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Physiologically based pharmacokinetic rat model for methyl *tertiary*-butyl ether; comparison of selected dose metrics following various MTBE exposure scenarios used for toxicity and carcinogenicity evaluation

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ABSTRACT

There are a number of cancer and toxicity studies that have been carried out to assess hazard from methyl *tertiary*-butyl ether (MTBE) exposure via inhalation and oral administration. MTBE has been detected in surface as well as ground water supplies which emphasized the need to assess the risk from exposure via drinking water contamination. This model can now be used to evaluate route-to-route extrapolation issues concerning MTBE exposures but also as a means of comparing potential dose metrics that may provide insight to differences in biological responses observed in rats following different routes of MTBE exposure. Recently an updated rat physiologically based pharmacokinetic (PBPK) model was published that relied on a description of MTBE and its metabolite *tertiary*-butyl alcohol (TBA) binding to α2u-globulin, a male rat-specific protein. This model was used to predict concentrations of MTBE and TBA in the kidney, a target tissue in the male rat. The objective of this study was to use this model to evaluate the dosimetry of MTBE and TBA in rats following different exposure scenarios, used to evaluate the toxicity and carcinogenicity of MTBE, and compare various dose metrics under these different conditions. Model simulations suggested that although inhalation and drinking water exposures show a similar pattern of MTBE and TBA exposure in the blood and kidney (i.e. concentration–time profiles), the total blood and kidney levels following exposure of MTBE to 7.5 mg/ml MTBE in the drinking water for 90 days is in the same range as administration of an oral dose of 1000 mg/kg MTBE. Evaluation of the dose metrics also supports that a high oral bolus dose (i.e. 1000 mg/kg MTBE) results in a greater percentage of the dose exhaled as MTBE with a lower percent metabolized to TBA as compared to dose of MTBE that is delivered over a longer period of time as in the case of drinking water.

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Methyl *tert*-butyl ether (MTBE) is an oxygenated fuel additive which can be used to improve combustion efficiency in unleaded gasoline and has been the most commonly used additive in Reformulated Gasoline in response to the 1990 Clean Air Act Amendment. Exposure via inhalation was a major concern for public health due to its use as a fuel additive, however currently the primary concern to the general public is exposure from contaminated groundwater (Stern and Tardiff, 1997). MTBE-contaminated water sources have been detected throughout the US; the range of detection in water sources is typically 0.26–210 μg/L; the majority of samples are < 5 μg/L with less than 1% of samples >20 μg/L. USEPA has a drinking water advisory for MTBE; the recommended range is 20–40 μg/L based on taste and odor (USEPA, 1997).

MTBE is rapidly absorbed from the gastrointestinal and respiratory tract of exposed rats (Miller et al., 1997). MTBE is eliminated mainly via two pathways; exhalation of unchanged MTBE in the expired air and demethylated by cytochrome P450; predominately via CYP2B1 with CYP2E1 having a minor role (Brady et al., 1990; Hong et al., 2001). MTBE is metabolized to *tertiary*-butyl alcohol (TBA) and formaldehyde, although measurements of formaldehyde have not been reported *in vivo* (Miller et al., 1997; McGregor, 2006). The two main metabolic products derived from metabolism of TBA are 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid (Bernauer et al., 1998), both of which have been detected in urine of rats and humans exposed to MTBE (Amberg et al., 1999).

MTBE is a health concern due to carcinogenic effects noted in rats and mice exposed either by oral gavage or inhalation. An increased incidence of hepatocellular adenomas occurred in female CD-1 mice following chronic inhalation exposure to 3000 ppm MTBE (Bird et al., 1997). However, due to the high exposure concentration and the controversy concerning the relevance of mouse

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liver tumors to humans, the responses observed in rats are primarily the main focus for risk assessment purposes. The subchronic and chronic studies conducted in rats to evaluate the carcinogenic effects from exposure to MTBE are summarized in Table 1. Inhalation exposure of MTBE caused increased incidence of interstitial cell adenomas of the testes and renal tubular cell adenomas and carcinomas in male F344 rats (Bird et al., 1997). Chronic oral gavage administration of MTBE to Sprague–Dawley (SD) rats resulted in an increase in Leydig cell tumors in male rats administered 1000 mg/kg MTBE and an MTBE dose-related increase in the incidence in combined lymphoma and leukemia in female rats (Belpoggi et al., 1995). The combined lymphomas and leukemia described in this study have been strongly debated as to their association with MTBE administration (Caldwell et al., 2008; Schoeb et al., 2009). At this time a chronic MTBE drinking water study is in progress that may provide further insight into the hazard associated with exposure to MTBE through a more relevant oral exposure scenario than gavage dosing.

Chronic exposure of *tertiary*-butyl alcohol (TBA), a major metabolite of MTBE, via drinking water caused renal tumors in male F344 rats and thyroid follicular cell tumors in female B6C3F1 mice (Cirvello et al., 1995). The male rat-specific renal tumors following exposure to MTBE and TBA has been postulated to be due in part to the ability of these chemicals to bind to α2u-globulin and elicit a syndrome referred to as α2u-globulin nephropathy (Borghoff et al., 1990; Prescott-Mathews et al., 1997, 1999; Borghoff et al., 2001). Chemical binding of MTBE and TBA to α2u-globulin in male rat kidneys has recently been included in a physiologically based pharmacokinetic (PBPK) model used to describe MTBE inhalation exposure to rats (Leavens and Borghoff, 2009). Incorporation of MTBE and TBA binding to α2u-globulin and a decrease in catabolism of the protein with this binding allowed the model to predict the dosimetry of both MTBE and TBA in the male rat kidney.

In evaluating MTBE-induced tumor responses in rats, the various routes of exposure and the sensitivity of the different strains of rats used in each of these assays need to be considered. Inhalation exposure for 6 h a day, 5 days a week was conducted in F344 male and female rats for 90 days and 2 years (Bird et al., 1997). Oral gavage of MTBE (in olive oil) was administered to Sprague–Dawley male and female rats 4 days a week for 104 weeks or 5 days a week (in corn oil) for 90 days (Belpoggi et al., 1995; Robinson et al., 1990). Most recently a 90-day study was conducted in male and female Wistar Han rats and currently a 2-year study is underway to evaluate the toxicity and carcinogenicity of MTBE administered in the drinking water (Bermudez et al., 2009). The responses observed in all three strains under the various exposure scenarios will be used as weight of evidence in hazard identification. The challenge comes in interpretation of various responses without the knowledge of how MTBE and TBA are handled by the different strains and under different exposure scenarios. Route of exposure and exposure scenario (timing of dose administration/exposure) will most likely have the most influence on total MTBE and TBA exposure. Specific dose metrics of MTBE and TBA (i.e. peak MTBE or TBA, area under the MTBE or TBA blood or target tissue concentration curve, amount of MTBE metabolized, etc.) following different exposure scenarios will provide insight in understanding possible response differences when comparing the various rodent toxicity and carcinogenicity assays. Since the current PBPK model does not describe testes or bone marrow as separate compartments, blood can be used as a surrogate tissue for these potential target sites.

The objective of this investigation is to compare specific dose metrics of MTBE and TBA under the exposure scenarios used to assess the toxicity and carcinogenicity of MTBE. The most recent PBPK model verified in rats was used with the incorporation of a description of oral administration either by gavage or via drinking water. Although the chronic exposures were for 2 years, the model

Table 1
MTBE toxicity and carcinogenicity studies conducted in rats.

Rat strain	Route of administration	Dose/exposure concentration	Subchronic study (~90 days)	Chronic study	Reference
F344	Inhalation, 6 h a day, 5 days per week, 13 weeks	0, 400, 3000, 8000 ppm	Male rats: increase in relative weight of liver and kidney, at 8000 ppm; increase in hyaline droplets in renal proximal tubules		Bird et al. (1997)
F344	Inhalation, 6 h a day, 5 days per week, for 104 weeks	0, 400, 3000, 8000 ppm		Renal and Leydig cell tumors in males rats	Bird et al. (1997)
Sprague–Dawley	Oral gavage in corn oil, 5 days per week for 90 days	0, 100, 300, 900, 1200 mg/kg	Male rats: increase in absolute and relative kidney weight; chronic nephropathy and an increase in hyaline droplets in proximal tubular cells		Robinson et al. (1990)
Sprague–Dawley	Oral gavage in olive oil, 4 days per week, 104 weeks, maintained until death (~166 weeks)	0, 250, 1000 mg/kg		No toxicity reported at any dose; Leydig cell tumors in male rats, lymphoma and leukemia combined in female rats	Belpoggi et al. (1995)
Wistar Han	Drinking water (24/7) for 93 days	0, 0.5, 3, 7, 15 mg/ml	Decreased water consumption and body weight gain; α2u-globulin nephropathy in males (7.5 and 15 mg/ml)		Unpublished final report
Wistar Han	Drinking water (24/7) for 6, 12 or 24 months	0, 0.5, 3, 7.5 mg/ml for males; 0, 0.5, 3, 15 mg/ml for females	6- and 12-month toxicity; Manuscript in preparation	24-month cancer Final Report in preparation	Bermudez et al. (2009); Final Report in preparation

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