Physiologically-Based Pharmacokinetic (PBPK) Models Application to Screen Environmental Hazards Related to Adverse Outcome Pathways (AOPs)

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PBPK models are useful in estimating exposure levels based on in vitro to in vivo extrapolation (IVIVE) calculations. Linkage of large sets of chemically screened vitro signature effects to in vivo adverse outcomes using IVIVE is central to the concepts of the National Academy of Sciences' Toxicology in 21st century vision. Except for metabolic clearance, most parameters used to develop PBPK models are readily available in literature, or calculated using chemical structure activity relationships. Lack of computational methods to determine clearance inhibits the application of PBPK models to large set of chemicals without conducting costly and time-consuming experiments. This problem, however, should not exclude the use of PBPK models to screen a large set of chemicals for possible environmental exposure levels that can lead to adverse outcome effects. This can be accomplished by developing "generic" PBPK models. Metabolic clearance capacity in the generic model is set to zero to estimate maximal exposure level (EXPmax) that will yield parent chemical tissue levels equivalent to in vitro levels identified for the signature effects along an identified adverse outcome pathway (AOP). EXPmax levels are then screened against environmental exposure levels (EXPenv). If EXPenv is less than EXPmax, then parent target tissue levels of the chemical under the environmental exposure scenarios will be less than toxicologically-effective in vitro levels (EC50s or LELs), indicating that the assumption of zero clearance is health hazard conservative. For chemicals where EXPenv is larger than EXPmax, metabolic clearance of these chemical may be a critical factor in determining their health risks. *This abstract does not necessarily reflect EPA policy.*