Attachment 1

Health Effects of Exposure to Methyl Tertiary Butyl Ether (MTBE)

Background

Methyl tertiary butyl ether (MTBE) (CAS No. 1634-04-4) is a volatile organic compound used almost exclusively as an oxygenate in unleaded gasoline to improve combustion efficiency. In the past it also had limited use as a therapeutic drug for dissolving cholesterol gallbladder stones. Currently, MTBE is added at 11% by volume to almost all of the gasoline used in California, although on March 25, 1999 Governor Gray Davis signed Executive Order D-5-99 requiring that its use in fuel in California be discontinued by December 31, 2002. Due to its use as a fuel additive, MTBE is produced in high volume; it was the second most-produced chemical in the U.S. in 1997.

MTBE is identified under the section 112(b) of the U.S. Clean Air Act Amendments of 1990 [42 USC Sec 7412(b)] as a Hazardous Air Pollutant (HAP). This followed the U.S. EPA's determination that it is known to have, or may have, adverse effects on human health or the environment. On April 8, 1993, the California Air Resources Board (ARB) identified, by regulation, all 189 of the then listed HAPs (including MTBE) as Toxic Air Contaminants (TACs). This was in response to the requirement of Health and Safety Code Section 39657(b).

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 Public Health Goals (PHGs) for contaminants in drinking water, based on public health considerations. OEHHA published a review of the health effects of MTBE. This review included identification of critical health effects, and a recommended PHG based on an estimated carcinogenic potency, which was adopted by OEHHA in March 1999. In the review, OEHHA concluded that the data on carcinogenicity of MTBE were sufficient to propose a public-health protective PHG based on carcinogenicity.

The ARB requested on April 26, 1999 that OEHHA provide a health risk assessment of MTBE for the inhalation exposure pathway, in support of its program for evaluation, and possible regulation of TACs. As noted by the ARB, groundwater cleanup technology may lead to airborne MTBE. Local air pollution control districts require permits and health risk assessments for such activities. Since OEHHA has recently performed a review and analysis of MTBE health effects under the PHG program, this report (OEHHA, 1999; attached) forms a suitable basis for the evaluation requested by ARB. The remainder of this memorandum summarizes the findings on MTBE health effects, and presents a calculation of carcinogenic potency in a form suitable for estimating risks from inhalation exposure to MTBE, using the same basis in data and calculation methods as were used for the PHG recommendation. As noted in Health and Safety Code Section 39650(e), while absolute and undisputed scientific evidence may not be available to

determine the exact nature and extent of risk from toxic air contaminants, it is necessary to take action to protect public health. Furthermore, a toxic air contaminant is identified in Health and Safety Code Section 39655 (a) as an air pollutant which may cause or contribute to an increase in mortality or in serious illness, or which may pose a present or potential hazard to human health. Thus, while there may be some controversy as to the applicability to humans of the specific animal carcinogenicity end-points observed with MTBE, OEHHA has based the PHG on carcinogenicity and develops herein a unit risk factor for use in estimating impacts of airborne exposures to MTBE.

Summary of Health Effects of MTBE

Some acute and chronic non-cancer health effects of MTBE have been reported. Irritant effects have been described in humans. In animal studies at or near lethal doses, ocular and mucous membrane irritation, ataxia, labored breathing, CNS depression, and general anesthetic effects were observed. The rat kidney is a target of toxicity in subacute, subchronic and chronic studies. However, most of these effects are observed at relatively high doses, and are not expected to be important at levels typical of human environmental exposure to MTBE.

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 inhalation exposure. While no effects on fertility endpoints were reported, these studies provide evidence for possible adverse effects of MTBE on development.

Carcinogenicity of MTBE has been observed in animals, by oral and inhalation routes. In lifetime gavage studies in rats (Belpoggi et al. 1995, 1998), increases in tumor incidences were observed in both sexes, while in 24-month inhalation studies in rats of a different strain (Chun et al. 1992), increases in tumors were observed in male rats. These included statistically significant increases in Leydig interstitial cell tumors of the testes in both the inhalation and gavage studies. Statistically significant increases in renal tubular tumors were also observed in male rats exposed via inhalation, and increases in leukemias and lymphomas (combined) in female exposed orally. In 18-month inhalation studies in mice (Burleigh-Flayer et al., 1992), statistically significant increases in hepatocellular carcinomas were observed in males, and adenomas and combined adenomas and carcinomas in females.

Epidemiological studies of the carcinogenic effects of MTBE are not available, so direct evidence of carcinogenicity in humans is lacking. The evidence for the carcinogenicity of methyl tertiary butyl ether (MTBE) is therefore based on the several findings in animal studies. However, critics have questioned the interpretation of each of the individual findings. The carcinogenicity studies have been reviewed, and the issues that have been raised are addressed, by OEHHA (1999). In spite of the acknowledged uncertainties in interpretation, OEHHA considers that the observed carcinogenic effect in animals is an appropriate basis for development of a health protective level for human exposures to MTBE, either in drinking water (as undertaken for the PHG) or in air.

At present, the mechanism by which MTBE induces the various tumors observed in animals remains unknown. MTBE is negative in most of the standard genotoxicity tests *in vitro* or *in vivo*. Two positive reports were identified, but the significance of these is unclear. Formaldehyde and tertiary butyl alcohol (TBA), both primary metabolites of MTBE, exhibit tumorigenic activity in animal studies. TBA and MTBE both induce renal tubular tumors in the male Fisher rat; and formaldehyde and MTBE both have produced lymphohematopoietic cancers in Sprague Dawley rats exposed orally.

Cancer Dose Response Assessment

Cancer potency estimates were made, based on the recommended practices of the 1996 United States Environmental Protection Agency proposed guidelines for carcinogenic risk assessment (U.S. EPA 1996). In view of the uncertainty over the mechanism(s) by which the tumorigenic effects of MTBE (or of its metabolite TBA) are produced, the default methodology, which involves linear extrapolation of the projected risk to low doses, was used for cancer dose response assessment. Carcinogenic potency is expressed as a cancer slope factor (CSF), which defines an upper 95% confidence bound on the relationship between estimated human risk and dose, at low levels of exposure.

A pharmacokinetic model was used in analyzing the tumor incidence data in the rat. This allowed comparison of the oral and inhalation routes, and corrected for nonlinearities in the relationship between applied and internal dose. However, pharmacokinetic data suitable for incorporation into a model are not available for the mouse. Therefore, only the potency estimates obtained in the rat were used in this risk assessment. The results (based on applied dose) in rats and mice are comparable, so the use of the rat data is consistent with the policy of selecting appropriately sensitive species as the basis for the estimate of human potency.

In the studies by Chun et al. (1992) and Burleigh-Flayer et al. (1992), relatively severe mortality was seen in the highest dose groups, and as a result the mice and the male rats were exposed for less than the standard lifetime. These experimental flaws are not so severe as to preclude the use of the data, nor worse than those seen in many studies that have been successfully used for risk assessment on other compounds. There are, however, additional problems in the case of the testicular interstitial cell tumors observed in male rats by Chun et al. (1992). The control incidence of these tumors in the experiment was lower than the historical incidence reported by the study authors in animals from the source colony. The potency estimate obtained with this data set is slightly divergent from the other estimates obtained in the rat. The value derived from this data set is therefore regarded with lower confidence than the others obtained in this analysis, and was not included in the determination of a recommended potency.

The other values obtained in the rat are consistent, and were judged to have similar confidence levels, and so were included in the preferred potency estimate. This is the geometric mean of the potency estimates obtained for kidney adenomas and carcinomas combined (1.8×10^{-3}) in the inhalation study in the male rat (Chun et al. 1992), and the estimates for male rat Leydig interstitial cell tumors (1.55×10^{-3}) and the leukemia and lymphomas in female rats (2.09×10^{-3}) in the rat oral study (Belpoggi et al. 1995, 1998).

The combined use of these data yields an estimated CSF of 1.8×10^{-3} (mg/kg-day)$^{-1}$. The true value of the human cancer potency may in fact have a lower bound of zero (*i.e.* there may be no human cancer risk at very low doses), 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 data showing, with a substantial level of confidence, that the animal tumors are irrelevant to humans at environmental exposure levels, a health protective default approach was taken to estimate cancer risk.

Since a pharmacokinetic model was not available for MTBE uptake, distribution and metabolism in humans, default assumptions were used to extrapolate from risk estimates in the experimental animals (rats) to the human situation. The CSF was calculated as a "oral equivalent" potency, in mg/kg-day. It is assumed that low oral doses would be essentially 100% absorbed, so no correction is required when this potency is used to estimate risks from oral exposures. However, in order to estimate risks from inhalation exposures it is necessary to have an estimate of the percentage uptake of inhaled MTBE at low atmospheric concentrations. OEHHA (1999) assumed that humans absorb 50% of inhaled MTBE at low doses. This estimate is derived primarily from the 42 to 49% respiratory uptake observed among 10 healthy male volunteers inhaling 5 to 50 ppm for 2 hours (Nihlen *et al.*, 1998). This represents a small study of short duration exposures to relatively high concentrations of MTBE, and respiratory uptake among humans inhaling low concentrations for long periods is unknown. As absorption at low concentrations may in some cases be greater than that at higher concentrations, the assumption of 50% absorption should be viewed as a best estimate rather than an upper-bound estimate or health-protective assumption.

On this basis, and assuming a 70 kg human inhaling 20 m^3 per day the oral equivalent potency estimate above can be converted to an inhalation potency estimate (cancer unit risk factor or URF) of 9.3×10^{-7} ppb^{-1}, or 2.6×10^{-7} ($\mu g/m^3$)$^{-1}$. As in the case of the oral estimate, this is subject to a number of statistical and biological uncertainties. It is an upper bound estimate of potency. The true value of the carcinogenic potency in humans might exceed this value, but this is considered unlikely. On the other hand the true value may be less than the upper bound estimate. A detailed discussion of both the statistical and biological uncertainties in the potency estimate for MTBE appears in the risk characterization section of the accompanying PHG document (OEHHA, 1999).

The health effects of MTBE, including estimates of cancer risk, were also reviewed and discussed in the Health Effects section (Froines *et al.*, 1998) of a report, prepared by the University of California, to the governor and legislature of the State of California. This was mandated by Senate Bill 521 (1997). Conclusions of this report on the human health effects of MTBE exposure were similar to those described in the PHG document (OEHHA 1998).

References

Belpoggi F, Soffritti M, Filippini F, Maltoni C (1997). Results of long-term experimental studies on the carcinogenicity of methyl tert-butyl ether. *Annals NY Acad Sci* **837**:77-95.

Belpoggi F, Soffritti M, Maltoni C (1995). Methyl tertiary-butyl ether (MtBE) - a gasoline additive - causes testicular and lymphohaematopoietic cancers in rats. *Toxicol Ind Health* **11**:119-149.

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.

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, PA: Bushy Run Research Center.

Froines J, Collins M, Fanning E, McConnell R, Robbins W, Silver K, Kun H, Mutialu R, Okoji R, Taber R, Tareen N, Zandonella C (1998). *Health & Environmental Assessment of MTBE: Report as sponsored by Senate Bill 521*. Volume II: Human Health Effects. An Evaluation of the Scientific Peer-Reviewed Research and Literature on the Human Health Effects of MTBE, its Metabolites, Combustion Products and Substitute Compounds. University of California: available at: http://tsrtp.ucdavis.edu/.

Nihlen A, Lof A, Johanson G (1998). Experimental exposure to methyl tertiary-butyl ether. I. Toxicokinetics in humans. *Toxicol Appl Pharmacol* **148**(2):274-80.

Office of Environmental Health Hazard Assessment (OEHHA, 1999). *Public Health Goal for Methyl Tertiary Butyl Ether (MTBE) in Drinking Water* (Final). Sacramento, CA.

U.S. EPA (1996). 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.