air partition coefficients of methyl and ethyl t-butyl ethers, t-amyl methyl ether, and t-butyl alcohol. J. Exposure Analyt. Environ. Epidemiol. 5(4): 573-592.

Nihlen A, Walinder R, Lof A, Johanson G (1994). Toxicokinetics and irritative effects of MTBE in man. Presented at the International Society for Environmental Epidemiology meeting. Durham, North Carolina.

NJDWQI (1994). Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water, Appendix A: Health-Based Maximum Contaminant Level Support Documents and Addenda. September 26. Newark, New Jersey: New Jersey Drinking Water Quality Institute (NJDWQI).

NRC (1996). Toxicological and Performance Aspects of Oxygenated Motor Vehicle Fuels. 160 pp. Committee on Toxicological and Performance Aspects of Oxygenated Motor Vehicle Fuels, Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council (NRC), National Academy of Sciences (NAS). Washington, D.C.: National Academy Press.

NSTC (1997). Interagency Assessment of Oxygenated Fuels. June. National Science and Technology Council (NSTC), Committee on Environment and Natural Resources (CENR) and Interagency Oxygenated Fuels Assessment Steering Committee. White House Office of Science and Technology Policy (OSTP) through the CENR of the Executive Office of the President. Washington, D.C.: NSTC.
Available at: http://www.whitehouse.gov/WH/EOP/OSTP/html/OSTP_Home.html

NSTC (1996). Interagency Assessment of Potential Health Risks Associated with Oxygenated Gasoline. February. OSTP through the President's NSTC, CENR and Interagency Oxygenated Fuels Assessment Steering Committee. Washington, D.C.: NSTC.

NTP (1998a). Summary of RG1, RG2 and NTP Board Subcommittee Recommendations for the Agents, Substances, Mixtures or Exposure Circumstances Reviewed in 1998 for Listing in or Delisting from the Report on Carcinogens, 9th Edition. December 4. National Toxicology Program (NTP) website: http://ntp-server.niehs.nih.gov/NewHomeRoc/

NTP (1998b). National Toxicology Program January 1998 Update. National Toxicology Program (NTP), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH). Research Triangle Park, North Carolina: NTP. January.

NTP (1997). Toxicology and carcinogenesis studies of isobutene (CAS No. 115-11-7) in Fischer 344/N rats and B6C3F1 mice (inhalation studies). Board Draft. National Toxicology Program Technical Report Series No. 487, NIH Publication No. 97-3977. NTP, NIEHS, NIH. Research Triangle Park, North Carolina: NTP.

NTP (1995). Toxicology and carcinogenesis studies of t-butyl alcohol (CAS No. 76-65-0) in Fischer 344/N rats and B6C3F1 mice (drinking water studies). National Toxicology Program Technical Report Series No. 436, NIH Publication No. 94-3167. NTP, NIEHS, NIH. Research Triangle Park, North Carolina: NTP.

Nyska A, Leininger JR, Maronpot RR, Haseman JK, Hailey JR (1998). Effect of individual versus group caging on the incidence of pituitary and Leydig cell tumors in F344 rats: proposed mechanism. Med. Hypoth. 50: 525-529.

O'Brien AK, Reiser RG, Gylling H (1997). Spatial Variability of Volatile Organic Compounds in Streams on Long Island, New York, and in New Jersey. USGS Fact Sheet FS-194-97. 6 pp. West Trenton, New Jersey: Department of Interior, USGS, NAWQA.

OEHHA (1998a). Evidence on the Carcinogenicity of Methyl Tertiary Butyl Ether (MTBE). Public Review Draft. September. Berkeley, California: Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency.

OEHHA (1998b). Evidence on the Developmental and Reproductive Toxicity of Methyl Tertiary Butyl Ether (MTBE). Public Review Draft. September. Berkeley, California: Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency.

OEHHA (1996). Air Toxics Hot Spots Program Risk Assessment Guidelines. Part IV. Exposure Assessment and Stochastic Analysis. Public Review Draft. December. Berkeley, California: Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency.

OEHHA (1991). MTBE Interim Action Level. February 19. Memorandum from the Pesticide and Environmental Toxicology Section (PETS), OEHHA to the Office of Drinking Water, DHS. Berkeley, California: PETS, OEHHA, DHS.

Okahara N, de Peyster A, McPherson SE, MacGregor JA (1998). Effect of MTBE on estrogen-sensitive tissues of immature female CD-1 mice [Abstract No. 862 presented at the 1998 Society of Toxicology Annual Meeting]. The Toxicologist 42(1-S): 174-175. March.

Pankow JF, Thomson NR, Johnson RL, Baehr AL, Zogorski JS (1997). The urban atmosphere as a non-point source for the transport of MTBE and other VOCs to shallow groundwater. Environ. Sci. Technol. 31(10): 2821-2828.

Patton A, Clementsen KL, Farahnak S, Drewry M, Ammon M, Arrieta D, Bevan AL, Charles T, Daniels D, Davis M, DiGiovanni D, Fortes F, Garrison R, Gebhart G, Jackson D, Kaiser S, Ray J, Rogow M, Rollins B, Smith DS, Tikannen M, Wilson D, Wolfe R (1999a). Report of the State Water Resources Control Board's Advisory Panel on Fueling and Refueling Practices at California Marinas. January. 34 pp. Sacramento, California: SWRCB.

Patton A, Farahnak S, Drewry M, Anderson L, Arrieta D, Bravinder JL, Camille D, Gilson D, Hamilton C, Johnson B, Jones J, Sarrantis M, Smith J, Steck C, Tulloch C, Welge S, Westbrook P, White J, Winsor C, Young T, Zedrick D (1999b). Report of the State Water Resources Control Board's Advisory Panel on Leak History of New and Upgraded Underground Storage Tank Systems. January. 8 pp. Sacramento, California: SWRCB.

Poet TS, Borghoff SJ (1998). Metabolism of methyl t-butyl ether in human liver microsomes [Abstract No. 464 presented at the 1998 Society of Toxicology Annual Meeting]. The Toxicologist 42(1-S): 94. March.

Poet TS, Borghoff SJ (1997a). In vitro uptake of methyl tert-butyl ether (MTBE) in male rat kidney: Use of a two-compartment model to describe protein interactions. Toxicol. Appl. Pharmacol. 145(2): 340-348. August.

Poet TS, Borghoff SJ (1997b). Metabolism of methyl t-butyl ether in methyl tert-butyl ether (MTBE) in F-344 rats liver microsomes [Abstract No. 1717 presented at the 1997 Society of Toxicology Annual Meeting]. The Toxicologist 36(1, pt. 2): 338. March.

Poet TS, Lalentine JL, Borghoff SJ (1997c). Pharmacokinetics of tertiary butyl alcohol in male and female Fischer 344 rats. Toxicol. Lett. 92: 179-186.

Poet TS, Murphy JE, Borghoff SJ (1996). In vitro uptake of MTBE in male and female rat kidney homogenate: Solubility and protein interactions [Abstract No. 1563 presented at the 1996 Society of Toxicology Annual Meeting]. The Toxicologist 30(1, pt. 2): 305. March.

Ponchon T, Baroud J, Pujol B, Valette PJ, Perrot D (1988). Renal failure during dissolution of gallstone by methyl tert-butyl ether. Letter to the Editor. Lancet 2: 276-277. July 30.

Poore M, Chang B, Niyati F, Madden S (1997). Sampling and analysis of methyl t-butyl ether (MTBE) in ambient air at selected locations in California. Paper ENVR 215. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 407.

Post G (1994). Methyl Tertiary Butyl Ether, Health-Based Maximum Contaminant Level Support Document. July. Division of Science and Research, New Jersey Department of Environmental Protection (NJDEP). Trenton, New Jersey: NJDEP.

Prah JD, Goldstein GM, Devlin R, Otto D, Ashley D, House D, Cohen KL, Gerrity T (1994). Sensory, symptomatic, inflammatory, and ocular responses to and the metabolism of MTBE in a controlled human exposure experiment. Inhalation Toxicol. 6(6): 521-538. Erratum. (1995) Inhalation Toxicol. 7(4): 575.

Prescott-Mathews JS, Wolf DC, Wong BA, Borghoff SJ (1997a). Methyl tert-butyl ether causes α_{2u}-globulin nephropathy and enhanced renal cell proliferation in male F-344 rats. Toxicol. Appl. Pharmacol. 143(2): 301-314. April.

Prescott-Mathews JS, Garrett MJ, Borghoff SJ (1997b). Chemical binding to α_{2u}-globulin following gavage dosing of ^{14}C - methyl tert-Butyl Ether (MTBE) in F-344 rats [Abstract No. 1726 presented at the 1997 Society of Toxicology Annual Meeting]. The Toxicologist 36(1, pt. 2): 340. March.

Prescott-Mathews JS, Wolf DC, Wong BA, Borghoff SJ (1996). MTBE-induced protein droplet nephropathy and cell proliferation in male F-344 rats [Abstract No. 1559 presented at the 1996 Society of Toxicology Annual Meeting]. The Toxicologist 30(1, pt. 2): 304. March.

Raabe GK (1993). API Health Complaint Survey. EPA/600/R-95/134. In: Proceedings of the Conference on MTBE and Other Oxygenates: A Research Update. July 26-28. Falls Church, Virginia.

Rao HV, Ginsberg GL (1997). A physiologically-based pharmacokinetic model assessment of methyl t-butyl ether in groundwater for a bathing and showering determination. Risk Anal. 17(5): 583-598. October.

Rathbun RE (1998). Transport, Behavior, and Fate of Volatile Organic Compounds in Streams. U.S. Geological Survey (USGS) Professional Paper 1589. 151 pp. Washington, D.C.: U.S. Department of the Interior, USGS.

Reese E, Kimbrough RD (1993). Acute toxicity of gasoline and some additives. Environ. Hlth. Perspect. 101(S6): 115-131.

Reisch MS (1994). Top 50 chemicals production rose modestly in the U.S. C&EN 72: 12-15. April 8.

Renner R (1999). Maine seeks to drop MTBE from its clean fuels program. Environ. Sci. Technol. 33(1): 9A-10A. January 1.

Reynolds G (1998). Oxyfuel advertisement offends readers. Letter to the Editor. J. Am. Water Works Assoc. 90(2): 4-4.

Robbins GA, Wang S, Stuart JD (1993). Using the static headspace method to determine Henry's Law Constants. Analyt. Chemistry 65(21): 3113-3118.

Robinson M, Bruner RH, Olson GR (1990). Fourteen- and ninety-day oral toxicity studies of methyl tertiary-butyl ether (MTBE) in Sprague-Dawley rats. J. Am. Coll. Toxicol. 9(5): 525-540.

Rousch JM, Sommerfeld MR (1998). Liquid-gas partitioning of the gasoline oxygenate methyl tert-butyl ether (MTBE) under laboratory conditions and its effect on growth of selected algae. Arch. Environ. Contam. Toxicol. 34(1): 6-11. January.

Rowe BL, Landrigan SJ, Lopes TJ (1997). Summary of published aquatic toxicity information and water-quality criteria for selected volatile organic compounds. USGS Open-File Report. OFR 97-563. 60 pp. USGS.

RTECS (1997). Registry of Toxic Effects of Chemical Substances (RTECS): Ether, Tert-Butyl Methyl. Last revision date: 1997. National Institute for Occupational Safety and Health (NIOSH). Cincinnati, Ohio: NIOSH.

Rudo KM (1995). Methyl tertiary butyl ether (MTBE) - evaluation of MTBE carcinogenicity studies. Toxicol. Ind. Hlth. 11(2): 167-173. March - April.

Saarinen L, Hakkola M, Pekari K, Lappapainen K, Aitio A (1998). Exposure of gasoline road-tanker drivers to methyl tert-butyl ether and methyl tert-amyl ether. Int. Arch. Occup. Environ. Hlth. 71(2): 143-147. March.

Savolainen H, Pfaffli P, Elovaara E (1985). Biochemical effects of methyl tertiary-butyl ether (MTBE) in extended vapor exposure in rats. Arch. Toxicol. 57(4): 285-288.

SCDEM (1997). Groungwater Monitoring Report: Project Status, Quarterly Monitoring, and NPDES Report for July to September 1997. October. Fairfield, California: Solano County Department of Environmental Management (SCDEM).

Scheible MH (1997). California's cleaner-burning gasoline regulations. Paper ENVR 96. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 368-369.

Scholl HR, Seelig B, Thomas PE, Iba MM (1996). Methyl t-butyl ether (MTBE) induced central nervous system (CNS) depression: effects of metabolism of the compound [Abstract No. 122 presented at the 1996 Society of Toxicology Annual Meeting]. The Toxicologist 30(1, Part 2): 24. March.

Schirmer M, Beker JF (1998). A study of long-term MTBE attenuation in the Borden aquifer, Ontario, Canada. Ground Water Monitoring and Remediation, Spring 1998: 113-122.

Schremp G, Glaviano T, Nelson Y, Stoner S, Gopal J, Ganeriwal R, Tang C Bemis G, Nix HD (1998). Supply and Cost of Alternatives to MTBE in Gasoline. October. P300-98-013. Sacramento, California: California Energy Commission, Energy Information and Analysis Division, Fuel Resources Office.

Sellakumar AR., Snyder CA, Solomon JJ, Albert RE (1985). Carcinogenicity of formaldehyde and hydrogen chloride in rats. Toxicol. Appl. Pharmacol. 81: 401-406.

Sernau RC (1989). Mutagenicity test on methyl tertiary butyl ether in Drosophila melanogaster sex-linked recessive lethal test. Final Report. HLA study no. 10484-0-461. Fiche # OYSO528039. Submitted to the U.S. Environmental Protection Agency with cover letter dated April 14, 1989. EPA/OTS DOC#40-8913430. Kensington, Maryland: Hazelton Laboratories America, Inc.

SFRWQCB (1998). Compilation of MTBE Contamination in Groundwater from 948 LUFT Sites in the Nine San Francisco Bay Area Counties. July 13. Mandated to be updated every three months. Leaking Underground Fuel Tank Program, San Francisco Regional Water Quality Control Board (SFRWQCB). Oakland, California: SFRWQCB. Also available in KTVU, San Francisco, web site at: http://bayinsider.com/ktvu/newsroom/mtbe/

Shaffer KL, Uchrin CG (1997). Uptake of methyl tertiary butyl ether (MTBE) by groundwater solids. Bull. Environ. Contam. Toxicol. 59(5): 744-749. November.

Shen YF, Yoo LY, Fitzsimmons SR, Yamamoto MK (1997). Threshold odor concentrations of MTBE and other fuel oxygenates. Paper ENVR 216. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 407-409.

Siljeholm J (1997). A hazard ranking of organic contaminants in refinery effluents. Toxicol. Ind. Hlth. 13(4): 527-551. July - August.

Sittig (1994). T-Butyl Methyl Ether. In: World-wide Limits for Toxic and Hazardous Chemicals in Air, Water and Soil. p. 135. Park Ridge, New Jersey: Noyes Publications.

Sjoberg KR (1998). California's Drinking Water: State and Local Agencies Need to Provide Leadership to Address Contamination of Groundwater by Gasoline Components and Additives. December. Report Number 98112. Sacramento, California: California State Auditor, Bureau of State Audits. Available at: http://www.bsa.ca.gov/bsa/

Smith SL, Duffy LK (1995). Odor and health complaints with Alaska gasolines. Chemical Hlth. Safety 32(3): 2-38.

Smith AE, Kemp PA (1998). Maximum Contaminant Level for Methyl Tertiary Butyl Ether (MTBE). Technical Support Document. February 1. Environmental Toxicology Program, Bureau of Health. Augusta, Maine: Maine Department of Human Services.

Soffritti M, Maltoni C, Maffei F, Biagi R (1989). Formaldehyde: an experimental multipotential carcinogen. Toxicol. Ind. Hlth. 5: 699-730.

Sonawane B (1994). Assessment of potential developmental toxicity risk of methyl tertiary butyl ether (MTBE). Teratology 49: 388A. May.

Spitzer HL (1997). An analysis of the health benefits associated with the use of MTBE reformulated gasoline and oxygenated fuels in reducing atmosphere concentrations of selected volatile organic compounds. Risk Anal. 17(6): 683-691. December.

Squillace PJ, Pankow JF, Korte NE, Zogorski JS (1998). Environmental behavior and fate of methyl tert-butyl ether (MTBE). USGS Fact Sheet FS-203-96. Revised February 1998. 6 pp. Rapid City, South Dakota: Department of Interior, USGS, NAWQA.

Squillace PJ, Pankow JF, Korte NE, Zogorski JS (1997a). Review of the environmental behavior and fate of methyl tert-butyl ether (MTBE). J. Environ. Toxicol. Chemistry 16(9): 1836-1844. September.

Squillace PJ, Zorgorski JS, Wilber WG, Price CV (1997b). Preliminary assessment of the occurrence and possible sources of MTBE in groundwater in the United States, 1993 - 1994. Paper ENVR 99. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 372-374.

Squillace PJ, Zorgorski JS, Wilber WG, Price CV (1996). Preliminary assessment of the occurrence and possible sources of MTBE in groundwater in the United States, 1993 - 1994. Environ. Sci. Technol. 30(5): 1721-1730.

Squillace PJ, Pope DA, Price CV (1995). Occurrence of the Gasoline Additive MTBE in Shallow Groundwater in Urban and Agricultural Areas. USGS Fact Sheet FS-114-95. 4 pp. Denver, Colorado: Department of Interior, USGS, NAWQA.

Stackelberg PE, O'Brien AK, Terracciano SA (1997). Occurrence of MTBE in surface and groundwater, Long Island, New York, and New Jersey. Paper ENVR 208. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 394-397.

Standeven AM, Blazer T, Goldsworthy TL (1994). Investigation of antiestrogenic properties of unleaded gasoline in female mice. Toxicol. Appl. Pharmacol. 127: 233-240.

Steffan RJ, McClay K, Vainberg S, Condee CW, Zhang D (1997). Biodegradation of the gasoline oxygenates methyl tert-butyl ether (MTBE), ethyl tert butyl ether (ETBE), and tert-amyl methyl ether (TAME) by propane-oxidizing bacteria. Appl. Environ. Microbiol. 63(11): 4216-4222. November.

Stelljes ME (1997). Issues associated with the toxicological data on MTBE Paper ENVR 212. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 401-403.

Stern BR, Kneiss JJ (1997). Methyl tertiary-butyl ether (MTBE): Use as an oxygenate in fuels. J. Appl. Toxicol. 17(S1): S1-S2. May.

Stern BR, Tardiff RG (1997). Risk characterization of methyl tertiary butyl ether (MTBE) in tap water. Risk Anal. 17(6): 727-743.

Stoneybrook Laboratories Inc. (1993). Activated mouse lymphoma (L5178Y/tk$^+$/tk$^-$) mutagenicity assay supplemented with formaldehyde dehyrogenase for methyl tertiary butyl ether. Status Report 65579. Princeton, New Jersey: Stoneybrook Laboratories Inc.

Stubblefield WA, Burnett SL, Hockett JR, Naddy R, Mancini ER (1997). Evaluation of the acute and chronic aquatic toxicity of methyl tertiary-butyl ether (MTBE). Paper ENVR 246. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 429-430.

Swenberg JA, Dietrich DR (1991). Immunohistochemical localization of α_{2u}-globulin in kidneys of treated and control rats of a 13-week vapor inhalation study undertaken with methyl tertiary butyl ether (MTBE). Report to John Kneiss, Manager, MTBE Task Force. July 26, 1991. Chapel Hill, North Carolina: University of North Carolina.

Tardiff RG, Stern BR (1997). Estimating the risks and safety of methyl tertiary butyl ether (MTBE) and tertiary butyl alcohol (TBA) in tap water for exposures of varying duration. Paper ENVR 247. In: Proceedings of the 213th American Chemical Society National Meeting, Division of Environmental Chemistry, Environmental Fate and Effects of Gasoline Oxygenates. April 13 - 17. San Francisco, California. 37(1): 430-432.

Terracciano SA, O'Brien AK (1997). Occurrence of volatile organic compounds in streams on Long Island, New York, and New Jersey. USGS Fact Sheet. FS 063-97. 4 pp. Washington, D.C.: USGS.

Thompson CB (1995). Apoptosis in the pathogenesis and treatment of disease. Science 267: 1456-1462.

Til HP, Woutersen RA,. Feron VJ, Hollanders VMH, Falke HE (1989). Two-year drinking-water study for formaldehyde in rats. Food Chem. Toxicol. 27: 77-87.

Tepper JS, Jackson MC, McGee JK, Costa DL, Graham JA (1994). Estimation of respiratory irritancy from inhaled MTBE in mice. Inhalation Toxicol. 6(6): 563-569.

Turini A, Amato G, Longo V, Gervasi PG (1998). Oxidation of methyl- and ethyl-tertiary-butyl ethers in rat liver microsomes: Role of the cytochrome P_{450} isoforms. Arch. Toxicol. 72(4): 207-214. March.

Tyl RW, Neeper-Bradley TL (1989). Developmental toxicity study of inhaled methyl tertiary butyl ether (MTBE) in CD-1 mice. Final Report. July 20. Bushy Run Research Center Report No. 51-266. Submitted to the U.S. EPA with cover letter dated July 26, 1989. TSCATS/403186. EPA/OTS #40-8913432. No. FYI-OTS-0889-0689. Export, Pennsylvania: Bushy Run Research Center.

Tyl RW (1989). Developmental toxicity study of inhaled methyl tertiary butyl ether (MTBE) in New Zealand white rabbits. Final Report. May 12. Bushy Run Research Center Report No. 51-268. Submitted to the U.S. EPA with cover letter dated July 12, 1989. EPA/OTS #40-8913426. No. FYI-OTS-0889-0689. Export, Pennsylvania: Bushy Run Research Center.

UC (1998). Health and Environmental Assessment of MTBE. Report to the Governor and Legislature of the State of California as Sponsored by SB 521. Five Volumes. 874 pp. Submitted through the University of California (UC) Toxic Substances Research and Teaching Program SB521 MTBE Research Program. November 12. Davis, California: University of California. Available at: http://tsrtp.ucdavis.edu/mtberpt/

U.S. EPA (1998a). Press Release: EPA Announces Blue-Ribbon Panel to Review Use of MTBE and Other Oxygenates in Gasoline. November 30 5 pp. EPA/R-159. U.S. Environmental Protection Agency (U.S. EPA). Washington, D.C.: U.S. EPA.

U.S. EPA (1998b). Research Strategy for Oxygenates in Water. External Review Draft. April 58 pp. EPA/600/R-98/048. National Center for Environmental Assessment, Office of Research and Development, U.S. EPA. April. Washington, D.C.: U.S. EPA.

U.S. EPA (1998c). 63 FR 10274. 40 CFR Parts 141 and 142, Announcement of the Drinking Water Contaminant Candidate List; Notice. U.S. Environmental Protection Agency. Federal Register 63(40): 10274-10287. Monday, March 2. Washington, D.C.: U.S. EPA.

U.S. EPA (1997a). Drinking Water Advisory: Consumer Acceptability Advice and Health Effects Analysis on Methyl Tertiary-Butyl Ether (MtBE). December. Fact Sheet 4 pp. and Advisory 42 pp. EPA-822-F-97-009. ODW 4304. Health and Ecological Criteria Division, Office of Science and Technology, Office of Water, U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA. Available at: http://www.epa.gov/oust/mtbe/index.htm

U.S. EPA (1997b). 62 FR 52193 40 CFR Parts 141 and 142, Announcement of the Draft Drinking Water Contaminant Candidate List; Notice. U.S. Environmental Protection Agency. Federal Register 62(128): 52193-52219. Monday, October 6. Washington, D.C.: U.S. EPA.

U.S. EPA (1997c). Integrated Risk Information System (IRIS): Methyl Tertiary-Butyl Ether (MTBE). Last revised on September 1, 1993 for Reference Concentration (RfC) assessment. U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

U.S. EPA (1997d). 40 CFR Parts 141 and 142, Drinking Water Monitoring Requirements for Certain Chemical Contaminants - Chemical Monitoring Reform (CMR) and Permanent Monitoring Relief (PMR); Proposed Rule. U.S. Environmental Protection Agency. Federal Register 62(128): 36100-36136. Thursday, July 3. Washington, D.C.: U.S. EPA.

U.S. EPA (1996a). Methyl-t-Butyl Ether (MTBE) Drinking Water Health Advisory (draft). December. Health and Ecological Criteria Division, Office of Science and Technology, Office of Water, U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

U.S. EPA (1996b). 40 CFR Part 131, National Toxics Rule: Remand of Water Quality Criteria for Dioxin and Pentachlorophenol to EPA for Response to Comments -- Response to Comments from American Forest and Paper Association on Two of the Exposure Assumptions Used by EPA In Developing the Human Health Water Quality Criteria for Dioxin and Pentachlorophenol. U.S. Environmental Protection Agency. Federal Register 61(239): 65183-65185. Wednesday, December 11. Washington, D.C.: U.S. EPA.

U.S. EPA (1996c). Benchmark Dose Technical Guidance Document. August 6. External Review Draft. EPA/600/P-96/002A. Risk Assessment Forum, Office of Health and Environmental Assessment, U.S. Environmental Protection Agency. Washington, DC.: U.S. EPA.

U.S. EPA (1996d). Fact Sheet on MTBE in Water. June. Office of Water, U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

U.S. EPA (1996e). Questions and Answers Fact Sheet on MTBE in Water. June. Office of Water, U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

U.S. EPA (1996f). 40 CFR Part 131, Proposed Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency. Federal Register 61(79): 17959-18011. Wednesday, April 23. Washington, D.C.: U.S. EPA.

U.S. EPA (1995a). Toxics Release Inventory. An online database maintained by the U.S. EPA and accessible via TOXLINE. 1993 data accessed June 1995. Office of Toxic Substances Control, U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

U.S. EPA (1995b). MTBE in Water. Draft. Draft by Evelyn Washington. August 1. Office of Ground Water and Drinking Water, U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

U.S. EPA (1995c). Summary of cancer risk derivations for MTBE, a screening evaluation. Appendix A of the NSTC 1996 report. November 29. By J. Jinot. Quantitative Risk Methods Group, National Center for Environmental Assessment, U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

U.S. EPA (1994a). Health Risk Perspectives on Fuel Oxygenates. EPA 600/R-94/217. December. Office of Research and Development (ORD), U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

U.S. EPA (1994b). Estimates of MTBE Exposures Related to Reformulated Gasoline. December 8. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, U.S. Environmental Protection Agency. Research Triangle Park, North Carolina: U.S. EPA.

U.S. EPA (1994c). Summary of Cancer Risk Derivatives for MTBE, A Screening Evaluation for Internal Consideration Related to Gasoline Oxygenates. December 2. Cancer Assessment Statistics and Epidemiology Branch, Office of Health and Environmental Assessment, U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

U.S. EPA (1994d). Reproductive and Developmental Effects from Gasoline Vapors, A Screening Evaluation for Internal Consideration Related to Gasoline Oxygenates. November 7. Reproductive and Developmental Toxicology Branch, Office of Health and Environmental Assessment, U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

U.S. EPA (1993). Assessment of Potential Health Risks of Gasoline Oxygenated with Methyl Tertiary-Butyl Ether (MtBE). EPA/600/R-93/206. NTIS PB91-187583/XAB November. Office of Research and Development, U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

U.S. EPA (1992a). 40 CFR Parts 141 and 142, National Primary Drinking Water Regulations (NPDWR); Synthetic Organic Chemicals and Inorganic Chemicals, Final Rule. U.S. Environmental Protection Agency. Federal Register 57(138): 31776-31849. Friday, July 17. Washington, D.C.: U.S. EPA.

U.S. EPA (1992b). Draft Report: A Cross-Species Scaling Factor for Carcinogen Risk Assessment Based on Equivalence of mg/kg 3/4/Day. U.S. Environmental Protection Agency. Federal Register 57(109): 24152-24173. June 5. Washington, D.C.: U.S. EPA.

U.S. EPA (1992c). Methyl t-Butyl Ether (MtBE) Drinking Water Health Advisory. January. Health and Ecological Criteria Division, Office of Science and Technology, Office of Water, U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

U.S. EPA (1991). α_{2u}-globulin association with chemically induced renal toxicity and neoplasia in the male rat. EPA/625/3-91/019F. Risk Assessment Forum, U.S. Environmental Protection Agency. Washington, D.C.: U.S. EPA.

U.S. EPA (1990). 40 CFR Parts 141, 142 and 143, National Primary and Secondary Drinking Water Regulations; Synthetic Organic Chemicals and Inorganic Chemicals, Proposed Rule. U.S. Environmental Protection Agency. Federal Register 55(143): 30370-30448. Wednesday, July 25. Washington, D.C.: U.S. EPA.

U.S. EPA (1987a). Technical Support Document - MtBE. Prepared for Test Rules Development Branch, Existing Chemicals Assessment Division, U.S. Environmental Protection Agency. OTS Publication SRC RT-86-394. Washington, D.C.: U.S. EPA.

U.S. EPA (1987b). Reference Dose (RfD): Description and use in health risk assessments. IRIS, Appendix A.. Integrated risk information system documentation, vol. 1. U.S. Environmental Protection Agency. EPA/600/8-66/032a. Washington, D.C.: U.S. EPA.

USGS (1996). Occurrence of the gasoline additive MTBE in shallow ground water in urban and agricultural areas. October. United States Geological Survey (USGS) Fact Sheet 114.95. Washington, D.C.: USGS. Available at: http://water.wr.usgs.gov/mtbe

Vainiotalo S, Peltonen Y, Ruonakangas A, Pfaffli P (1999). Customer exposure to MTBE, TAME, C6 alkyl methyl ethers, and benzene during gasoline refueling. Environ. Hlth. Perspect. 107 (2): 133-140. February.

Vainiotalo S, Pekari K, Aitio A (1998). Exposure to methyl tert-butyl ether and tert-amyl methyl ether from gasoline during tank lorry loading and its measurement using biological monitoring. Int. Arch. Occup. Environ. Hlth. 71: 391-396.

Vergnes JS, Chun JS (1994). Methyl tertiary butyl ether: In vivo in vitro hepatocyte unscheduled DNA synthesis assay in mice. Bushy Run Research Center Laboratory project ID 93N1316. Submitted to the U.S. EPA with cover letter dated June 13, 1994 with draft submitted dated October 15, 1993. EPA/OTS DOC#86940000975 and #86940000009. Export, Pennsylvania: Bushy Run Research Center.

Vergnes JS, Kintigh WJ (1993). Methyl tertiary butyl ether: Bone marrow micronucleus test in mice. Bushy Run Research Center Laboratory project ID 93N1244. Submitted to the U.S. EPA with cover letter dated November 15, 1993. EPA/OTS #86940000031. Export, Pennsylvania: Bushy Run Research Center.

Vergnes JS, Morabit ER (1989). Methyl tertiary butyl ether repeated exposure vapor inhalation study in rats: In vivo cytogenetic evaluation. Bushy Run Research Center Project report 51-635. Fiche # OTSO528040 Doc # 40-8913431. Export, Pennsylvania: Bushy Run Research Center.

Vojdani A, Brautbar N (1998). Contaminated drinking water with MTBE and gasoline: Immunological and cellular effects. Eur. J. Oncol. 3(3): 191-199.

Vojdani A, Mordechai E, Brautbar N (1997a). Abnormal apoptosis and cell cycle progression in humans exposed to methyl tertiary butyl ether and benzene contaminating water. Human Exp. Toxicol. 16(9): 485-494. September.

Vojdani A, Namatalla G, Brautbar N (1997b). Methyl tertiary butyl ether antibodies among gasoline service station attendants. Annals N. Y. Acad. Sci. 837: 96-104. December 26.

Von Burg R (1992). Toxicological update: Methyl tertiary butyl ether (MTBE). J. Appl. Toxicol. 12(1): 73-74.

Ward Jr. JB, Au WW, Whorton EB, et al. (1994). Genetic toxicity of methyl-tertiary butyl ether. Division of Environmental Toxicology, Department of Preventive Medicine and Community Health. Galveston, Texas: University of Texas Medical Branch.

Ward Jr. JB, Daiker DH, Hastings DA, Ammenheuser MM, Legator MS (1995). Assessment of the mutagenicity of methyl-tertiary butyl ether at the HPRT gene in CD-1 mice [Abstract No. 417 presented at the 1995 Society of Toxicology Annual Meeting]. The Toxicologist 15: 79.

WDOH (1995). Methyl Tert-Butyl Ether (MTBE). February. Wisconsin Division of Health (WDOH), Department of Natural Resources. Madison, Wisconsin: WDOH.

Weil CS (1970). Significance of organ-weight changes in food safety evaluation. In: Metabolic Aspects of Food Safety. Roe FJ eds. pp. 419-454. New York, New York: Academic Press.

White MC, Johnson CA, Ashley DL, Buchta TM, Pelletier DJ (1995). Exposure to methyl tertiary-butyl ether from oxygenated gasoline in Stamford, Connecticut. Arch. Environ. Hlth. 50(3): 183-189. May - June.

Wibowo AAE (1994). Methyl t-Butyl Ether: Health Based Recommended Occupational Exposure Limit. Dutch Expert Committee on Occupational Standards: Werkgroep van Deskundigen ter Vaststeling van MAL-waarden. 75 pp. Arbete. Och. Halsa, No. 22. 24 pp. Gezondheidsrad, Postbus 90517, 2509 Lm Den Haag, Netherlands.

Wiley K (1998). Clean air versus clean water: Does California need MTBE? California Senate position paper on MTBE. February. 15 pp. Sacramento, California: Senate Office of Research. Available at: http://www.sen.ca.gov/ftp/sen/sor/environ/98mtbe.htm

Woutersen RA, van Garderen-Hoetmer A, Bruijntjes JP, Swart A, Feron VJ (1989). Nasal tumors in rats after severe injury to the nasal mucosa and prolonged exposure to 10 ppm formaldehyde. J. Appl. Toxicol. 9: 39-46.

Wyngaarden JB (1986). New nonsurgical treatment removes gallstones. JAMA 256(13): 1692. October 3.

Yoshikawa M, Arashidani K, Katoh T, Kawamoto T, Kodama Y (1994). Pulmonary elimination of methyl tertiary-butyl ether after intraperitoneal administration in mice. Arch. Toxicol. 68(8): 517-519.

Young WF, Horth H, Crane R, Ogden T, Arnott M (1996). Taste and odour threshold concentrations of potential potable water contaminants. Water Res. 30(2): 331-340.

Zakko SF, Scirica JC, Guttermuth MC, Dodge J, Hajjar JJ (1997). Ethyl propionate is more effective and less cytotoxic than methyl tert-butyl ether for topical gallstone dissolution. Gastroenterology 113(1): 232-237.

Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K, Speck W (1987). Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. Environ. Mutagen. 9(S9): 1-110.

Zhang YP, Macina OT, Rosenkranz HS, Karol MH, Mattison DR, Klopman G (1997). Prediction of the metabolism and toxicological profiles of gasoline oxygenates. Inhalation Toxicol. 9(3): 237-254. April.

Zielinska B, Shire J, Harshfield G, Pasek R (1997). Paper 97-RP139.06. In: Proceedings of the 90th Annual Meeting of the Air and Waste Management Association (AWMA). June 8 - 13. Toronto, Canada.

Zogorski JS, Delzer GC, Bender DA, Squillace PJ, Lopes TJ, Baehr AL, Stackelberg PE, Landmeyer JE, Boughton CJ, Lico MS, Pankow JF, Johnson RL, Thomson NR (1998). MTBE: Summay of findings and research by the U.S. Geological Survey. In: Proceedings of the 1998 Annual Conference of the American Water Works Association. 23 pp. Amherst, Massachusetts.

Zogorski JS, Baehr AL, Bauman BJ, Conrad DL, Drew RT, Korte NE, Lapham WW, Morduchowitz A, Pankow JF, Washington ER (1997). Significant findings and water-quality recommendations of the Interagency Oxygenated Fuel Assessment. In: Proceedings of the 11th Conference on Contaminated Soils. pp. 661-679. Amherst, Massachusetts.

Zogorski JS, Morduchowitz A, Baehr AL, Bauman BJ, Conrad DL, Drew RT, Korte NE, Lapham WW, Pankow JF, Washington ER (1996). Fuel Oxygenates and Water Quality: Current Understanding of Sources, Occurrence in Natural Waters, Environmental Behavior, Fate and Significance. Final Report. September. Prepared for Interagency Oxygenated Fuel Assessment as Chapter 2 of the NSTC 1997 final report, pp. 2-1 - 2-80. Coordinated by OSTP. Washington, D.C.: NSTC.

Appendix E

Multiple Time Point Testing of MTBE and TBA—NSF International

NSF International

August 6, 2008

Plastic Pipe and Fittings Association
800 Roosevelt Road
Building C, Suite 312
Glen Ellyn, Illinois 60137

RE: Testing of Cross-linked Polyethylene Tubing to NSF/ANSI Standard 61
LAB REPORT #'s: J-00056621, J-00056620, J-00057146, J-00057147, J-00057148, J-00057149, J-00057150, J-00057151, J-00057152 and J-00057153

To whom it may concern,

NSF International has completed the testing and has summarized the test results for ten samples of Cross-linked Polyethylene Tubing to evaluate the long term extraction of t-butanol and methyl t-butyl ether (MTBE). To determine the long term extraction of these contaminants samples of cross-linked polyethylene tubing were conditioned for 16 days prior to the critical water collection on day 17. For these overtime exposures the water was also collected and analyzed on days 1, 2, 3, 8, 10, 21, 36, 49, 78 and 107. Analyzing water samples from days throughout the exposure was necessary to perform a regression analysis. The purpose of this review is to determine the point at which the t-butanol and MTBE extraction result would be lower than 13 and 12 ppb respectively.

Table 1 summarizes the normalized results for t-butanol and MTBE for Day 107. All samples tested for MTBE had normalized levels below 12 ppb by day 107. Of the samples tested for t-butanol, two of ten were below 13 ppb after the 107 day exposure.

Table 1. Day 107 normalized results for t-butanol and MTBE.

Sample	t-butanol (ppb)	MTBE (ppb)
Sample 1 - J-00056620	15	5.4
Sample 2 - J-00056621	†ND (10)	7.3
Sample 3 - J-00057146	21	†ND (0.3)
Sample 4 - J-00057147	55	†ND (0.3)
Sample 5 - J-00057148	21	8.8
Sample 6 - J-00057149	62	11
Sample 7 - J-00057150	34	0.47
Sample 8 - J-00057151	41	†ND (0.3)
Sample 9 - J-00057152	62	†ND (0.3)
Sample 10 - J-00057153	†ND (10)	†ND (0.3)

† Non-Detectable.

789 N. Dixboro Road, Ann Arbor, Michigan 48105-9723 USA
1-800-NSF-MARK 734-769-8010
www.nsf.org

Even though all MTBE samples were below 12 ppb by day 107 regression analyses were performed to determine which decay model (power or exponential) best predicts day 107 extraction results. In 9 of the 10 samples, the power model demonstrated the best fit based upon the highest coefficient of determination (r^2 value). Graphical results of the t-butanol and MTBE regression analyses can be found in Appendix A.

For the t-butanol samples that exceeded 13 ppb on day 107, the levels were extrapolated to determine the day when that level would be below 13 ppb based upon the model that was selected for the regression. Table 2 summarizes the results of these regression analyses.

Table 2. Results of the 107 day regression analyses performed on t-butanol samples.

Sample	r^2 value (Model)	Predicted day that t-butanol would reach 12 ppb
Sample 1 - J-00056620	0.99131 (Exponential)	97
Sample 2 - J-00056621	N/A	Level below 12 ppb by day 107
Sample 3 - J-00057146	0.97599 (Power)	241
Sample 4 - J-00057147	0.93866 (Power)	> 2 years
Sample 5 - J-00057148	0.99205 (Exponential)	112
Sample 6 - J-00057149	0.99724 (Exponential)	135
Sample 7 - J-00057150	0.91662 (Exponential)	137
Sample 8 - J-00057151	0.92825 (Power)	> 2 years
Sample 9 - J-00057152	0.86628 (Exponential)	147
Sample 10 - J-00057153	N/A	Level below 12 ppb by day 107

The model used was selected based on the best fit to either the power or exponential model. In 6 of the 10 samples the exponential model demonstrated the best fit. In the other 4 samples the power model demonstrated the better fit. The extraction and decay of t-butanol results vary by the amount of peroxide used, the age of the tubing, the cross-linking method and the variability that can be introduced during the manufacture of this material. Regression analysis indicates that the 8 samples reporting t-butanol levels above 13 ppb on day 107 would decay to below 13 ppb in as few as 97 days to a maximum of greater than 2 years.

If you have any further questions, please contact me at 734-913-5737.

Sincerely,

Clifton J. McLellan
Director of Toxicology Services
NSF International

Appendix A

Figure 1. PSF# J-57146 - MTBE

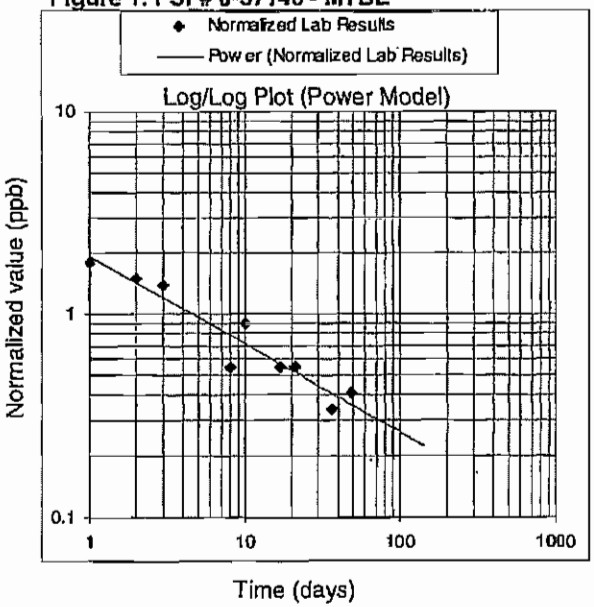


Figure 2. PSF# J-57146 – t-butanol

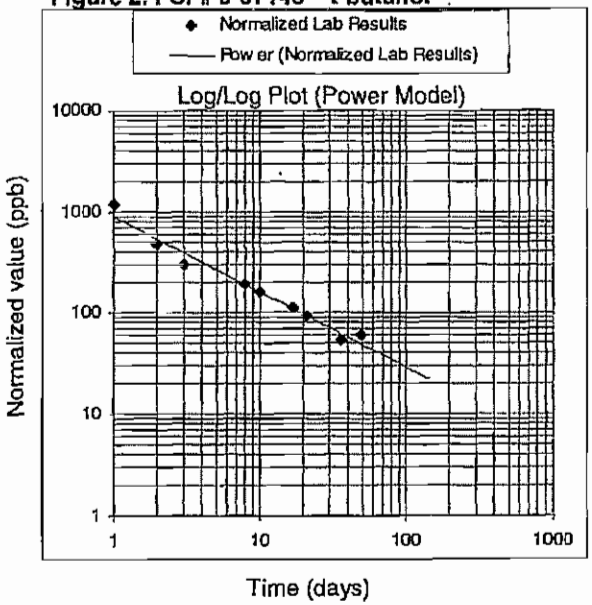


Figure 3. PSF# J-57147 - MTBE

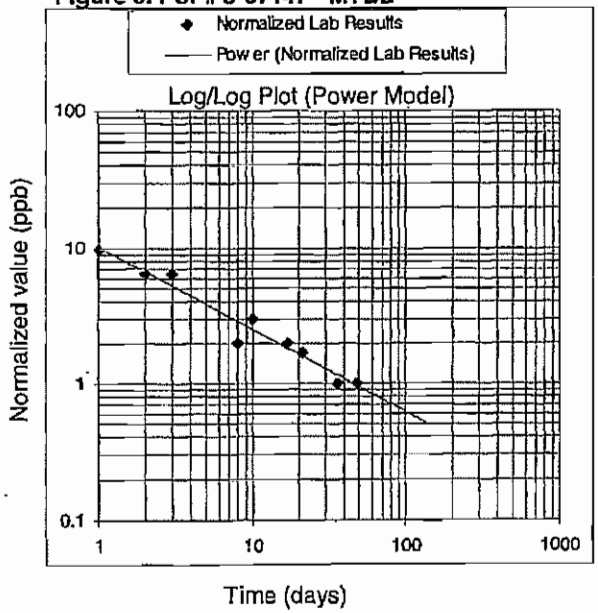


Figure 4. PSF# J-57147 – t-butanol

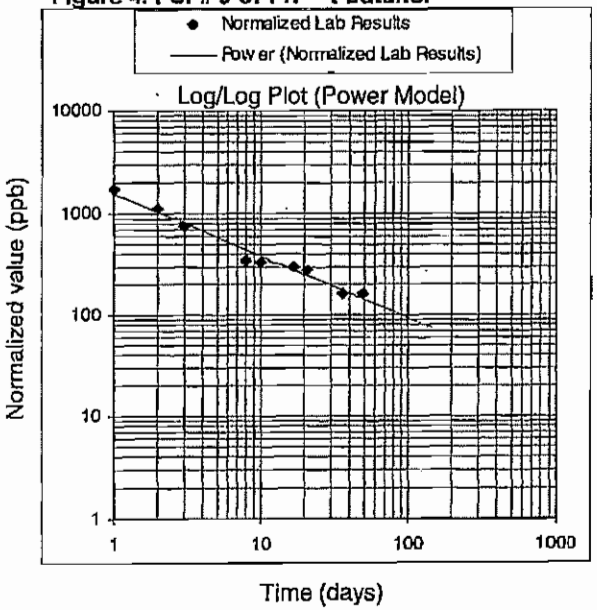


Figure 5. PSF# J-57148 - MTBE

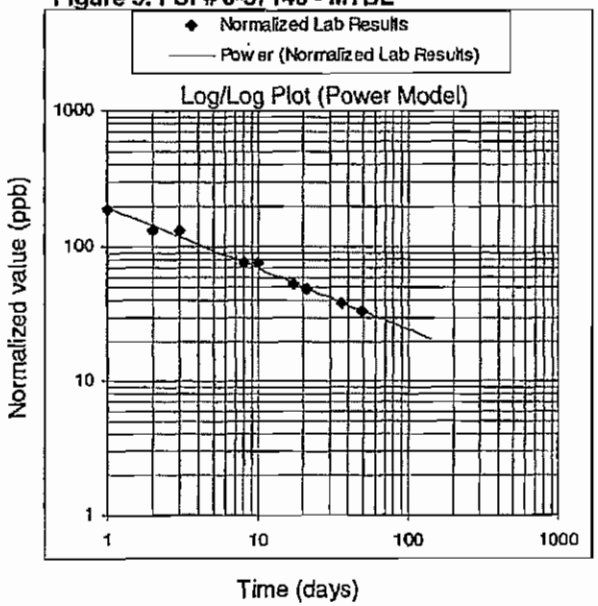


Figure 6. PSF# J-57148 – t-butanol

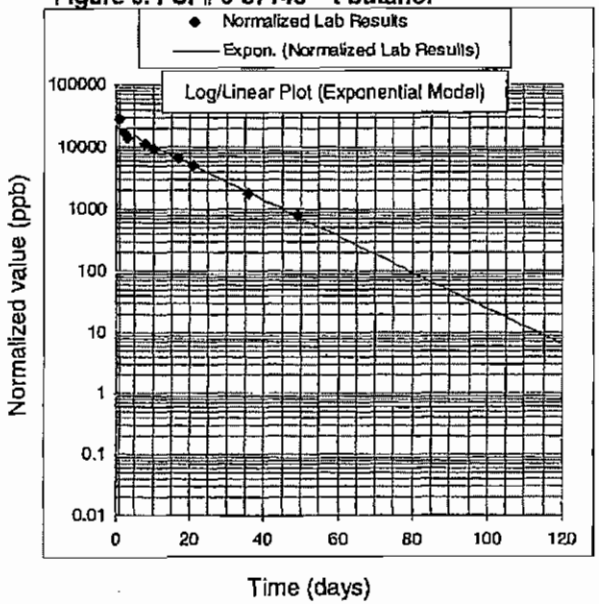


Figure 7. PSF# J-57149 - MTBE

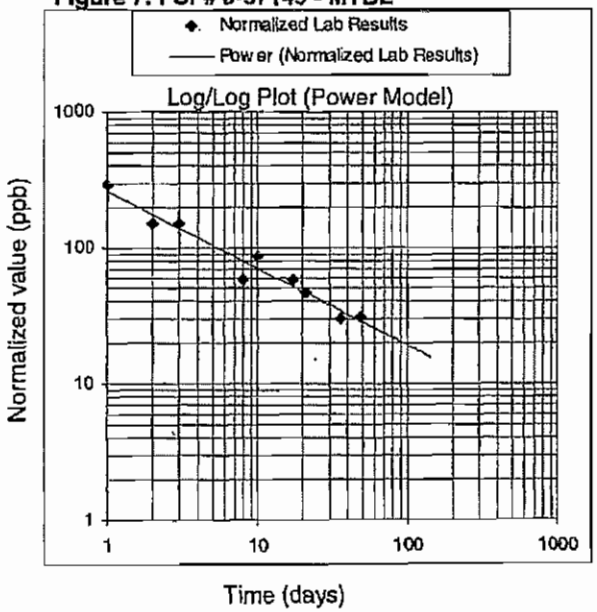


Figure 8. PSF# J-57149 – t-butanol

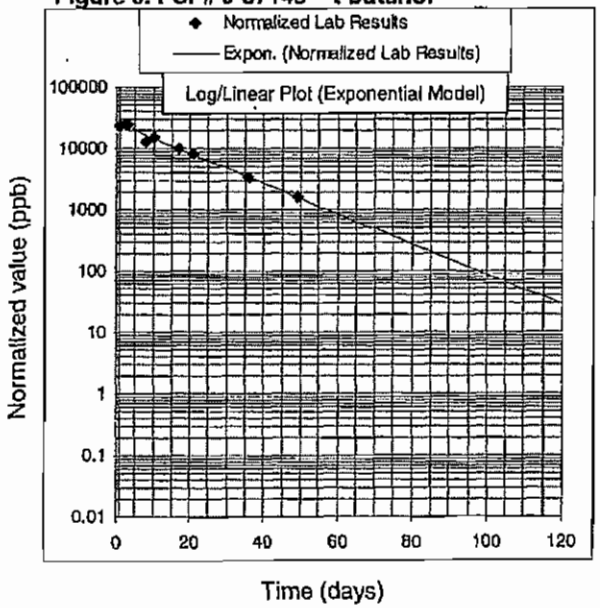


Figure 9. PSF# J-57150 - MTBE

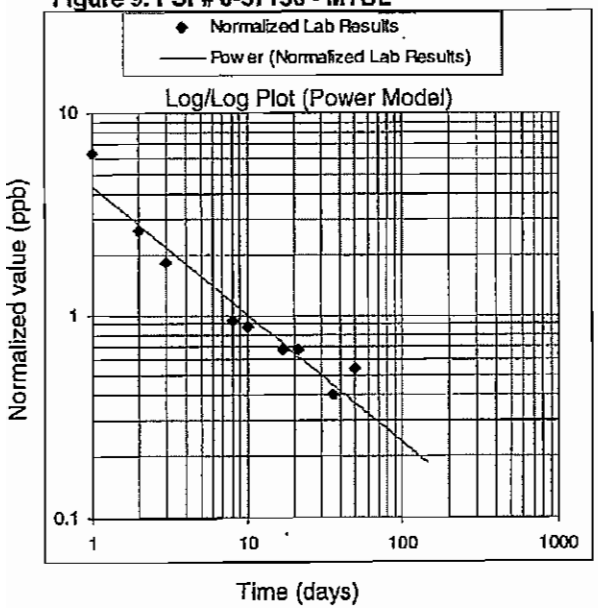


Figure 10. PSF# J-57150 – t-butanol

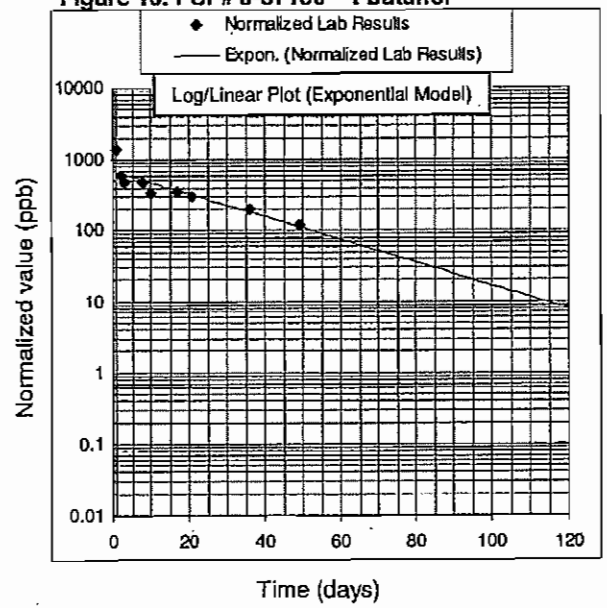


Figure 11. PSF# J-57151 - MTBE

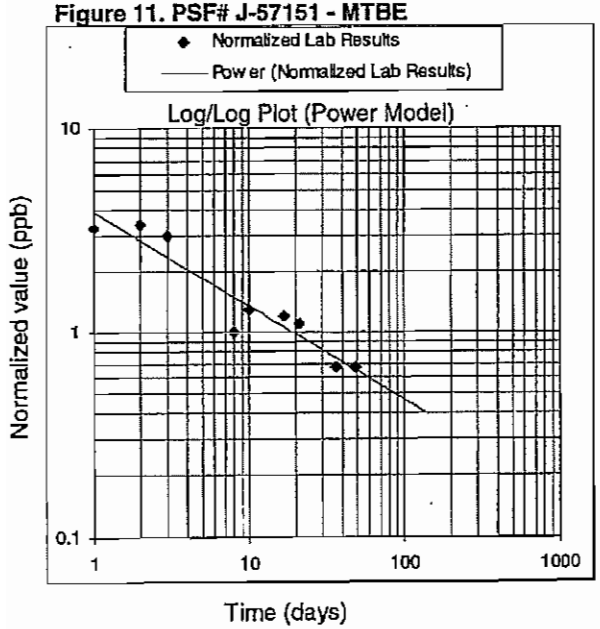


Figure 12. PSF# J-57151 – t-butanol

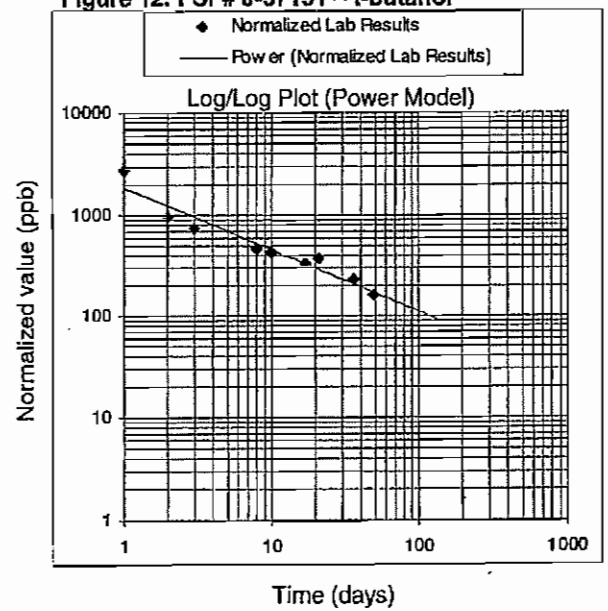


Figure 13. PSF# J-57152 - MTBE

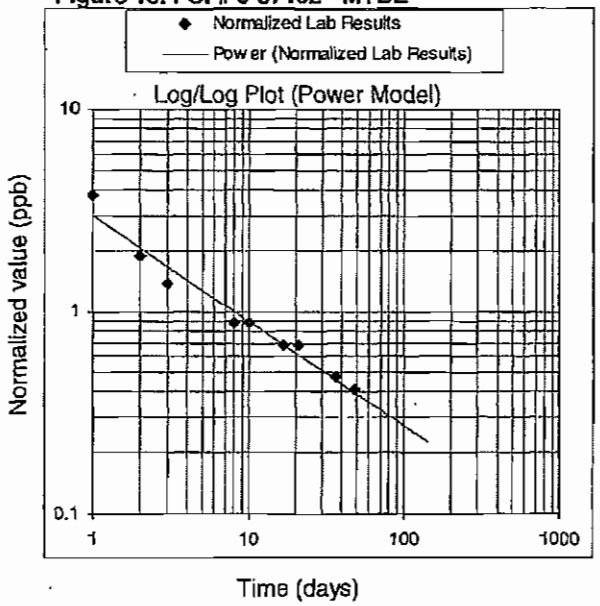


Figure 14. PSF# J-57152 – t-butanol

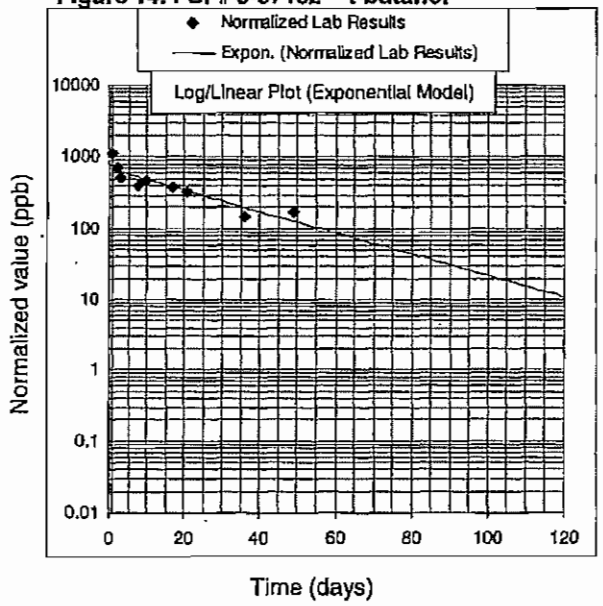


Figure 15. PSF# J-57153 - MTBE

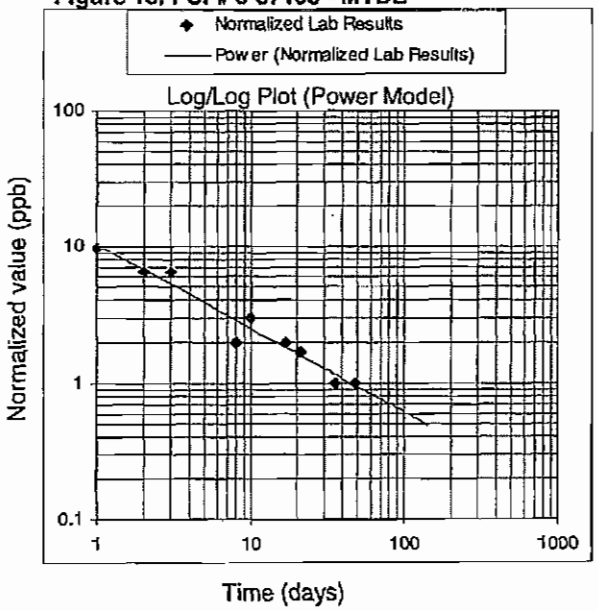


Figure 16. PSF# J-57153 – t-butanol

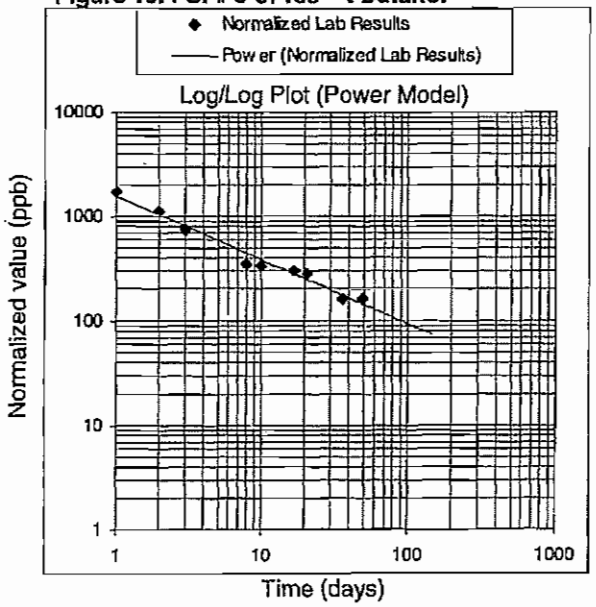


Figure 17. PSF# J-56220 - MTBE

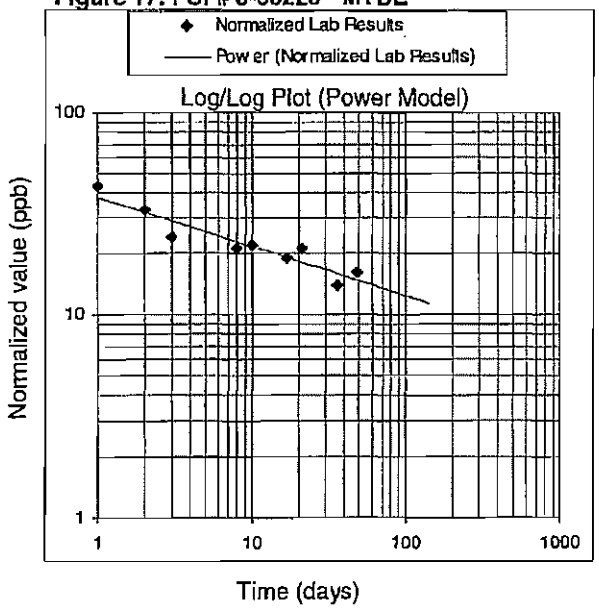


Figure 18. PSF# J-56220 – t-butanol

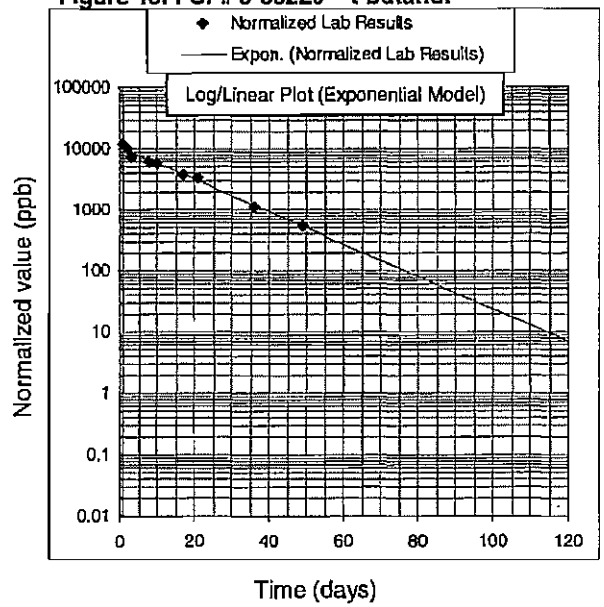


Figure 19. PSF# J-56221 - MTBE

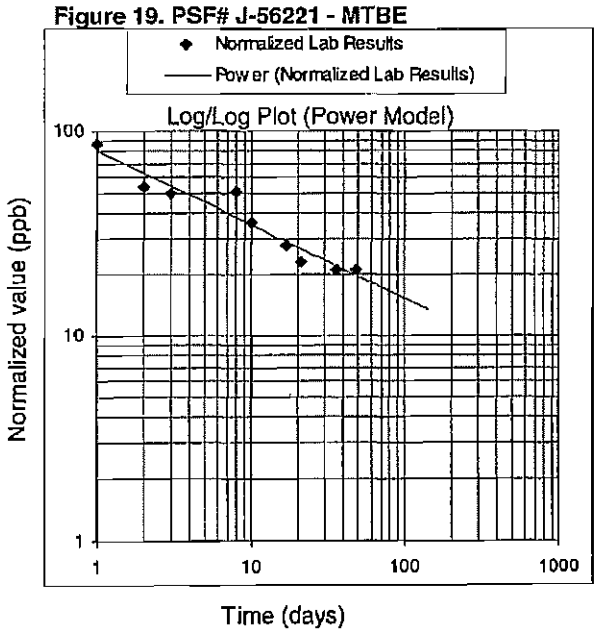
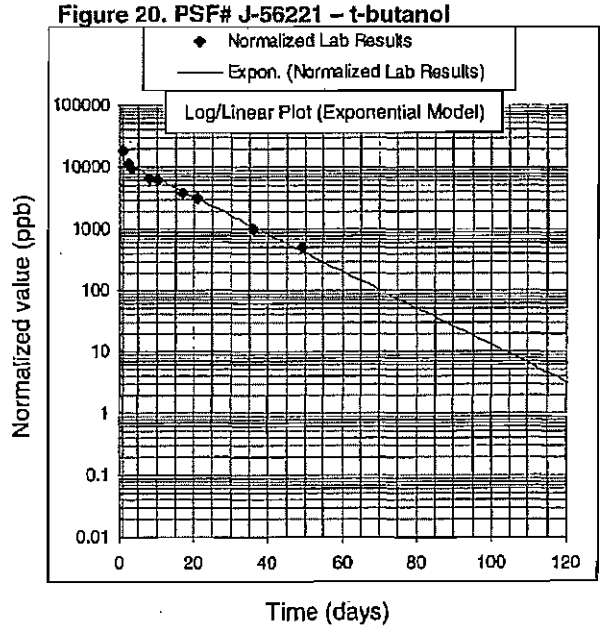


Figure 20. PSF# J-56221 – t-butanol



Appendix F

Calculations of Maximum Lifetime Dose of MTBE from PEX and Associated Cancer Risk

Important Definitions for Understanding Cancer Risk Assessment

Term	Definition	Source(s)
Dose-Response Model	A mathematical relationship (function) that relates (predicts) a measure of an effect to a dose.	EPA 2008
Cancer slope factor	The slope of the dose response line, known as the slope factor, is an upper-bound estimate of risk per increment of dose that can be used to estimate risk probabilities for different exposure levels. When depicted on a graph the response, which is the percentage of an exposed population with tumors, is represented by the y-axis and the dose is represented on the x-axis.	EPA 2008
Lifetime average daily dose (LADD)	For cancer effects, where the biological response is usually described in terms of lifetime probabilities, even though exposure does not occur over the entire lifetime, doses are often presented as lifetime average daily doses (LADDs). Exposure is evaluated by calculating the LADD.	EPA 1997; OEHHA 2003
Maximum (allowable) lifetime dose	The total maximum dose, measured in mass, of a chemical that an individual is exposed to over his/her lifetime. The lifetime dose is usually calculated assuming a 70-year lifetime.	EPA 1997; OEHHA 2003

Sources

EPA. 2008 (September 30). *Benchmark Dose Software, Appendix C: Glossary of Terms* . Available: <http://www.epa.gov/ncea/bmds/bmds_training/appendices/glossary.htm#bmdl>. Accessed May 4, 2010. Last updated September 30, 2008.

EPA. 1997 (August). Exposure Factors Handbook. National Center for Environmental Assessment. Available: <http://www.epa.gov/ncea/pdfs/efh/efh-complete.pdf>. Accessed: April 15, 2010.

OEHHA. 2003 (August). Air Toxics Hot Spots Program Risk Assessment Guidelines: The Air Toxics Hot Spots Program Guidance Manual for Preparation of Health Risk Assessments. Oakland, CA. Available: <http://www.oehha.org/air/hot_spots/pdf/HRAguidefinal.pdf>. Accessed: April 1, 2010.

Lifetime Average Daily Dose

Calculation of the lifetime average daily dose of MTBE that would result in a risk level of 1 in one milllion (1E-6)

	value	units	source/notes
concentration-based standard, C	13	µg/L (or ppb)	This is the PHG established by OEHHA (OEHHA 1999) and the primary MCL adopted by DPH.
drinking water rate	3	L/day	This is the drinking water rate that OEHHA used to devlope the PHG of 13 µg/L (ppb) (OEHHA 1999).
lifetime average daily dose	39	µg/day (or ppb)	calculation

Sources

OEHHA. 1999 (March). Public Health Goal for Methyl Tertiary Butyl Ether (MTBE) in Drinking Water. Prepared by OEHHA, Pesticide and Environmental Toxicology Section, Anna M. Fan, Chief; and Deputy Director for Scientific Affairs, George V. Alexeeff. Available: <http://oehha.ca.gov/water/phg/pdf/mtbe_f.pdf>. Accessed April 6, 2010.

Maximum Allowable Total Lifetime Dose of MTBE (µg/life)

Calculation of the maximum allowable lifetime dose of MTBE that would be protective against an increased cancer risk level of 1 in one million (1E-6)

	value	units	source
lifetime average daily dose	39	µg/day (or ppb)	worksheet "Lifetime Average Daily Dose (µg/day)"
lifetime duration	70	years/life	OEHHA 2001; EPA 1997; McLellan, pers. comm., 2010
days per year	365	days/year	
days per lifetime	25,550	days/life	calculation
maximum allowable lifetime dose	996,450	µg/life	calculation

Findings

This calculation indicates that a human population would experience an incremental increase in cancer risk of 1 in one million (1E-6) if it were exposed to 996,450 µg of MTBE via oral ingestion during its lifetime.

In other words, the increased probability of contracting cancer by an individual who orally ingests 996,450 µg of MTBE during his/her lifetime would increase by 1 in one million.

Sources

OEHHA. 2001. *A Guide to Health Risk Assessment.* Available: <http://www.oehha.org/pdf/HRSguide2001.pdf>. Accessed: April 1, 2010.

EPA. 1997 (August). Exposure Factors Handbook. National Center for Environmental Assessment. Available: <http://www.epa.gov/ncea/pdfs/efh/efh-complete.pdf>. Accessed: April 15, 2010.

EPA. 2008x (September 30). *Benchmark Dose Software, Appendix C: Glossary of Terms* . Available: <http://www.epa.gov/ncea/bmds/bmds_training/appendices/glossary.htm#bmdl>. Accessed May 4, 2010. Last updated September 30, 2008.

McLellan, Clifton. Director of toxicology services. NSF International, Ann Arbor, MI. March 24, 2010—e-mail to Austin Kerr of Ascent Environmental, Inc. regarding a reference level for noncancer risk and a short-term exposure level for MTBE in drinking water.

Natural Decay Function

Key Equation $C_t = C_o * e^{(-k*t)}$

where,

t	=	point in time (e.g., a time point or day)
C_t	=	concentration at time t
C_o	=	concentration at time zero
k	=	slope of decay function, a positive value

K can be solved if using two known time points.

<u>one time point</u>

C_1 on day 1

<u>last time point</u>

C_{107} on day 107

$$C_1 = C_o * e^{(-k*1)}$$

$$C_{107} = C_o * e^{(-k*107)}$$

$$C_1/C_{107} = (C_o/C_o) * e^{(107*k-1*k)}$$

$$C_1/C_{107} = e^{(106*k)}$$

$$\ln(C_1/C_{107}) = \ln(e^{(106*k)})$$

$$k = (\ln(C_1/C_{107}))/106$$

Decay Rates from Multiple Time Point Test Results (k-values)

Sample #	Corresponding Figure in Appendix A of McLellan 2008	Day 1 MTBE Concentration - C_1 (µg/L or ppb)	Day 107 MTBE Concentration - C_{107} (µg/L or ppb)	k-value $k = (\ln (C_1/C_{107}))/106$
1	17	43	5.4	0.020
2	19	85	7.3	0.023
3	1	1.7	0.3	0.016
4	3	9.5	0.3	0.033
5	5	180	8.8	0.028
6	7	280	11	0.031
7	9	6.1	0.47	0.024
8	11	2.1	0.3	0.018
9	13	3.5	0.3	0.023
10	15	9.5	0.3	0.033

Because it represents the slowest rate of decay the most conservative k-value calculated among the 10 samples of PEX is: 0.016

Maximum concentration on Day 107: 11

Notes

The concentractions of day 1, C1, were estimated based on the graphs provided for each sample in Appendix A of McLellan 2008. In order to be conservative, the low range of these values was estimated because this results in a lower decay rate (k-value).

Sample 6 had the maximum concentration of PEX on both day 1 and 107.

Source

McLellan, Clifton. Director of toxicology services. NSF International, Ann Arbor, MI. August 6, 2008x—letter to the Plastic Pipe and Fittings Association presenting the results of multiple point tests on cross-linked polyethylene tubing to the multiple time point protocol of NSF/ANSI Standard 61.

Solving for a Concentration Level at a Future Time Point (C_t) (µg/L)

If the k-value and the concentration at one time point is known than the concentration can be determined for any unit of time, Ct.
Here, the concentration C_{180} is solved for day 180, t.

	value	units	source/notes
Maximum concentration on Day 10 107	11	µg/L	worksheet "Decay Rates from Multiple Time Point Test Results (k-values)"
Lowest k-value (slowest decay rate)	0.016	—	worksheet "Decay Rates from Multiple Time Point Test Results (k-values)"

Key Equation $C_t = C_o * e^{(-k*t)}$

where,

t	=	point in time (e.g., a time point or day)
C_t	=	concentration at time t
C_o	=	concentration at time zero
k	=	slope of decay function, a positive value

last time point	another time point
C_{107} on day 107	C_t on day t

$$C_{107} = C_o * e^{(-k*107)}$$

$$C_t = C_o * e^{(-k*t)}$$

$$C_{107}/C_t = (C_o/C_o) * (e^{(-k*107)})/ (e^{(-k*180)})$$

$$C_{107}/C_t = e^{(-k*(107-t))}$$

$$C_t = C_{107}/e^{(-k*(107-t))}$$

Thus, on day number 180
the concentration would be 3.3 µg/L

Maximum Lifetime Dose of MTBE from PEX and Associated Risk Level

	value	units	source/notes
Drinking water consumption rate (DWR)	3	L/day	OEHHA 1999.
maximum allowable lifetime dose of MTBE that would result in a risk level of 1 in one million (1E-6)	996,450	µg/life	worksheet "Maximum Allowable Total Lifetime Dose (µg/life)"

Sample 6 (J-00057149)
(represented by Figure 7 of Appendix A of McLellan 2008)

Time Point (day #)	Concentration (µg/L, or ppb)	# of days represented (forward) by each time point	Subtotal of exposure during each period (µg)
1	280	1	840
2	180	1	540
3	180	5	2,700
8	90	2	540
10	90	11	2,970
21	90	15	4,050
36	90	13	3,510
49	90	29	7,830
78	90	29	7,830
107	11	73	2,409
180	3.3	25,370	253,532
25,550	—	—	—

Maximum Total Dose from PEX over lifetime (µg/lifetime)	**286,751**			
Lifetime Average Daily Dose from PEX (µg/day)	11.2			
risk level of PEX product	**2.9E-07**	**or**	**0.29**	**in one million**

Notes

1 The highest concentration of MTBE measured on Day 107 during the multiple time point testing was from Sample 6, as shown in
2 The Time Point refers to the day when the concentration of a water sample was measured during the multiple timw point testing.
3 The concentration at each time point is estimated based on the corresponding figure in Appendix A of the multiple time point testing results (Figure 7 in Appendix A of McLellan, pers. comm., 2008x). In order to be conservative, a high value was estimated for each data point on the graph.
4 For each interval between time points, the subtotal of exposure during that interval is calcluated using the product of the highest concentration measures at the beginning of this interval and the number of days represented by the interval.
5 The number of days represented by each time point is equal to the number of days until the next time point concentration was measured.
6 The concentration at day 180 is estimated using the worst-case k-value and, as another conservative measure, it is assumed that the concentration of MTBE will not diminish further byond day 180 (and through day 25,550).
7 The units for the lifetime average daily does from PEX are µg/day and not to be confused with the units for the concentration-based standard of L/day.

Sources

OEHHA. 1999 (March). *Public Health Goal for Methyl Tertiary Butyl Ether (MTBE) in Drinking Water* . Prepared by OEHHA, Pesticide and Environmental Toxicology Section, Anna M. Fan, Chief; and Deputy Director for Scientific Affairs, George V. Alexeeff. Available: <http://oehha.ca.gov/water/phg/pdf/mtbe_f.pdf>. Accessed April 6, 2010.

McLellan, Clifton. Director of toxicology services. NSF International, Ann Arbor, MI. August 6, 2008x—letter to the Plastic Pipe and Fittings Association presenting the results of multiple point tests on cross-linked polyethylene tubing to the multiple time point protocol of NSF/ANSI Standard 61.

NSF International. 2008 (February). *Methyl Tertiary-Butyl Ether Oral Risk Assessment Document* . CAS # 1634-04-4. Ann

EPA. 1997 (August). *Exposure Factors Handbook* . National Center for Environmental Assessment. Available: <http://www.epa.gov/ncea/pdfs/efh/efh-complete.pdf>. Accessed: April 15, 2010.