

**Toxicogenomics, Dose-Dependent Transitions, and Quantitative Risk Assessment: Phase II**

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Complex dose-response curves are characterized by both thresholds and U-shaped relationships and 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 exposure levels. 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. Short-term research in Phase I (the 2007 portion) extended the database for chlorine, a promising prototype compound. Chlorine toxicity *in vitro* showed 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 in 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 II will produce two papers: one experimental paper on mapping the intracellular factors involved in Nrf2 activation by chlorine, and a second modeling paper on nonmonotonic dose response (hormesis) due to cross-activation of Nrf2 via nuclear receptors.

**Implications:** Risk assessments utilize two dose response defaults: linear and threshold approaches. The ability to move beyond these defaults requires the combination of toxicity test results and mechanistic studies of perturbations of cellular toxicity pathways. After developing an intuitive model of the toxicity pathways, computational systems biology methods must be applied to predict the dose response for pathway response in relation to perturbations by exposures to chemicals. This project extends the intuitive model building with chlorine hydrolysis products to the stage of building a computational systems biology model for chemicals that produce oxidative stress in tissues.

**Start date:** January 2008 – December 2008 (Phase I ended in December 2007)

**Presentations:**

Pi, J., Zhang, Q., Wong, V., Collins, S., and Andersen, M. E. (2007). Hypochlorous acid activates transcription factor Nrf2-mediated antioxidant response in raw 264.7 macrophages. Society of Toxicology 46th Annual Meeting, Charlotte, NC. March 25–29, 2007. (Abstract 1579).

Zhang, Q., Pi, J., and Andersen, M. E. (2007). Computational modeling of Nrf2-mediated oxidative/electrophilic stress response. Society of Toxicology 46th Annual Meeting, Charlotte, NC, March 25–29, 2007. (Abstract 397).

Anderson, M. E., Clewell, H. J., Jarabek, A. M., Pi, J., and Zhang, Q. (2007). Activation of adaptive cellular networks and hormetic dose responses relationships. The 6th International Conference of Hormesis: Implications for Toxicology, Medicine, and Risk Assessment, Amherst, MA, May 1–2, 2007.

Zhang, Q. and Andersen, M. E. (2007). Control theory and dose response transition in anti-stress gene regulatory networks. International Science Forum on Computational Toxicology, Durham, NC, May 21–23, 2007. (Abstract 32).

Pi, J., Fu, J., Zhang, Q., Woods, C. G., Sun, G., Andersen M. E., and Collins, S. (2008). Arsenic impairs pancreatic beta-cell function: involvement of oxidative stress response. Society of Toxicology 47th Annual Meeting, Seattle, WA, March 16–20, 2008. (Accepted).

Woods, C. G., Zhang, Q., Thomas, R. S., Boellmann, F., Wang, J., Wolf, R. C., Andersen, M. E., and Pi, J. (2008). Regulatory mechanism of Nrf2 activation by hypochlorous acid and concomitant activation of cellular inflammatory pathways. Society of Toxicology 47th Annual Meeting, Seattle, WA, March 16–20, 2008. (Accepted)

Zhang, Q., Pi, J., and Andersen, M. E. (2008). Phase I to II cross-induction of xenobiotic metabolizing enzymes: a potential source for hormetic responses. Society of Toxicology 47th Annual Meeting, Seattle, WA. March 16–20, 2008. (Accepted)

**Peer-reviewed publications:**

Zhang, Q. and Andersen, M. E. (2007). Dose Response Relationship in Anti-Stress Gene Regulatory Networks. *PLoS Comput Biol.* 3(3): e24.

Pi, J., Zhang, Q., Woods, C. G., Wong, V., Collins, S., and Andersen, M. E. (2008). Activation of Nrf2-mediated oxidative stress response in macrophages by hypochlorous acid. *Toxicol. Appl. Pharmacol.* 226(3): 236–243.

Zhang, Q., Pi, J., Woods, C. G., Jarabek, A. M., Clewell, H. J. III, and Andersen, M. E. Hormesis and Adaptive Cellular Control Systems (Under review)

Zhang, Q., Pi, J., and Andersen, M. E. Phase I to II cross-activation of xenobiotic metabolizing enzymes: a feedforward control mechanism for potential hormetic responses. (In preparation)

**Other publication(s):** None to date.

**Sponsors in addition to the LRI:** None.

**Abstract revision date:** March 2008