

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

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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 Phase I (the 2007 portion) extends the database for chlorine, a promising prototype compound. Chlorine toxicity *in vitro* showed a U-shaped dose response in several cell types. In Phase I, 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 have also developed a generic computational model of oxidative/electrophilic stress response, based on the experimental data generated for chlorine. In Phase II (planned for 2008), we will establish generalized human antioxidant response element (ARE) reporter systems. We will also continue to map the circuitry responsible for NF-E2-related factor-2 (Nrf2) activation, using genomic approaches. We will also extend the current mathematical model to include nuclear receptor-mediated bioactivation of xenobiotics, and cross-activation of Nrf2 and antioxidant enzymes via nuclear receptors. The research in Phase I will produce two papers: one paper on a generic model for considering these transitions in chemical risk assessment with a focus on chlorine and a second paper on criteria for selecting candidate chemicals for conducting mechanistically-based risk assessments based on dose-dependent transitions.

Implications: Risk assessments utilize two major dose-response defaults—linear and threshold responses with multiple uncertainty factors. 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 develops 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.

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Presentation(s):

McLanahan, E. D., Andersen, M. E., and Fisher, J. W. (2008). A biologically based dose-response model for dietary iodide and the adult rat thyroid axis: Application to iodide deficiency and perchlorate exposure. *The Toxicologist* 102 (S-1): 208. (Abstract 1013).

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Woods, C. G., Zhang, Q., Thomas, R. S., Boellmann, F., Wang, J., Wolf, C., Andersen, M. E., and Pi, J. (2008). Regulatory mechanism of Nrf2 activation by hypochlorous acid and concomitant activation of

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