Dosimetry of Inhaled Irritant Gases and Vapors in the Respiratory Tract: Epithelial Tissue Responses

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Many inhaled irritant gases and vapors induce responses in the epithelial cells lining the respiratory tract. Responses observed in exposed laboratory animals are often located in specific sites that may differ among species, making the development of regulatory guidelines for safe human exposure difficult. In the absence of an understanding of species-specific factors affecting dose and response, current regulatory practices use the most sensitive animal species and conservative risk estimation methods to assess human health risks. Information on both the biology and dose underlying inhaled irritant-induced epithelial cell responses is necessary for selecting effects in animals that best predict potential effects in humans at relevant human exposure levels. The long-term objective of this project was to understand how local tissue dose influences epithelial cell responses to inhaled irritant gases and vapors throughout the respiratory tract. This objective was achieved by generalizing the measurement and prediction of regional dose for two important commodity chemicals, chlorine and hydrogen sulfide, in the context of information available for other inhaled gases and vapors such as aldehydes, ozone, acidic vapors, acrylates, esters, epoxides, and sensitizing agents. The proposed research identified and measured tissue dosimeters that are related to the likely mode of action underlying epithelial responses of interest, predicted upper and lower respiratory tract dose in animals and humans using computational fluid dynamics and other mathematical models, confirmed model predictions by comparison with dosimeter measurements, and developed strategies for the use of human dose predictions in risk assessments. These results will help determine which responses are best used for extrapolation to human risk, what role localized, species-specific dose may be playing in the induction of these responses, and how best to incorporate this information into the risk assessment process.

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