Advancing Respiratory Tract Cell Culture NAM Models for Risk-Based Decision-Making

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The high cost and large numbers of animals associated with classical in vivo toxicology for portal of entry effects from inhalation exposures combined with significant anatomical and physiological differences between animal and human respiratory systems make the translation of in vivo inhalation results into predicted human effects difficult. The concept of New Approach Methodologies (NAM) has been introduced to encourage the development of alternative methods that can be used to predict chemical hazard or risk assessment in humans. The objective of this research is to develop in vitro aerosol chemical screening assays for risk-based decision-making. The aims of the research are to: 1) Perform dose-range finding studies to determine the in vitro toxicity of aerosol chemicals and the maximum tolerated dose for each chemical following acute exposure using 3D rat and human airway tissues and monolayer primary human airway epithelial cells in two laboratories. 2) Perform repeat chemical application experiments over a 14-day period using rat and human airway tissues. 3) Conduct aerosol optimization studies and evaluate effect of acute and repeat application of aerosol to 3D human airway tissues. 4) Undertake respiratory tract dosimetry model (MPPD and CFD) to compare existing rodent aerosol delivered datasets. 5) Determine reproducibility of chemical toxicity endpoints using human airway tissues reconstructed from 3 donors. 6) Develop prediction model to test unknown chemicals..

Implications: There is a high cost and large numbers of animals associated with classical in vivo toxicology for portal of entry effects from inhalation exposures. This, combined with significant anatomical and physiological differences between animal and human respiratory systems (including chemical deposition, obligate nose-only breathing in rodents and breathing modes) make the translation of in vivo inhalation toxicity results from traditional lab animal studies to predicted human effects difficult. This project is focused on developing data that can be used in evaluating the scientific confidence of this in vitro respiratory tract NAM so that this method can be used to predict chemical hazards and be used in human health risk assessment in place on in vivo inhalation tests.

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