A Computer Simulation Model of Dynamic Interactions Among VOC Hematotoxins in Bone Marrow

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This effort will create a quantitative pharmacokinetic-and-pharmacodynamic (PK-PD) computer simulation model of how hematotoxic volatile organic compounds (VOCs) interact with each other and with hematopoietic cell populations. Its main goal is to develop and test a simulation model that can explain and predict the time course of hematotoxic and cytogenetic damage, including aneuploidy, in animals and people exposed to mixtures of VOCs such as benzene, toluene, ethylbenzene, xylenes, styrene, tetrachloroethylene, and dichloromethane. The results will be submitted for publication and the resulting model can be downloaded and used by other investigators to model interactions among VOCs in affecting detectable endpoints. Endpoints considered include cell kinetics, cell mutation rates, premature recruitment of early (CD34+) hematopoietic stem cells into active cycling and proliferation, and cumulative chromosomal and hematotoxic damage (including aneusomy and aneuploidy, which may be indicators of potential leukemia risk). The computer model will allow investigators to specify time courses for exposures to components of the mixture and will predict resulting time courses for the different endpoints.

Three secondary goals are to (a) use the model to explain and interpret published data on hematotoxic effects of VOC mixtures; (b) use the model to make testable predictions about the toxicity of different time courses of exposures to mixtures; and (c) quantify uncertainties in the model, using sensitivity analyses and Monte Carlo uncertainty analysis. This will show what insights from the model are relatively robust and dependable and where predictions are contingent on assumptions that require more research to validate.

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