Use of Biologically Based Computational Modeling in Mode of Action-Based Risk Assessment – An Example of Chloroform

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Chloroform causes hepatic and renal cancer in rodents through a mode of action characterized by chronic cytolethality and regenerative cellular proliferation. The objective of current work is to develop a new cancer dose-response assessment for chloroform using a physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) model. The PBPK/PD model is based on a mode of action in which the cytolethality of chloroform occurs when the rate of generation of toxic metabolites exceeds the capacity of cellular repair mechanisms. The model specifies a relationship between cytolethality and cell regeneration to simulate labeling index (LI) in rodents exposed to chloroform through inhalation. We are calibrating the model with hepatic and renal LI data and close-chamber gas uptake data on the metabolism of chloroform in both genders of mice and rats, using a Markov Chain Monte Carlo approach. The model scaling behaviors among rodents will provide guidance on the scale-up of the rodent model to a human model. The human model will be used to predict the dose-response for chloroform-mediated cytolethality and proliferative regeneration in liver and kidneys. This human model will be linked to a clonal growth model to predict the additional cancer risk for human exposures associated with cytolethality. The clonal growth model would allow prediction, for example, of chloroform exposures associated with cytolethality but with associated cancer risks below the *de minimus* level of 10-6. A similar modeling approach could be extended to other disinfection-byproducts.