



STATEMENT

Synopsis of Research Report 102

HEALTH
EFFECTS
INSTITUTE

Metabolism of Ether Oxygenates Added to Gasoline

INTRODUCTION

The Clean Air Act Amendments of 1990 required use of oxygenated fuels in areas that exceeded the National Ambient Air Quality Standards for carbon monoxide and in areas with very high ozone levels. Adding oxygenates, such as MTBE (methyl *tert*-butyl ether), to gasoline promotes more efficient combustion and reduces emission of carbon monoxide, ozone-forming hydrocarbons, and some air toxics, by increasing the oxygen content of the fuel. On the other hand, some oxygenates may increase emission of toxic compounds such as formaldehyde or acetaldehyde. Increased use of MTBE in fuel in the early 1990s led to complaints of unpleasant odor, headaches, and burning of eyes and throat. After reviewing the literature, HEI issued a request for applications to fund research on the comparative metabolism of ether oxygenates, such as MTBE, ETBE (ethyl *tert*-butyl ether), and TAME (*tert*-amyl methyl ether). The three studies funded are presented in this Research Report.

APPROACH

The studies reported here were initiated to increase our knowledge of the metabolism of ether oxygenates in humans and other species. Dr Jun-Yan Hong (the University of Medicine and Dentistry of New Jersey – Robert Wood Johnson Medical School) used rat and human liver cells to determine the relative contribution of different members of a family of liver enzymes (cytochrome P450 [CYP] isozymes) to the metabolism of MTBE, ETBE and TAME. Blood samples from human volunteers who reported that they were sensitive to the health effects of MTBE were examined by Hong and colleagues, in order to determine whether genetic variants of CYP isozymes were present. Dr Wolfgang Dekant (University of Würzburg) exposed rats and human volunteers by inhalation to two concentrations of MTBE, ETBE or TAME in order to provide detailed

data for interspecies comparison. He also exposed human volunteers by ingestion to MTBE or TAME to compare metabolic pathways after inhalation and ingestion of these compounds. Dr Janet Benson (Lovelace Respiratory Research Institute) exposed rats by inhalation to several concentrations of MTBE alone or to MTBE in combination with gasoline vapors in order to determine how the presence of gasoline affects the uptake, kinetics, metabolism and excretion of MTBE.

RESULTS AND IMPLICATIONS

These three studies have advanced our understanding of the metabolism of gasoline ethers after inhalation. The study by Dr Hong identified one particular CYP isozyme, CYP2A6, as a major enzyme involved in metabolism of MTBE, ETBE and TAME at the concentrations studied. Although the relative importance of this isozyme over others (such as CYP2E1, which was found to be important in previous studies) remains undetermined, the results invite research into the involvement of these and other isozymes in the health effects of ethers. Dr Hong also found several genetic variants of CYP2A6 in some human volunteers who reported sensitivity to MTBE. Further research should evaluate a larger group of sensitive individuals to identify the prevalence of such isozymes in the general population and to determine whether expression of these isozymes may contribute to the reported sensitivity.

The study by Dr Dekant provides a detailed characterization of metabolites of MTBE, ETBE and TAME. The pathways for metabolism of MTBE and ETBE were found to be similar, whereas the metabolism of TAME followed a slightly different pathway with more steps involved and the formation of more metabolites. For all three ethers the pathways of metabolism in rats and humans were similar, and the blood levels were not significantly

This Statement, prepared by the Health Effects Institute, summarizes three research projects funded by HEI from 1996 to 1999 and conducted by Dr Jun-Yan Hong at University of Medicine and Dentistry of New Jersey – Robert Wood Johnson Medical School, Dr Wolfgang Dekant at the University of Würzburg, and Dr Janet Benson at the Lovelace Respiratory Research Institute. The Research Report, *Metabolism of Ether Oxygenates Added to Gasoline*, contains the three detailed Investigators' Reports, a Preface, and a Commentary on the studies prepared by the Institute's Health Review Committee. It can be requested from HEI (see reverse side). OXYGENATES 102

different although the rate of metabolism was more rapid in rats. The metabolic pathway after ingestion of MTBE and TAME in humans was almost identical to the pathway after inhalation. No first pass effect—in which the liver metabolizes a compound before it enters into the general circulation—was observed after ingestion, and rates of metabolism were similar for both exposure routes. These data can be used, therefore, in extrapolating results across species and routes of exposure for the human health risk assessment of ether exposure by inhalation or ingestion.

The study by Dr Benson and coworkers has provided detailed data on the metabolism and disposition of MTBE and its metabolites in rats after inhalation of MTBE alone and of MTBE with gasoline vapors. The investigators showed that MTBE was rapidly taken up into the blood and distributed evenly over body compartments (such as liver, kidney, and lungs). The uptake and metabolism were not linear between 4 and 400 ppm, suggesting that saturation may have occurred at the highest dose. These results indicate that caution is needed in using linear extrapolation of high doses to low doses for human health risk assessment of MTBE

exposure. Inhalation of MTBE in combination with gasoline vapor (200 ppm) reduced the total amount of MTBE taken up into the body and increased the amount of MTBE and metabolites exhaled in breath, suggesting that the toxic effects of MTBE during refueling may be lower compared to exposure to MTBE by itself.

In conclusion, the investigators successfully addressed the relative importance of certain CYP isozymes, the metabolic pathways after ether inhalation and ingestion, and the effects of coexposure to gasoline vapors on ether metabolism; some results will require further research to understand the range of their implications. Some avenues of needed research include: investigating the prevalence of different CYP isozymes in the general population, and determining whether the lack of a specific enzyme correlates with increased susceptibility to the health effects of oxygenates; further research into the toxicity of ether metabolites; and further research into the effects of exposure to mixtures (including gasoline vapors) on metabolism and the health effects of exposure to individual compounds, such as oxygenates.

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