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

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Backgrounds & Objectives

Exposure to inorganic arsenic in drinking water causes cancers of the urinary bladder, lung and skin in human populations. The current cancer risk assessment for inorganic arsenic 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 react directly with DNA or, (2) the mode of action is unknown or insufficiently characterized. In the latter case, linear low dose extrapolation is considered to be a conservative, health protective approach. When this approach to extrapolation is not data-based, however, it may not identify the actual risk for non DNA-reactive chemicals. Consideration of biological adaptive processes suggests that dose-response functions non-DNA-reactive modes of carcinogenic action for inorganic arsenic are likely to be non-linear. The objective of this project is to develop a biologically based dose response (BBDR) model for arsenic carcinogenicity in humans to reduce the uncertainties associated with the current risk assessment. This BBDR model consists of (1) a PBPK submodel (El-Masri and Kenyon, *Journal of Pharmacokinetics and Pharmacodynamics*) to predict tissue dosimetry, (2) one or more sequences of key events leading to tumor formation, and (3) a multistage clonal growth submodel to predict tumor incidence.

Systems Biology and Dose Response Modeling

Dose response modeling is a key component of quantitative risk assessment for environmental stressors. Quantitative dose response modeling has, however, traditionally made only limited use of data on the biological mechanisms that determine actual dose-response behaviors.

Systems biology involves quantitative evaluation of biological systems through the combination of laboratory experiments and computational modeling. The overall goal of systems biology is to understand how components at lower levels of biological organization, including genes, proteins, and signaling networks, are organized to provide structure and function at the higher levels of organization represented by tissues, organs, individuals and populations.

Incorporation of the systems biology approach into toxicological dose response modeling has the potential to provide more accurate descriptions of the underlying biological mechanisms that determine dose-response behaviors.

In the following section, linkage of a computational model of the cell cycle with a two-stage clonal growth model is described as a conceptual example for integration of systems biology into dose response modeling (Figure 3).

Figure 4 describes the cell cycle model. The description of checkpoint control in the cell cycle is based on Tyson and Novak (*J. Theor. Biol, 210, 249-263, 2001*). The cell cycle consists of G1, S (synthesis), G2 and M (mitosis) phases. Two cell cycle checkpoints are described: G1/S and G2/M. Activation of either one of these checkpoints temporarily halts progression of the cycle to ensure that conditions for progression to the next stage of the cycle are acceptable. For example, activation of a checkpoint provides extra time for repair of DNA damage. Checkpoint arrest increases the cell cycle time and decreases the cell proliferation rate. The rate of cell proliferation is a risk factor in carcinogenesis. Alteration of cell cycle times is thus expected affect the shape of the dose-response curve for cancer.

Approach

1) Use expert opinion to identify the mode or modes of action, characterized by sequences of key events, most likely to link tissue doses, predicted by PBPK modeling, with arsenic induced cancers;
2) Identify measurable entities that are directly associated with each key event or, alternatively, that are surrogate indicators of the key events. A combination of *in vivo* & *in vitro* measurements is likely (Figure 1);
3) Develop the BBDR structure based on the hypothesized identified modes of action (Figure 2). Availability of data will be the primary determinant of the level of biological detail incorporated into the BBDR model;
4) Design experiments to obtain dose-response & time-course information for the perturbation of key events by arsenic.
5) An iterative process of data collection, quantitative analysis, and refinement of the BBDR model will be used to minimize the uncertainty of the description linking arsenic dosimetry with carcinogenic outcomes.

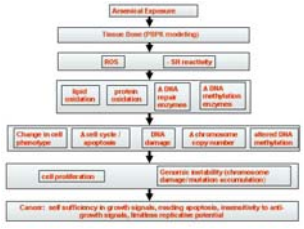

Figure 1 Potential key events representing the most probable modes of action for arsenic

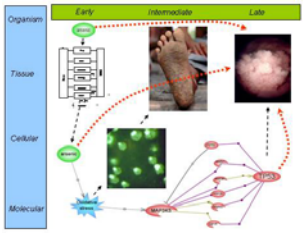

Figure 2 Illustration of framework for biologically-based dose response modeling for arsenic risk assessment

Conceptual Model & Simulations Results

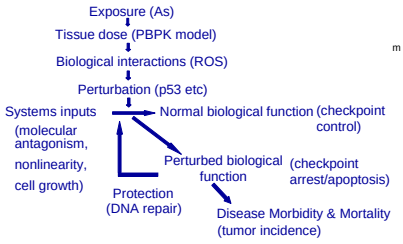

Figure 3 Framework for integration of computational systems biology into dose response modeling. Specific biological functions in the conceptual model are indicated in brackets

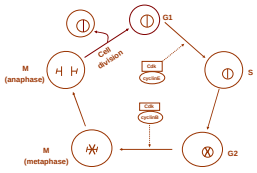

Figure 4 Cell cycle model. Cyclin E and its cyclin dependent kinase (Cdk) regulate the G1 to S transition, Cyclin B and its Cdk regulate the G2 to M transition.

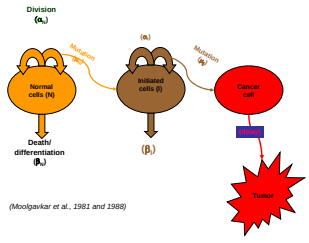

Figure 7 Two-stage clonal growth model for cancer.

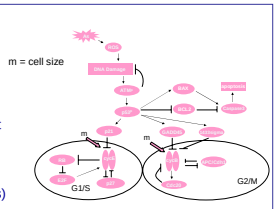

Figure 5 Signaling pathway linking DNA damage due to oxidative stress with activation of the G1/S and G2/M checkpoints and apoptosis. This is a potential mode of carcinogenic action for inorganic arsenic.

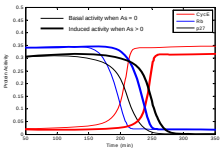

Figure 6. Simulation of the possible switch-like changes in levels of key regulatory proteins in the G1/S checkpoint when As dose = 0 and As dose > 0

Figure 5 describes a potential mode of action for arsenic where DNA damage due to formation of reactive oxygen species activates the signaling pathway that induces G1/S and G2/M checkpoint arrest and apoptosis. Figure 6 shows the model-predicted switch-like behavior of proteins in the G1/S checkpoint when As dose = 0 and As dose > 0. The delay of the switch in time indicates G1/S checkpoint arrest, providing a longer time for DNA repair. The increased time in cell cycle due to checkpoint arrest directly influences the cell division rate, which is a risk factor for cancer (Figure 7).

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