Computational Modeling to Evaluate Candidate Modes of Action for the Carcinogenicity of Arsenic

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Several candidate modes of action, including cytolethality, direct genotoxicity, and oxidative stress, have been proposed to explain the carcinogenic effects of arsenic. The goals of our work are to (1) develop biologically-based computational models of the modes of action to better understand their dose- and time-response behaviors and (2) prioritize the modes with respect to relevance for risk assessment. Our approach in developing a computational model of a mode of action is to first develop a qualitative map of key events. Inclusive and accurate identification of key events is critical. The value of computational modeling lies in its ability to provide non-intuitive insights into dynamic behaviors. This value can only be realized, however, if the model accurately reflects state-of-the-art knowledge about the modes of action. Close consultation between computational modelers and arsenic experimentalists is required to ensure that the model does, in fact, incorporate this knowledge. Identification of the appropriate level of biological detail is also an important aspect of the consultation. There is little point in incorporating large amounts of molecular-level information if corresponding data for parameterization and for the comparison with model predictions are lacking. Thus, to a large extent, the available data, or data that can reasonably be expected to become available, determine level of biological detail. Finally, the quantitative version of the qualitative model is prepared by specifying the appropriate functional relationships between the components of the qualitative model and the associated quantitative parameter values. Ideally, parameters are set to measured values, though values of some parameters can often inferred by optimizing the fit of model predictions to dose-response and time course data. Lack of sufficient, relevant data, however, hinder successful translation of the qualitative model into its quantitative counterpart. Once the quantitative models for candidate modes of action are available, they will be ranked according to their relative abilities to reproduce time-course and dose-response data for endpoints of regulatory interest such as bladder cancer. Use of the preferred model for risk assessment will first require analysis of uncertainty. The uncertainty of the biologically-motivated model should be comparable to or preferably less than that of its default-based counterpart. *This presentation may not reflect the official policies of the U.S. EPA.*