Toxicological Review of Methyl- and Ethyl-tertiary-Butyl Ethers

Douglas McGregor

Toxicity Evaluation Consultants, Aberdour KY3 0TU, UK
mcgregortec@btinternet.com

Abstract Metabolism and kinetic studies have shown that the overall elimination of ETBE and MTBE from blood in volunteers was multiphasic, (two or four phases in the case of ETBE and two or three phases for MTBE). The half-lives varied in different experiments and ranged from a few minutes for early phases up to a terminal half-life of 33 h in one experiment each with ETBE and MTBE. The kinetic data obtained from experiments with rats exposed to ETBE are restricted to a statement that the apparent half-life of elimination of ETBE from blood is about 0.8 h, but it is not clear if this only refers to an initial half-life. Some guidance may be possible from the known behaviour of MTBE. Its elimination from rat blood appears to be biphasic, with an initial half-life of less than 1 h and second half-lives ranging from 37 h to 92 h (reviewed in McGregor 2006). Elimination occurs in exhaled air (mainly unchanged ethers) and urine (metabolites).
The main circulating metabolite is TBA formed by oxidation of ethers by cytochrome isoenzymes, while the main urinary metabolites are 2-hydroxyisobutyrate and 2-methyl-1,2-propanediol. The half-life of TBA in the blood of volunteers exposed to the ethers is about 8 to 12 h. Comparable measurements have not been made in rodents. Exposure of volunteers to the ethers at concentrations of up to 25 or 50 ppm (106 or 212 mg/m³) for 2 h produced a slight impairment (3.2 to 4.4%) in pulmonary function, but other measures and subjective reports show little effect of exposure. Non-human experimental studies have not revealed significant general toxicity, neurotoxicity, toxicity to reproduction or genotoxicity. Neither MTBE nor ETBE is acutely toxic following oral, dermal or inhalation administration or an eye irritant, while MTBE, but not ETBE is considered to be a skin irritant. Sensitisation has not been demonstrated with either compound in guinea-pig maximisation tests.

Other studies of systemic toxicity of MTBE and ETBE were largely restricted to a nephropathy in male rats that was associated with the accumulation of hyaline droplets that immunohistochemically stained for α₂u-globulin. Apparently, the same type of nephropathy occurs in TBA-treated rats. In addition, MTBE exposure during a two-year study in rats led to exacerbation in males of the spontaneously occurring chronic progressive nephropathy (CPN), even to the most severe or “end-stage” in some cases. The effects of MTBE, ETBE and TBA on renal tubule cells are weak, specific to male rats, and not observed in mice of either sex. They are not necessarily due to metabolically generated TBA alone, although this metabolite, which is common to both ethers, does persist in the blood of rats at higher concentrations and for a longer time than the parent ethers. In vitro studies with MTBE demonstrated its specific binding to kidney proteins from male rats and that it interacts with α₂u-globulin. Under the conditions of these experiments, metabolism of MTBE to TBA was not likely to be significant. It is reasonable to predict that similar experiments with ETBE would produce similar results. The available data on ETBE are not extensive, but they support the hypothesis that the mode of action is dependent on α₂u-globulin nephropathy, which is widely considered to be of no human relevance. In CD-1 mice of both sexes there was a minimal renal nephropathy, but this occurred in all groups, including controls, at frequencies that varied between 27% and 64% with little indication of a dose-response relationship. It is unlikely to have been caused by ETBE treatment. The only other effect of note was treatment-associated bone marrow congestion in female rats exposed to 1750 ppm (7420 mg/m³) ETBE for 3 months. There was no accompanying effect on the haematopoietic cell population, and an increase in mean corpuscular volume was not considered clinically relevant. No similar effect was reported for male rats or for mice of either sex.

With regard to carcinogenicity, low incidences of renal tubule cell adenomas were found in male rats treated with MTBE. This effect appears to be associated with exacerbation of CPN to end-stage as well as α₂u-globulin nephropathy induction. Both conditions are male rat specific. TBA also induces adenomas of the renal tubule cells and this response is also associated with α₂u-globulin nephropathy. Neither of the conditions predisposing to renal tubule cell neoplasia has human relevance. ETBE has not been tested for carcinogenicity, but results from short-term studies suggest that it would also induce kidney tumours by the same modes of action as MTBE.

Thyroid follicular cell adenomas were increased in female mice treated with TBA, but this result lacks any independent supporting evidence from a number of studies in mice and rats. There was no evidence for a hepatic effect of TBA within this mouse carcinogenicity study; therefore, no internal evidence exists for a hormonal mechanism of thyroid follicular cell induction. No thyroid neoplasms were increased in the carcinogenicity studies of MTBE.