

Sapphire News

Assessing the dose-dependency of allometric scaling performance using physiologically based pharmacokinetic modeling

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The performance of allometric scaling of dose as a power of body weight under a variety of extrapolation conditions with respect to species, route, exposure intensity, and mechanism/mode of action, remains untested in many cases. In this paper, animal–human internal dose ratio comparisons have been developed for 12 chemicals (benzene, carbon tetrachloride, chloroform, diisopropyl-fluorophosphate, ethanol, ethylene oxide, methylene chloride, methylmercury, styrene, tetrachloroethene, trichloroethene, and vinyl chloride). This group of predominantly volatile and lipophilic chemicals was selected on the basis that their kinetics have been well-studied and can be predicted in mice, rats, and humans using physiologically based pharmacokinetic (PBPK) models. PBPK model predictions were compared to the allometric scaling predictions for interspecies extrapolation. Recommendations for the application of the allometric scaling are made with reference to internal dose measure (mode of action) and concentration level. The results of this assessment generally support the use of scaling factors recommended in the published literature, which includes scaling factors of 1.0 for risk assessments in which toxicity is attributed to the parent chemical or stable metabolite, and -0.75 for dose–response assessments in which toxicity is attributed to the formation of a reactive metabolite from an inhaled compound. A scaling factor of 0.75 is recommended for dose–response assessments of orally administered compounds in which toxicity is attributed to the parent chemical or stable metabolite and 1.0 for risk assessments in which toxicity is attributed to the formation of a reactive metabolite from a compound administered by the oral route. A dose-dependency in the results suggests that the scaling factors appropriate at high exposures may differ from those at low exposures, primarily due to the impact of saturable metabolism.