Development of a Biologically Based Dose Response Model for Arsenic Induced Cancer

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BIOLOGICAL MODELS

Backgrounds & Objectives

Exposure to inorganic arsenic in drinking water is known to cause cancers of the bladder, lung and skin in human populations. The current cancer risk assessment for inorganic arsenic exposure in drinking water utilizes the default method of linear low dose extrapolation applied to epidemiologic data from Taiwan. Linear low dose extrapolation is used in cancer risk assessment for chemicals when (1) they act as directly DNA-reactive mutagens, or (2) the mode of action is known or insufficiently characterized. In the latter case, this is a conservative health protective default approach used in the absence of information. Use of the default low dose extrapolation approach is controversial for inorganic arsenic because it has not been demonstrated to be a directly DNA-reactive mutagen. In addition, the dose-response function for several proposed modes of action for inorganic arsenic carcinogenesis (for which there is experimental evidence) are likely to be non-linear. The objective of this project is to develop a biologically based dose response model for arsenic carcinogenicity in order to reduce these uncertainties. This model will link predictions of tissue dose obtained by PBPK modeling with one or more modes of action leading to arsenic induced cancer.

Approaches

Ongoing efforts include:

1) Use of expert judgment to identify the mode or modes of action most likely to link tissue dose (predicted by PBPK modeling) with arsenic induced cancer;
2) Development of the modeling framework based on the identified modes of action;
3) Data review to characterize the appropriate level of biological detail to incorporate into the first generation model.

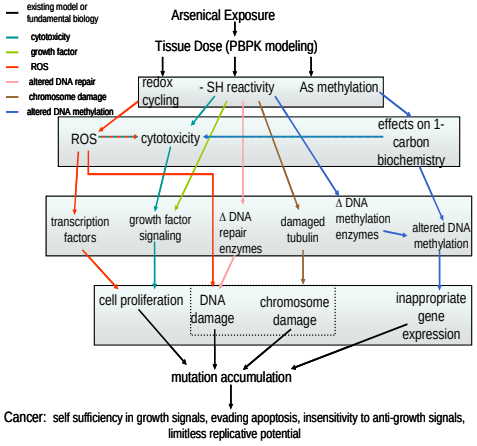

Figure 1 Proposed Framework for Biologically-based Dose Response Modeling for Arsenic Risk Assessment

Results & Conclusions

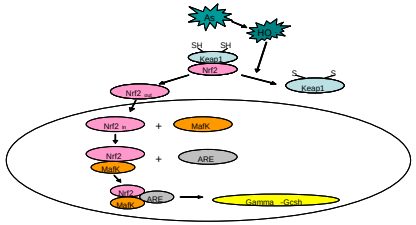

Figure 2 Example Network Indicating the Potential Level of Biological Detail for Arsenic Dose Response Modeling – ROS pathway

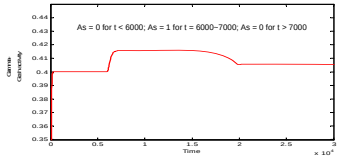

Figure 3 Simulated Time Course of Gamma-Gcsh Activity Induced by Pulse Arsenic Exposure Based on the Example Network

The proposed model will integrate available experimental information (including signaling pathway, gene network, etc) into arsenic dose response modeling to provide reliable prediction of the dose response in low dose region. The model will also be used to help guide experimental design so that the experimental results can be more directly and efficiently applied to low dose extrapolation in arsenic risk assessment.