Functional Genomics, Dose-Dependent Transitions, and Quantitative Risk Assessment: Phase I

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Complex dose-response curves, having both thresholds and U-shaped relationships, are commonly observed. Risk assessments, in general, do not take these complex behaviors into account due to a lack of understanding of the underlying biology. Many of these complex dose-response behaviors are likely to be associated with differential activation of gene families at different exposures. Low doses activate gene families to counteract stress, thereby, extending regions of homeostasis and serving as an adaptive response to low levels of stress. Much higher doses lead to expression of gene families more related to toxicity pathways, such as those for inflammation, cell proliferation, and cell death. These phenomena have been referred to as dose-dependent transitions with different modes of action contributing in different dose regions. Research in this phase, Phase I, of a two-phase project extended the database for chlorine, a promising prototype compound. Chlorine toxicity in vitro showed a U-shaped dose response in several cell types. We examined the genes involved in oxidative stress and inflammatory responses to chlorine, and mapped the circuitry causing activation of anti-oxidant stress response element signaling. We also developed a generic computational model of oxidative/electrophilic stress response, based on the experimental data generated for chlorine. Phase II, which continued this project through 2008, is described in the project abstract for MTH0801.

Implications: Risk assessments utilize two major dose-response defaults: linear and threshold approaches. The ability to move beyond these two defaults requires approaches that combine toxicity test results with mechanistic studies of cellular responses examined in relation to perturbations of cellular ‘toxicity pathways’. This project developed quantitative models of these toxicity pathways, leading to various dose response options for extrapolation. The outcomes here, with oxidative stress pathways, will improve the credibility of chemical risk assessment approaches for diverse stakeholders and bring more quantitative computational systems biology approaches to bear in contemporary risk assessments.

Key words: Nrf2, nonlinear dose response, hormesis, redox homeostasis

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Blaauboer, B.J. and Andersen, M.E. (2007). The need for a new toxicity testing and risk analysis paradigm to implement REACH or any other large scale testing initiative. Archives of Toxicology 81: 385–387.


This abstract was prepared by the principal investigator for the project. Please see www.americanchemistry.com/lri for more information about the LRI.

**Other publication(s):**


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