

Toxicogenomic Analysis of Irritant Gas (IG)-Induced Airway Epithelial Toxicity

Yin Chen. *The Hamner Institutes for Health Sciences.*

EPA and other regulatory entities set health guidelines for hazardous air pollutants primarily on the basis of observations of toxicity in animals. Exposure guidelines are then developed using linear or threshold models to extrapolate to low dose risks. For threshold responses these guidelines apply various uncertainty factors (UCFs). These UCFs are treated as if they are independent. This approach tends to produce conservative risk estimates (i.e., very low acceptable concentrations). New toxicogenomic technologies are differentiating dose regions for adaptive changes from those doses causing toxicity. We propose to use genomic tools with reactive products formed from respiratory tract irritant gases (i.e., hypochlorous acid with chlorine and formalin with formaldehyde) to develop alternative, biologically-based risk assessment approaches based on dose-dependent transitions for activation of adaptive and toxicity-related signaling pathways. The product of this research, a prototypical approach for irritant gas (IG) risk assessment, will compare and contrast the current approach with a genomics-based approach. A paper utilizing these approaches for a prototype irritant gas risk assessment will be prepared for publication and be shared with U.S. EPA regulatory personnel to initiate discussions on these novel approaches.

Implications: Dose dependent transitions in toxic processes lead to alternative dose response models for risk assessment and risk management. Identification of dose-dependent, biological processes requires studies both in intact animals and in tissues in culture with reproducible treatment conditions. This work examined genomic responses of human tracheal bronchial epithelium *in vitro* to hypochlorous acid, a hydrolysis product of chlorine gas. The results here, in combination with studies of responses in intact animals, provide unique opportunities for incorporating knowledge of dose-dependent transitions in risk assessment and for expanding the dose-response options for chemical risk assessments with irritant gases.

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Zhu, L., Zhao, Y., Pi, J., Andersen, M. E., Jarabek, A. M., and Chen, Y. (2007). Proinflammatory oxidant hypochlorous acid (HOCL) induces dual signaling pathways in airway epithelial cells. Proceedings. Annual Meeting of the American Thoracic Society, San Francisco, CA, May 18-23, 2007. (Accepted).

Zhu, L., Pi, J., Wachi, S., Andersen, M. E., Wu, R., and Chen, Y. (2008). Identification of nrf2-dependent airway epithelial adaptive response to proinflammatory oxidant-hypochlorous acid (HOCL) challenge by transcription profiling. *The Toxicologist* 102 (S-1): 418. (Abstract 2033).

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