A Section 508–conformant HTML version of this article
is available at https://doi.org/10.1289/EHP5572.

Methyl Tertiary-Butyl Ether Exposure from Gasoline in the U.S. Population, NHANES 2001–2012

Lalith K. Silva,[1] Michael F. Espenship,[1] Brittany N. Pine,[1] David L. Ashley,[2] Víctor R. De Jesús,[1] and Benjamin C. Blount[1]

[1]Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA
[2]School of Public Health, Georgia State University, Atlanta, Georgia, USA

Background: Methyl tertiary-butyl ether (MTBE) was used as a gasoline additive in the United States during 1995–2006. Because of concerns about potential exposure and health effects, some U.S. states began banning MTBE use in 2002, leading to a nationwide phaseout in 2006.

Objectives: We investigated the change in blood MTBE that occurred during the years in which MTBE was being phased out of gasoline.

Methods: We used data from the National Health and Nutrition Examination Survey (NHANES) from 2001–2012 to assess the change in blood MTBE over this period. We fit sample-weighted multivariate linear regression models to 12,597 human blood MTBE concentrations from the NHANES 2001–2002 to 2011–2012 survey cycles.

Results: The unweighted proportion of the individuals with MTBE blood levels above the limit of detection (LOD) of 1.4 ng/L was 93.9% for 2001–2002. This portion dropped to 25.4% for the period 2011–2012. Weighted blood MTBE median levels (ng/L) (25th and 75th percentiles) decreased from 25.8 (6.08, 68.1) ng/L for the period from 2001–2002 to 4.57 (1.44, 19.1) ng/L for the period from 2005–2006. For the entire postban period (2007–2012), MTBE median levels were below the detection limit of 1.4 ng/L.

Discussion: These decreases in blood MTBE coincided with multiple statewide bans that began in 2002 and a nationwide ban in 2006. The multivariate log-linear regression model for the NHANES 2003–2004 data showed significantly higher blood MTBE concentrations in the group who pumped gasoline less than 7 h before questionnaire administration compared to those who pumped gasoline more than 12 h before questionnaire administration ($p = 0.032$). This study is the first large-scale, national-level confirmation of substantial decrease in blood MTBE levels in the general population following the phaseout of the use of MTBE as a fuel additive. https://doi.org/10.1289/EHP5572

Introduction

Fuel oxygenates are added to gasoline to boost the octane rating of lead-free gasoline and increase fuel oxygen content for cleaner combustion and reduced tailpipe emissions (National Science and Technology Council 1997). Between 1979 and 2006, methyl tertiary-butyl ether (MTBE) was used nationwide at low levels in gasoline to replace lead as an octane rating booster or antiknocking agent (National Science and Technology Council 1997). The Clean Air Act amendments of 1990 established a fuel oxygenate standard under which reformulated gasoline must contain at least 2% oxygen by weight (U.S. Congress 2005). The oil industry responded by making substantial investments in MTBE production capacity and systems to deliver MTBE-containing gasoline to the marketplace. Until 2006, MTBE was the most widely used fuel oxygenate in the United States, followed by ethanol. Overall, MTBE was the second-most-produced chemical in the United States, with approximately 47 million barrels produced in 2005 (U.S. Energy Information Administration 2019). However, because of exposure and health concerns, some states banned or restricted the use of MTBE as a fuel oxygenate starting in 1999 (McCarthy and Tiemann 2006). The U.S. Congress passed a law that stated the federal government would not offer liability protection for oil companies still using MTBE in fuel by May 2006, which caused MTBE to be completely phased out as a fuel oxygenate. At that time, refiners switched to using ethanol (U.S. Energy Information Administration 2016).

Inhalation exposure to fuel oxygenates commonly occurs during vehicle refueling or from incomplete burning of fuel. Dermal exposure occurs when gasoline is used as a hand cleanser (e.g., to remove paint) or gets on skin during refueling (Brown 1997; Dourson and Felter 1997; National Research Council 1996). These chemicals may potentially contaminate groundwater aquifers via leakage and spills from underground storage tanks or from precipitation of the vapor released into the atmosphere as industrial discharge or automobile exhaust (Ahmed 2001; Carter et al. 2006; Vainiotalo et al. 2006; Vayghani and Weisel 1999). Fuel oxygenates such as MTBE are a more significant groundwater problem than many other gasoline components. Because of its water solubility, MTBE contamination from spills or leaking underwater fuel tanks can spread over a wider area than would more hydrophobic gasoline components such as benzene and toluene. When water supplies are contaminated with fuel oxygenates, human exposure can occur by direct ingestion and during showering or bathing through dermal and inhalation pathways (Kim et al. 2007; Prah et al. 2004).

Most MTBE absorbed by the body is metabolized by the liver and then eliminated in urine, primarily as 2-hydroxyisobutyrate with *tert*-butyl alcohol and 2-methyl-1,2-propanediol as minor urinary metabolites (Amberg et al. 2001). Amberg et al. also investigated MTBE metabolites to estimate exposure, half-life, or susceptibility to exposure by oral administration of MTBE with three adults. Depending upon the dose, more than one-third of inhaled MTBE and *tert*-butyl alcohol may be excreted in exhaled air.

MTBE exhibits toxic and carcinogenic effects in laboratory animals. Rats exposed to MTBE through ingestion or inhalation show hepatic and reproductive toxicity, including cancers of the liver, testes, and other organs (Borghoff et al. 1996). After inhalation of high concentrations of MTBE (>3,000 ppm), rats and mice show adverse central nervous system effects (Bevan et al. 1997). Despite the widespread use of fuel oxygenates, epidemiological and clinical data on human health effects associated with fuel oxygenates are very limited. Acute human health effects of MTBE exposure include respiratory tract and eye irritation,

Address correspondence to Lalith K. Silva, Division of Laboratory Sciences, National Center for Environmental Health, CDC, 4770 Buford Highway, NE, Mail Stop F47, Atlanta, GA 30341, USA. Telephone: (770) 488-3559. Fax: (770) 488-0181. Email: zox1@cdc.gov

Supplemental Material is available online (https://doi.org/10.1289/EHP5572).

The authors declare they have no actual or potential competing financial interests.

Received 3 May 2019; Revised 14 November 2019; Accepted 19 November 2019; Published 10 December 2019.

nausea, headache, dizziness, and disorientation (Costantini 1993; Moolenaar et al. 1994; Nihlén et al. 1998).

Direct measurement of MTBE in blood provides an accurate measure of internal dose, accounting for exposure from all sources and routes and providing a basis for individual exposure assessment. Despite the potential health effects of MTBE, internal dose data available from a population-representative sample have not been previously examined. This paper provides these results through an evaluation of data from the National Health and Nutrition Examination Survey (NHANES) (https://www.cdc.gov/nchs/nhanes/index.htm). Population-based biomonitoring data are useful to understand the prevalence and magnitude of exposure and the effect of regulatory changes (Pirkle et al. 1995). We assessed blood MTBE data from 2001–2012 for 16,937 NHANES participants ≥ 12 years of age from multiple cycles of NHANES and used sample-weighted multivariate linear regression models to explore significant predictors of these levels.

Methods

Study Design

NHANES is a cross-sectional study designed to assess the health and nutritional status of the U.S. population by collecting questionnaire and physical examination data as well as biologic samples during 2-y sampling cycles (https://www.cdc.gov/nchs/nhanes/index.htm). Initially, each participant was interviewed at home, followed by a questionnaire and physical examination performed in a mobile examination center (MEC). A total of 16,937 participants 12 years of age and older had blood MTBE data measured during the 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012 NHANES cycles. We also assessed 11,899 corresponding tap water samples obtained from NHANES participants' households. MTBE water data was not collected for the NHANES 2011–2012 cycle.

Analytical Methodology

We previously published the method used to quantify MTBE in human blood in the NHANES survey samples (Bonin et al. 2005). Briefly, whole blood (3 mL) was spiked with stable isotope-labeled MTBE ($^{13}C_3$-MTBE) internal standard and hermetically sealed in a 10-mL vial with a Teflon-lined silicone septum. The vial headspace was sampled via solid-phase microextraction using a Carboxen/polydimethylsiloxane fiber (Supelco) and analyzed using gas chromatography–high-resolution mass spectrometry (GC/MS). We used a 6890 Series GC (Agilent) and a MAT 95 XP magnetic sector MS (Thermo Fisher Scientific) for the measurements. We used Xcalibur software (version 1.3; Thermo Fisher Scientific) to process and quantify MTBE results. Reported results met the accuracy and precision specifications of the quality control/quality assurance program of the Centers for Disease Control and Prevention (CDC), National Center for Environmental Health, Division of Laboratory Sciences (Caudill et al. 2008). Blood samples were received weekly and never frozen. Samples were analyzed within 4 wk of receipt and could be stored up to 10 wk at 4°C. Samples were analyzed continuously between 2001 and 2013.

A similar method was used to quantify MTBE in household tap water (5 mL) (Cardinali et al. 2008). A GC Ultra (Thermo Finnigan) and a DSQ GC MS (Thermo Finnigan) were used. Xcalibur software (v1.3, Thermo Fisher Scientific Inc.) was used to process and quantify MTBE results.

Statistical Analysis

NHANES uses a multistage probability sample design. Respecting this complex design, we used survey sample weights to produce unbiased, nationally representative statistics and estimated their variance using Taylor series linearization, properly accounting for clustering. We used the SURVEYREG and SURVEYMEANS subroutines of SAS (version 9.4; SAS Institute Inc.) to obtain estimates, all of which are weighted with appropriate volatile organic compound (VOC) subsample weights. Sample-weighted multivariate linear regression models were fit to data from NHANES survey cycles 2001–2002 to 2011–2012, where the dependent variable was blood MTBE concentration (ng/L). The distribution of blood MTBE measurements was strongly right-skewed, which could have adversely affected hypothesis testing if analyzed without being transformed to have an approximately normal distribution. Therefore, we used the natural logarithm to transform the blood MTBE measurements for regression analysis. For blood and water, MTBE concentrations less than the limit of detection (LOD) were imputed using $\mathrm{LOD}/\sqrt{2}$. The LODs for blood and water MTBE measurements were $1.4\ \mathrm{ng/L}$ and $0.1\ \mu\mathrm{g/L}$, respectively. We report slopes from these models along with their 95% confidence intervals (CIs) and *p*-values. In addition, to make interpretation easier, we report the exponentiated slopes to represent the proportional difference in biomarker concentration. Statistical significance was set to $\alpha = 0.05$.

The sample-weighted regression model included the following variables as predictors: sex, age, race/ethnicity, body mass index (BMI), poverty–income ratio (PIR), and NHANES cycle. PIR is the ratio of self-reported family income to the U.S. Census poverty threshold. Impoverishment was indicated by PIR ≤ 1 (https://www.cdc.gov/nchs/nhanes/index.htm). Information for these potential confounders was self-reported. Age was categorized into the following ranges: 12–19 y, 20–39 y, 40–59 y, and ≥ 60 y. BMI ($\mathrm{kg/m^2}$) was measured during physical examination. Standard definitions for underweight ($\mathrm{BMI} < 18.5$), healthy weight ($18.5 \leq \mathrm{BMI} < 25$), and overweight/obese ($\mathrm{BMI} \geq 25$) apply to adults ≥ 20 years of age. Participants <20 years of age were classified based on their BMI percentile for their sex and age: below the 5th percentile (underweight), between the 5th and 85th percentiles (healthy weight), and above the 85th percentile (overweight/obese) (https://www.cdc.gov/nchs/nhanes/index.htm). We also included the NHANES cycle as a predictor to see if there were any significant changes in blood MTBE over time.

The VOCs subsample A of the NHANES 2001–2012 cycles had 16,937 participants. Of those, 725 participants had zero or missing sampling weights and were excluded from the analysis. We removed another 3,615 participants who were missing at least one predictor used in the regression model. This left a sample size of 12,597 participants for our analysis.

People could be exposed to the MTBE used as a gasoline additive by breathing in fugitive emissions from gasoline. They also could have skin exposure to MTBE contaminate in groundwater. Assessment of three exposure situations was possible with questionnaire data available in the NHANES 2003–2004 cycle: *a*) indoor residential exposure from emissions emanating from vehicles stored in an attached garage, *b*) exposure during gasoline refueling, and *c*) exposure while showering/bathing (https://www.cdc.gov/nchs/nhanes/index.htm). A subset of the previous regression model was fit to only 2003–2004 data with the addition of these variables and a categorical variable for whether household water MTBE levels were above or below the LOD. An interaction between recent shower and detectable water MTBE was also included in the model because persons can inhale and have skin contact with MTBE in shower water. The 2003–2004 cycle was selected for behavioral exposure analysis because it was the first to include these exposure questions, and it preceded the complete phaseout of MTBE from gasoline in 2006.

NHANES 2003–2004 asked participants if their home had an attached garage. Participants were also asked if they had pumped gasoline into their vehicle within the last 3 d. Respondents who answered yes to this question were then asked how long since they had pumped gasoline: <7 h, 7–12 h, or >12 h. For participants responding no to the question about pumping gas in the last 3 d, the response was categorized as >12 h. The exposure intervals were selected to be relevant to the time scale of MTBE's pharmacokinetics but still provide adequate numbers of participants in each category, particularly its 2- to 4-h half-life in blood (Lee et al. 2001).

Time since last shower was categorized into 1–6 h and >6 h, based on the questions "In the last 3 d, did you take a hot shower or bath for 5 min or longer" and the number of hours since "...your last shower or hot bath." If respondents answered no to whether they had showered or bathed for 5 min or longer in the last 3 d, time since last shower was categorized as >6 h.

A sample-weighted multivariate linear regression model was fit to data from the NHANES 2003–2004 survey cycle in which the dependent variable was blood MTBE concentration (ng/L). The sample-weighted regression model included the primary model covariates (other than NHANES cycle and with age dichotomized as 20–39 or 40–59 y) plus recent gas pump exposure prior to the NHANES visit (<7 h, 7–12 h, >12 h), having an attached garage (yes, no), having showered within 6 h of the study visit (yes, no), having a detectable MTBE water level (yes, no), and an interaction between taking a hot shower within 6 h and having a detectable MTBE water level. The interaction between time of last shower and detectable water MTBE was included in the model to test whether a recent shower modified the association between blood MTBE and household water MTBE. Residential water MTBE concentrations were not included in regression models because levels of detection in water were low (16.2%) for the 2003–2004 cycle. Instead, we used a categorical variable indicating residential water MTBE concentrations above or below the detection limit. One participant was excluded because of missing questionnaire data, and 205 were excluded because of missing water concentration values.

After exclusion ($n = 206$), the sample size for NHANES 2003–2004 statistical analysis was 1,015 participants. We report slopes from the model and their 95% CIs and p-values. We also report the exponential slopes to represent the proportional change in biomarker concentration.

Results

Blood Methyl Tertiary-Butyl Ether Exposure: NHANES 2001–2012

Sample-weighted demographic distributions of participants eligible for statistical analysis ($n = 12{,}597$) indicate that most were 20–39 or 40–59 years of age (36.8% and 37.0%, respectively), 64.2% were overweight/obese, and 85.8% had incomes above the poverty level (Table 1). The majority (69.0%) were non-Hispanic white, followed by 11.1% non-Hispanic black, 8.5% Mexican American, and 11.4% other race/ethnicity groups (combined). Male and female participants were roughly equally represented.

A total of 16,937 blood samples were assayed for MTBE during 2001–2012. The percentage of samples with blood MTBE concentrations above the detection limit decreased from 94% in 2001–2002 to 77% in 2007–2008 and to 23–28% during subsequent NHANES cycles (Table 2).

We estimated that MTBE levels among women were significantly lower (by 4.9%; 95% CI: 0.4, 9.1) than levels among men ($p = 0.035$). Participants ≥60 years of age had significantly higher MTBE levels (14%; 95% CI: 3, 25) than those of the age 20- to 39-y reference group. Levels for ages 12–19 y and 40–59 y were not significantly different from the reference group (Table 3). Adjusted mean blood MTBE levels for NHANES cycles 2001–2002, 2003–2004, and 2005–2006 were 11.7 (95% CI: 4.31, 32.0), 8.15 (95% CI: 4.69, 14.2), and 4.53 (95% CI: 2.28, 9.00) times higher, respectively, than the mean blood MTBE level for the 2011–2012 NHANES cycle. Blood MTBE levels for the 2007–2008 and 2009–2010 NHANES cycles were not statistically different from the 2011–2012 cycle. Mean blood MTBE concentrations for each 2-y NHANES cycle decreased in parallel with decreasing 2-y mean consumption of MTBE-containing

Table 1. Sample-weighted demographic distributions and blood methyl tertiary-butyl ether (MTBE) sample-weighted medians (ng/L) with minimum; 25th, 50th, and 75th percentiles; and maximum for National Health and Nutrition Examination Survey (NHANES) 2001–2012 participants ≥12 years of age ($n = 12{,}597$).

				Blood MTBE (ng/L)				
Predictor	Level	n[a]	Demographic distribution [SE (%)]	Minimum[b]	25th percentile	50th percentile	75th percentile	Maximum
All	—	12,597	100	<LOD	<LOD	<LOD	6.05	3,800
Sex	Male	6,216	49.5 (0.434)	<LOD	<LOD	<LOD	6.40	3,800
	Female	6,381	50.5 (0.434)	<LOD	<LOD	<LOD	5.70	1,200
Age (y)	12–19	2,186	9.89 (0.384)	<LOD	<LOD	<LOD	2.90	530
	20–39	4,100	36.8 (0.860)	<LOD	<LOD	1.41	8.31	630
	40–59	3,575	37.0 (0.680)	<LOD	<LOD	1.59	9.27	1,500
	≥60	2,736	16.3 (0.674)	<LOD	<LOD	<LOD	3.38	3,800
Race/ethnicity	Non-Hispanic white	5,589	69.0 (1.46)	<LOD	<LOD	<LOD	5.97	1,500
	Non-Hispanic black	2,760	11.1 (0.822)	<LOD	<LOD	0.997	7.23	3,800
	Mexican American	2,366	8.47 (0.747)	<LOD	<LOD	1.59	7.50	530
	Other race	1,882	11.4 (0.747)	<LOD	<LOD	<LOD	5.04	600
BMI	Underweight	219	1.64 (0.156)	<LOD	<LOD	<LOD	6.45	880
	Healthy weight	4,287	34.1 (0.739)	<LOD	<LOD	<LOD	5.91	3,800
	Overweight/obese	8,091	64.2 (0.744)	<LOD	<LOD	<LOD	6.12	240
Impoverished	No	9,803	85.8 (0.584)	<LOD	<LOD	<LOD	6.29	3,800
	Yes	2,794	14.2 (0.584)	<LOD	<LOD	<LOD	4.90	240
NHANES cycle	2001–2002	625	7.78 (1.51)	<LOD	6.08	25.8	68.1	286
	2003–2004	1,221	13.1 (0.787)	<LOD	2.46	9.96	46.2	680
	2005–2006	2,905	20.0 (1.03)	<LOD	1.44	4.57	19.1	3,800
	2007–2008	2,681	19.8 (1.07)	<LOD	<LOD	<LOD	1.42	600
	2009–2010	2,924	19.2 (1.06)	<LOD	<LOD	<LOD	<LOD	448
	2011–2012	2,241	20.2 (1.09)	<LOD	<LOD	<LOD	1.62	59.7

Note: —, not calculated; BMI, body mass index; LOD, limit of detection; SE, standard error.
[a]Unweighted sample size.
[b]Lowest detection limit in blood = 1.4 ng/L.

Table 2. National Health and Nutrition Examination Survey (NHANES) 2001–2012 percentage of methyl tertiary-butyl ether (MTBE) levels above the detection limit for blood ($n = 16,937$) and water ($n = 11,899$).

NHANES cycle	Number of blood sample assayed (n)	Overall unweighted detect rate in blood (%)	Number of water samples assayed (n)	Overall unweighted detect rate in water (%)
2001–2002	1,449	93.9	1,023	24.8
2003–2004	1,489	81.6	1,224	16.2
2005–2006	3,545	77.4	3,267	8.51
2007–2008	3,415	27.8	3,177	1.23
2009–2010	3,745	22.6	3,208	3.02
2011–2012	3,294	25.4	—[a]	—[a]

Note: Limit of detection for blood = 1.4 ng/L and water = 0.1 μg/L.
[a]Water data not measured for the 2011–2012 NHANES cycle.

fuel in the United States (Figure 1 and Table S1) (U.S. Energy Information Administration 2019).

Water Methyl Tertiary-Butyl Ether: NHANES 2001–2010

We also assessed 11,899 corresponding household tap water samples, which were obtained from NHANES participants' households. MTBE water data was not reported for NHANES 2011–2012 cycle. The percentage of water MTBE levels above the detection limits decreased until 2008, after which it remained at a low overall unweighted detection rate of about 1%–3% in 2009–2010. Household tap water MTBE levels were below the LOD up to the 75th percentile for all NHANES cycles, and for the last two NHANES cycles (2007–2008 and 2009–2010) (Table 2), MTBE levels were below the LOD up to the 95th percentile (Table S2). These data are also consistent with the decline in MTBE-containing fuel consumption over time.

The median MTBE concentration in household tap water was below the LOD for all NHANES cycles, while the concentration at the 95th percentile decreased from 0.494 μg/L in 2001–2002 to <LOD (0.1 μg/L) in 2007–2008 and 2009–2010 (Table S2).

Water Methyl Tertiary-Butyl Ether Exposure from Gasoline and Water Use: NHANES 2003–2004

With adjustment for other covariates, female participants in 2003–2004 had 19.0% (95% CI: 2.20, 33.0) lower blood MTBE level than males (Table S3). Model estimates based on blood MTBE data from 1,015 participants in the 2003–2004 NHANES cycle indicated that those who pumped gas <7 h before their NHANES study visit had significantly higher MTBE levels (83%; 95% CI: 11, 201) than did those who did not pump gas within 12 h of the study visit (Table 4). However, the model had a relatively low R^2 value (0.051), and estimates should therefore be interpreted with caution. Detection of MTBE in household tap water was associated with higher blood MTBE levels, although the association was not significant (121% higher; 95% CI: –5, 412; $p = 0.09$). Blood MTBE levels were not associated with taking a hot shower within 6 h before the study visit or with having an attached garage. The interaction of taking a hot shower within 6 h before the study visit and having a detectable water MTBE concentration was not significant.

Discussion

Our analyses show that mean blood MTBE concentrations in the U.S. population decreased in parallel with the decreased consumption of MTBE-containing fuel between 2001 and 2006. In addition, participants who reported having pumped gasoline <7 h before their study visit had significantly higher blood MTBE levels than those who had not pumped gasoline within the previous 12 h. Together, these findings together support a relationship between the use of MTBE in fuel and exposure to this chemical.

In November of 1990, amendments to the Clean Air Act were adopted; one required the use of reformulated or alternative fuels

Table 3. Sample-weighted multivariate linear regression model for blood methyl tertiary-butyl ether (MTBE) (ng/L) using National Health and Nutrition Examination Survey (NHANES) 2001–2012 data ($n = 12,597$).

Predictor	Level	Slope (95% CI)	p-Value	Exponentiated slope (95% CI)[a]
Sex	Male	Ref	—	Ref
	Female	−0.0500 (−0.0963, −00368)	0.035	0.951 (0.909, 0.996)
Age (y)	12–19	0.00105 (−0.0925, 0.0946)	0.98	1.00 (0.913, 1.10)
	20–39	Ref	—	Ref
	40–59	0.0701 (−0.0159, 0.156)	0.11	1.07 (0.985, 1.17)
	≥60	0.127 (0.0318, 0.223)	0.0095	1.14 (1.03, 1.25)
Race/ethnicity	Non-Hispanic white	Ref	—	Ref
	Non-Hispanic black	0.0723 (−0.170, 0.314)	0.55	1.07 (0.846, 1.37)
	Mexican American	0.114 (−0.113, 0.340)	0.32	1.12 (0.896, 1.40)
	Other Hispanic or other/multirace	−0.00786 (−0.161, 0.146)	0.92	0.992 (0.853, 1.15)
BMI	Underweight	−0.000816 (−0.227, 0.225)	0.99	0.999 (0.799, 1.25)
	Healthy weight	Ref	—	Ref
	Overweight/obese	0.0337 (−0.0360, 0.103)	0.34	1.03 (0.966, 1.11)
Impoverished	No	Ref	—	Ref
	Yes	0.0360 (−0.0653, 0.137)	0.48	1.04 (0.938, 1.15)
NHANES cycle	2001–2002	2.46 (1.45, 3.48)	<0.0001	11.7 (4.31, 32.0)
	2003–2004	2.10 (1.54, 2.66)	<0.0001	8.15 (4.69, 14.2)
	2005–2006	1.51 (0.815, 2.21)	<0.0001	4.53 (2.28, 9.00)
	2007–2008	0.0298 (−0.139, 0.199)	0.73	1.03 (0.872, 1.22)
	2009–2010	0.00944 (−0.0951, 0.114)	0.86	1.01 (0.910, 1.12)
	2011–2012	Ref	—	Ref

Note: Unweighted sample size. The dependent variable, MTBE (ng/L), was natural log transformed for the regression model after replacing values below the limit of detection (LOD) (1.4 ng/L) with LOD/$\sqrt{2}$. Adjusted $R^2 = 0.38$. —, not calculated; BMI, body mass index; CI, confidence interval; Ref, reference group for predictor.
[a]For each predictor, the expected biomarker concentration in ng/L is multiplied by the exponentiated coefficient (controlling for other predictors in the model).

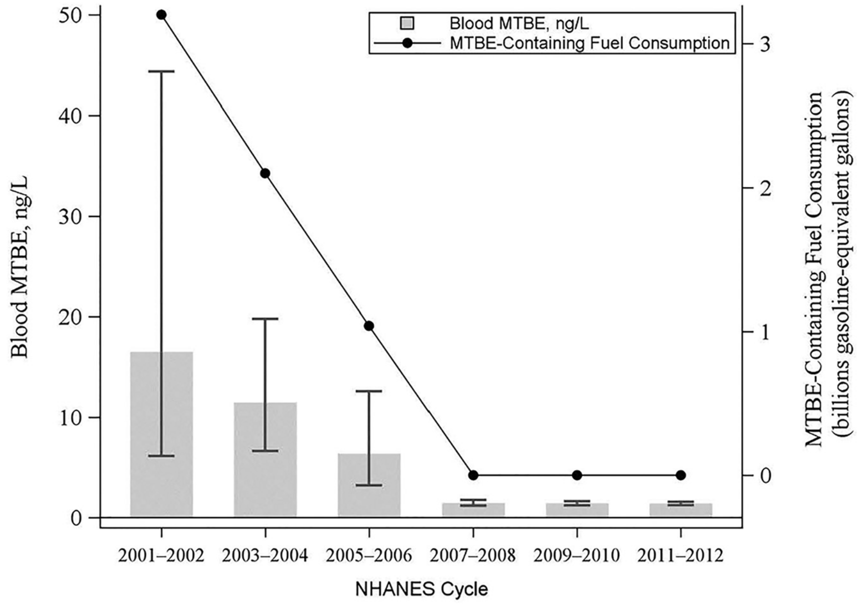

Figure 1. Two-year mean levels of blood methyl tertiary-butyl ether (MTBE) [least squares mean with $\pm 95\%$ confidence interval (CI) as error bars] in the U.S. population as determined from the National Health and Nutrition Examination Survey vs. 2-y mean use of MTBE-containing fuel consumption (closed circles and line) (U.S. Energy Information Administration 2019). Blood data were adjusted for sex, age, race/ethnicity, body mass index, and poverty level. The dependent variable, MTBE (ng/L), was natural log transformed for the regression model after replacing values below the limit of detection (LOD) (1.4 ng/L) with $\mathrm{LOD}/\sqrt{2}$. Adjusted $R^2 = 0.38$. See Table S1 for corresponding numeric data.

in the nation's most polluted areas (U.S. Congress 2005). The fuel additive most commonly used was MTBE. In 1995, the requirement for reformulated gasoline went into effect. However, California banned the use of MTBE fuel in 2002 and New York in 2004 because of concerns about widespread exposure. Until then, these two states used 40% of the MTBE-containing fuel in the United States. Subsequently, in 2006, the United States phased out the use of gasoline reformulated with MTBE nationwide. Figure 1 and Table S1 show the temporal change in mean blood MTBE levels for NHANES 2001–2012 and U.S. consumption of gasoline containing MTBE (U.S. DOE 2014). Nationwide consumption of MTBE-containing gasoline decreased sharply until 2007–2008 and then remained low. Blood MTBE levels decreased simultaneously with decreased use of MTBE-containing gasoline.

Exposure to MTBE through inhalation and dermal contact may occur when pumping gasoline (Moolenaar et al. 1994). Consistent

Table 4. Sample-weighted demographic distributions and median blood methyl tertiary-butyl ether (MTBE) concentrations (ng/L) with 25th and 75th percentiles and regression slopes for the NHANES 2003–2004 model, ages 20–59 y ($n = 1{,}015$) for behavioral predictors.

Predictor	Level	n[a]	Demographic distribution [SE (%)]	Median (25th, 75th percentile) blood MTBE (ng/L)[b]	Slope (95% CI)[c]	p-Value	Exponentiated slope (95% CI)[c]
All	—	1,015	100	9.93 (2.49, 46.1)	—	—	—
Gas pump exposure	<7 h before	61	4.79 (0.729)	28.0 (3.90, 97.2)	Ref	—	Ref
	7–12 h before	45	4.33 (0.760)	16.7 (4.53, 41.1)	0.330 (−0.312, 0.972)	0.29	1.39 (0.770, 2.51)
	>12 h before	909	90.9 (1.04)	9.02 (2.40, 42.2)	0.603 (0.0594, 1.15)	0.032	1.83 (1.11, 3.01)
Attached garage	No	691	63.0 (3.25)	8.97 (2.55, 46.6)	Ref	—	Ref
	Yes	324	37.0 (3.25)	10.8 (2.46, 44.4)	0.0611 (−0.415, 0.537)	0.79	1.06 (0.686, 1.65)
Hot shower within 6 h	No	604	55.9 (3.25)	9.99 (3.05, 34.0)	Ref	—	Ref
	Yes	411	44.1 (3.25)	8.97 (2.27, 61.0)	−0.0161 (−0.414, 0.381)	0.93	0.984 (0.683, 1.42)
Detectable water MTBE	Below detectable limit	844	83.9 (5.76)	8.83 (1.66, 38.5)	Ref	—	Ref
	Detectable result	171	16.1 (5.76)	19.0 (5.61, 64.1)	0.791 (−0.124, 1.71)	0.085	2.21 (0.951, 5.12)
Hot shower within 6 h and detectable water MTBE	No hot shower and water MTBE <LOD	517	48.9 (4.24)	9.22 (2.28, 29.3)	Ref	—	Ref
	No hot shower and detectable water MTBE	87	7.03 (2.10)	15.6 (6.26, 59.1)	Ref	—	Ref
	Hot shower and water MTBE <LOD	327	35.1 (4.55)	7.49 (1.38, 54.9)	Ref	—	Ref
	Hot shower and detectable water MTBE	84	9.02 (3.94)	21.1 (4.94, 70.3)	0.007 (−0.008, 0.008)	0.99	1.01 (0.486, 2.08)

Note: —, not calculated; CI, confidence interval; LOD, limit of detection; Ref, reference group for predictor; SE, standard error.
[a]Unweighted sample size.
[b]The dependent variable, MTBE (ng/L), was natural log-transformed for the regression model after replacing values below the limit of detection (1.4 ng/L) with $\mathrm{LOD}/\sqrt{2}$. Adjusted $R^2 = 0.051$.
[c]Slope estimates derived using adjusted multivariable linear regression model of ln-transformed blood MTBE (ng/L) adjusted for the variables shown plus gender, age (20–39 or 40–59 y), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other), body mass index (BMI) (underweight, normal, overweight/obese), and poverty [impoverished: no/yes; based on poverty–income ratio (PIR)].
Model formula: predicted blood MTBE concentration = 0.051; blood MTBE = intercept + $\beta1 * \text{Female} + \beta2 * \text{Age } 40-59 + \cdots + \beta14 * \text{hot shower within 6 hours} * \text{detectable water MTBE concentration}$, where βx = corresponding slope.

with this, our model estimates show an association between blood MTBE and pumping gas based on data from NHANES 2003–2004 that was significant for those who pumped gasoline within 7 h of their study visit, and positive though nonsignificant for those who pumped gas within 7–12 h compared with other participants. These associations are consistent with the estimated half-life of MTBE, which is approximately 2–4 h (Lee et al. 2001).

The 95th percentile levels of MTBE levels in household tap water from NHANES decreased from 0.494 ng/L to less than the detection limit between 2001 and 2008. The fraction of water samples with detectable MTBE was about 25% for 2001–2002, decreasing to about 3% for 2009–2010. We expected to see such a decrease because MTBE was removed from gasoline production nationally in 2006. MTBE can leak into groundwater (and potentially get into drinking water sources) wherever gasoline is stored, transported, or transferred. Although federal and state programs minimize the potential for leaks and spills, no system is foolproof (U.S. EPA 2016).

Although detectable MTBE in residential water was associated with nominally higher blood MTBE, this association was not significant ($p = 0.085$). Brown (1997) discussed the percentage of the public and people in specific occupations exposed to MTBE. He reported that 98.5% of the population is exposed to MTBE in residential water with less than the detection limit of 0.2 to 5 μg/L. Although our water MTBE detection limit was lower than the lowest discussed by Brown, our analyses were still limited by the low frequency of detectable MTBE in water samples (16.2%) and the relatively small sample size ($n = 1{,}015$) of the 2003–2004 model. Furthermore, the half-life of MTBE in blood is only 2–4 h (Lee et al. 2001), so variable exposure kinetics among participants who commute to the MEC could have diminished the relationship of MTBE in residential water to MTBE in blood. The detailed model did not include data from the 2001–2002 cycle because questions about pumping gas and using water were not asked before 2003. All of these factors likely contribute to the relatively poor $R^2(0.051)$ for the 2003–2004 model. Conversely, the 2001–2012 model has a better $R^2(0.38)$, likely because it effectively uses temporality as a surrogate for MTBE prevalence in the environment.

An earlier air quality study evaluated how the location of parked vehicles relative to home living areas affect indoor concentrations of MTBE in 114 residences in either Los Angeles County, California (38), Elizabeth, New Jersey (21), or Houston, Texas (55) (Hun et al. 2011). These investigators found that single-family homes with vehicles in an attached garage had a higher median difference between indoor and outdoor MTBE concentrations ($2.7\ \mu g/m^3$) compared to other situations including adjacent carports, detached garages, attached garages with no cars, and homes without both attached garages and cars. However, in our study, having a home with an attached garage was not associated with blood MTBE concentrations in participants in the NHANES 2003–2004 cycle. This might be because MTBE as an additive was rapidly being phased out of use at this time, and levels of exposure in an attached garage likely would be low. This also might be because of the relatively short half-life of MTBE (Lee et al. 2001) and the potentially long latency period between participant exposure in the home and time of blood draw. Another possibility could be that participants who responded yes to having an attached garage do not regularly park inside of it.

Conclusion

Our study revealed a decreasing trend in blood-MTBE levels in the United States from 2001–2012, suggesting a decrease in exposure to MTBE over that period. This trend coincides with the reformulation of gasoline in the United States to exclude MTBE, beginning in the 1990s, and the complete phasing out in 2006.

Acknowledgments

The authors thank Nathan B. Geldner for his valuable input and discussions of data for this study, and Mitchell M. Smith for his laboratory assistance. We also thank Dr. Samuel P. Caudill for his valuable statistical suggestions.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Use of trade names is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention, the Public Health Service, or the U.S. Department of Health and Human Services.

References

Ahmed FE. 2001. Toxicology and human health effects following exposure to oxygenated or reformulated gasoline. Toxicol Lett 123(2–3):89–113, PMID: 11641038, https://doi.org/10.1016/S0378-4274(01)00375-7.

Amberg A, Rosner E, Dekant W. 2001. Toxicokinetics of methyl tert-butyl ether and its metabolites in humans after oral exposure. Toxicol Sci 61(1):62–67, PMID: 11294975, https://doi.org/10.1093/toxsci/61.1.62.

Bevan C, Neeper-Bradley TL, Tyl RW, Fisher LC, Panson RD, Kneiss JJ, et al. 1997. Two-generation reproductive toxicity study of methyl tertiary-butyl ether (MTBE) in rats. J Appl Toxicol 17(S1):S13–19, PMID: 9179723, https://doi.org/10.1002/(sici)1099-1263(199705)17:1+<s13::aid-jat406>3.3.co;2-3.

Bonin MA, Silva LK, Smith MM, Ashley DL, Blount BC. 2005. Measurement of trihalomethanes and methyl tert-butyl ether in whole blood using gas chromatography with high-resolution mass spectrometry. J Anal Toxicol 29(2):81–89, PMID: 15902975, https://doi.org/10.1093/jat/29.2.81.

Borghoff SJ, Murphy JE, Medinsky MA. 1996. Development of physiologically based pharmacokinetic model for methyl tertiary-butyl ether and tertiary-butanol in male Fisher-344 rats. Fundam Appl Toxicol 30(2):264–275, PMID: 8812274, https://doi.org/10.1093/toxsci/30.2.264.

Brown SL. 1997. Atmospheric and potable water exposures to methyl tert-butyl ether (MTBE). Regul Toxicol Pharmacol 25(3):256–276, PMID: 9237328, https://doi.org/10.1006/rtph.1997.1104.

Cardinali FL, Blount BC, Schmidt R, Morrow J. 2008. Measurement of fuel oxygenates in tap water using solid-phase microextraction gas chromatography-mass spectrometry. J Chromatogr Sci 46(5):381–387, PMID: 18492345, https://doi.org/10.1093/chromsci/46.5.381.

Carter JM, Grady SJ, Delzer GC, Koch B, Zogorski JS. 2006. Occurrence of MTBE and other oxygenates in CWS source waters. J Am Water Works Assoc 98(4):91–104, https://doi.org/10.1002/j.1551-8833.2006.tb07637.x.

Caudill SP, Schleicher RL, Pirkle JL. 2008. Multi-rule quality control for the age-related eye disease study. Statist Med 27(20):4094–4106, PMID: 18344178, https://doi.org/10.1002/sim.3222.

Costantini MG. 1993. Health effects of oxygenated fuels. Environ Health Perspect 101(suppl 6):151–160, PMID: 8020439, https://doi.org/10.1289/ehp.93101s6151.

Dourson ML, Felter SP. 1997. Route-to-route extrapolation of the toxic potency of MTBE. Risk Anal 17(6):717–725, PMID: 9463928, https://doi.org/10.1111/j.1539-6924.1997.tb01278.x.

Hun DE, Corsi RL, Morandi MT, Siegel JA. 2011. Automobile proximity and indoor residential concentrations of BTEX and MTBE. Build Environ 46(1):45–53, https://doi.org/10.1016/j.buildenv.2010.06.015.

Kim D, Andersen ME, Pleil JD, Nylander-French LA, Prah JD. 2007. Refined PBPK model of aggregate exposure to methyl tertiary-butyl ether. Toxicol Lett 169(3):222–235, PMID: 17336003, https://doi.org/10.1016/j.toxlet.2007.01.008.

Lee CW, Mohr SN, Weisel CP. 2001. Toxicokinetics of human exposure to methyl tertiary-butyl ether (MTBE) following short-term controlled exposures. J Expo Anal Environ Epidemiol 11(2):67–78, PMID: 11409007, https://doi.org/10.1038/sj.jea.7500149.

McCarthy JE, Tiemann M. 2006. MTBE in Gasoline: Clean Air and Drinking Water Issues. Congressional Research Service Reports 26. https://digitalcommons.unl.edu/crsdocs/26 [accessed 25 October 2019].

Moolenaar RL, Hefflin BJ, Ashley DL, Middaugh JP, Etzel RA. 1994. Methyl tertiary butyl ether in human blood after exposure to oxygenated fuel in Fairbanks, Alaska. Arch Environ Health 49(5):402–409, PMID: 7524452, https://doi.org/10.1080/00039896.1994.9954993.

National Research Council. 1996. *Toxicological and Performance Aspects of Oxygenated Motor Vehicle Fuels*. Washington, DC: The National Academies Press.

National Science and Technology Council. 1997. *Interagency Assessment of Oxygenated Fuels*. Washington, DC: National Science and Technology Council, Committee on Environment and Natural Resources.

Nihlén A, Wâlinder R, Löf A, Johanson G. 1998. Experimental exposure to methyl tertiary-butyl ether. II. Acute effects in humans. Toxicol Appl Pharmacol 148(2):281–287, PMID: 9473536, https://doi.org/10.1006/taap.1997.8342.

Pirkle JL, Sampson EJ, Needham LL, Patterson DG, Ashley DL. 1995. Using biological monitoring to assess human exposure to priority toxicants. Environ Health Perspect 103(Suppl 3):45–48, PMID: 7635111, https://doi.org/10.1289/ehp.95103s345.

Prah J, Ashley D, Blount B, Case M, Leavens T, Pleil J, et al. 2004. Dermal, oral, and inhalation pharmacokinetics of methyl tertiary butyl ether (MTBE) in human volunteers. Toxicol Sci 77(2):195–205, PMID: 14600279, https://doi.org/10.1093/toxsci/kfh009.

U.S. Congress. 2005. H.R.6–Energy Policy Act of 2005. 109th Congress (2005–2006). https://www.congress.gov/bill/109th-congress/house-bill/6 [accessed 16 October 2019].

U.S. DOE (U.S. Department of Energy). 2014. U.S. Consumption of Ethanol and MTBE Oxygenates. https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fafdc.energy.gov%2Ffiles%2Fu%2Fdata%2Fdata_source%2F10322%2F10322_ethanol_mtbe_oxygenate_consumption.xlsx [accessed 16 October 2019].

U.S. Energy Information Administration. 2016. Almost all U.S. gasoline is blended with 10% ethanol. Today in Energy, May 4, 2016. https://www.eia.gov/todayinenergy/detail.php?id=26092 [accessed 16 October 2019].

U.S. Energy Information Administration. 2019. Petroleum & other liquids. https://www.eia.gov/dnav/pet/hist/LeafHandler.ashx?n=PET&s=M_EPOOXT_YOP_NUS_1&f=M [accessed 16 October 2019].

U.S. EPA (Environmental Protection Agency). 2016. Methyl Tertiary Butyl Ether (MTBE). Underground Storage Tanks. https://archive.epa.gov/mtbe/web/html/storage.html [accessed 16 October 2019].

Vainiotalo S, Kuusimäki L, Pekari K. 2006. Exposure to MTBE, TAME and aromatic hydrocarbons during gasoline pump maintenance, repair and inspection. J Occup Health 48(5):347–357, PMID: 17053301, https://doi.org/10.1539/joh.48.347.

Vayghani SA, Weisel C. 1999. The MTBE air concentrations in the cabin of automobiles while fueling. J Expo Anal Environ Epidemiol 9(3):261–267, PMID: 10412674, https://doi.org/10.1038/sj.jea.7500037.