Development of a biologically based dose response (BBDR) model for arsenic induced cancer

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Inorganic arsenic is considered a human carcinogen. The current risk assessment is based on a linear extrapolation of the epidemiological data from a study of exposed populations in Taiwan. However, the proposed mode(s) of action (e.g. altered DNA methylation, altered DNA repair, induced reactive oxygen species, etc.) for arsenic-induced carcinogenesis suggest the possibility of a nonlinear exposure response model at low doses. We are developing a biologically based dose response (BBDR) model for arsenic carcinogenicity. This model will link predictions of tissue dose obtained by PBPK modeling with one or more modes of action leading to arsenic induced cancer. Ongoing efforts include use of expert judgment to identify the mode or modes of action most likely to be linked with arsenic induced cancer (including inorganic arsenic and arsenic metabolites), development of the modeling framework based on the identified modes of action and on data review to characterize the appropriate level of biological detail to incorporate into the first generation model. The trade-off between uncertainty related to model complexity and the amount of biological detail incorporated into the model is an important consideration. In the longer run, this concern will be addressed by iterative rounds of model development and targeted data collection that specifically address model uncertainties. [This abstract does not represent EPA opinion or policy]