

## A PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODEL FOR METHYL TERTIARY BUTYL ETHER (MTBE): A REVIEW OF EXISTING MODELS.

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MTBE is a volatile organic compound used as an oxygenate additive to gasoline, added to comply with the 1990 Clean Air Act. Previous PBPK models for MTBE were reviewed and incorporated into EPA's present model designed using the Exposure Related Dose Estimating Model (ERDEM) software. EPA's model also included an explicit pulmonary compartment. Organs (compartments) included in the model were: liver (for metabolism), fat, kidney, brain, and slowly and rapidly perfused compartments. Both inhalation and oral dosing were included as routes of exposure. Numerous simulations were performed to compare performance between present and previous MTBE PBPK models with available data : (400 and 8000 ppm inhalation exposure for 6 hours, and oral dosing of 40 and 400 mg/kg to a 215g rat). Physiological and metabolic parameters were changed to human values and model performance was re-examined. Using available human data (inhalation, dermal and oral exposures), model comparisons were matched to MTBE peak values, MTBE area under the curve, and peak concentration for the metabolite TBA. The largest percent difference observed between rat data and simulations was 40 % (peak MTBE). For humans, the modeled output was within 3-fold of the reported experimental value. An uncertainty analysis (representing errors due to parameters or model structure) and variability analysis (attempting to include assumed changes due to differences in the general population) were performed for different species. The simulation results showed the variability in rats and humans to be similar. In summary, a revised EPA PBPK model for MTBE has been tested against previous models and across different species. Exposure to dose relationships obtained using this PBPK model may be useful in extrapolation across species and routes of exposure. *(This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.)*