Risk Assessment Approaches for Chlorine and Other Respiratory Tract Irritant Gases

Melvin E. Andersen¹, Annie M. Jarabek², Rusty Thomas¹, Jingbo Pi¹, and Qiang Zhang¹. ¹The Hamner Institutes for Health Sciences. ²U.S. EPA.

Chlorine is an important commercial gas used as an intermediate in many chemical syntheses and in water disinfection. Chlorine is highly reactive in water, causing irritant and corrosive effects in the respiratory tract when inhaled by experimental animals and humans. Nasal extraction is large and lesions show a proximal to distal distribution, indicating that airflow patterns and exposure concentration play a key role in pathogenesis. We hypothesized that irritant responses by chlorine are caused by an oxidative stress that is mediated initially by hypochlorous acid formed by hydrolysis of chlorine in epithelial tissues, and then subsequently by downstream biological responses, including neurogenic inflammation. In vitro and ex vivo studies were used to evaluate concentration and duration dependencies of oxidative stress, to examine the potential role for pH changes in causing toxicity, and to assess the cell pathways activated by chlorine. In addition to testing the oxidative stress hypothesis, the results of the more mechanistic studies, together with the dosimetry model, will support non-cancer risk assessment strategies with chlorine.

Implications: Risk assessments require both toxicity information and understanding of how chemicals affect tissue. This project examined both chlorine dosimetry and oxidative stresses from hypochlorous acid. Oxidative stress responses were examined using ex vivo and in vitro epithelial tissues. A hybrid Computational Fluid Dynamics (CFD) - Physiologically-Based Pharmacokinetic (PBPK) model described delivery and epithelial reactions in rodents and humans. The risk assessment used comparable data on other gases, such as ozone, thereby aiding generalization between irritant gases and reducing uncertainties for the larger class of respiratory tract irritants. The tools developed here should be applicable for many inhaled irritants.

Key words: chlorine, Nrf2, oxidative stress, systems biology, computational modeling

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