

Sapphire News

Using Physiologically Based Pharmacokinetic Modeling to Address Nonlinear Kinetics and Changes in Rodent Physiology and Metabolism Due to Aging and Adaptation in Deriving Reference Values for Propylene Glycol Methyl Ether and Propylene Glycol Methyl Ether Acetate.

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Reference values, including an oral reference dose (RfD) and an inhalation reference concentration (RfC), were derived for propylene glycol methyl ether (PGME), and an oral RfD was derived for its acetate (PGMEA). These values were based upon transient sedation observed in F344 rats and B6C3F1 mice during a two-year inhalation study. The dose-response relationship for sedation was characterized using internal dose measures as predicted by a physiologically based pharmacokinetic (PBPK) model for PGME and its acetate. PBPK modeling was used to account for changes in rodent physiology and metabolism due to aging and adaptation, based on data collected during weeks 1, 2, 26, 52, and 78 of a chronic inhalation study. The peak concentration of PGME in richly perfused tissues (i.e., brain) was selected as the most appropriate internal dose measure based upon a consideration of the mode of action for sedation and similarities in tissue partitioning between brain and other richly perfused tissues. Internal doses (peak tissue concentrations of PGME) were designated as either no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) based upon the presence or absence of sedation at each time-point, species, and sex in the two year study. Distributions of the NOAEL and LOAEL values expressed in terms of internal dose were characterized using an arithmetic mean and standard deviation, with the mean internal NOAEL serving as the basis for the reference values, which was then divided by appropriate uncertainty factors. Where data were permitting, chemical-specific adjustment factors were derived to replace default uncertainty factor values of ten. Nonlinear kinetics, which were predicted by the model in all species at PGME concentrations exceeding 100 ppm, complicate interspecies and low-dose extrapolations. To address this complication, reference values were derived using two approaches which differ with respect to the order in which these extrapolations were performed: (1) default approach of interspecies extrapolation to determine the human equivalent concentration (PBPK modeling) followed by uncertainty factor application; and (2) uncertainty factor application followed by interspecies extrapolation (PBPK modeling). The resulting reference values for these two approaches are substantially different, with values from the latter approach being 7-fold higher than those from the former approach. Such a striking difference between the two approaches reveals an underlying issue that has received little attention in the literature regarding the application of uncertainty factors and interspecies extrapolations to compounds where saturable kinetics occur in the range of the NOAEL. Until such discussions have taken place, reference values based on the former approach are recommended for risk assessments involving human exposures to PGME and PGMEA.