

Subject: Response to RFI on Inhalation Toxicity Studies
Date: Wednesday, July 16, 2014 9:43:41 PM Eastern Daylight Time
From: Grego, Sonia
To: NIEHS NICEATM

Dear Sir or Madam,
Please find attached pdf and text below in response to the RFI on inhalation toxicity studies.
I look forward to the opportunity of discussing further this topic and RTI solutions in this space.
Sincerely,

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Response to NICEATM RFI for Devices and Technologies for Identifying Potential Inhalation Hazards

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For non-animal systems to recapitulate the features of in vivo testing, the systems need to reproduce both the biological response and the agent delivery that are involved in respiratory hazards. Advances in cellular constructs and aerosol science enable these objectives and remove many of the caveats of in vivo testing, including anatomical and physiological differences between humans and animals. A cellular platform modeling the lung is physiologically relevant when the cells are cultured at air-liquid interface (ALI) on a nanoporous membrane support. In addition to bronchial and alveolar cell lines, primary bronchial epithelial cells obtained from surgical waste tissues can be cultured at ALI to achieve highly differentiated 3D epithelium cultures closely emulating the in vivo physiology with features such as mucus secretion and cilia beating. These primary cells can be used at low passages (1 and 2), can be frozen and thawed for experimental convenience and a single donor tissue provides cells for several hundred cultures. In the human lung, inhaled agents may deposit on the airway epithelium and contact its mucus, interact with macrophages, enter the interstitium making contact with fibroblasts, endothelial cells or other immune cells. All of these cell types are key targets for observing toxicant effects and biomimetic multicellular tissue models are indispensable tools to capture the complexities of the toxicant-tissue interactions.

RTI International has a program to develop engineered cell cultures as human physiologically relevant models for the lung, the heart and the brain for compound screening applications. Additionally, RTI International is experienced in primary airway cultures and in developing heterotypic three-dimensional co-cultures. This group has demonstrated unique co-cultures of all primary lung cells, which present challenges due to specific media requirement for each cell type (Sellgren et al, Lab on a Chip 2014). RTI has evaluated the biological responses of these constructs to respiratory inflammatory agents like lipopolysaccharide and to pulmonary toxic drugs.

RTI also has more than 30 years of corporate experience conducting aerosol exposure research. In

2012, RTI initiated a program to evaluate the exposure of in vitro cellular co-cultures to aerosolized materials. This group constructed a novel exposure device that allows for the selection of particle sizes and diffusive delivery to viable cell cultures. Selection of particle sizes allows for a more realistic exposure scenario by matching particle size with cell types located within different areas of the respiratory tract. The diffusive aerosol delivery is more representative of actual exposure scenarios than traditional inoculation methods. This device produces a continuous realistic exposure atmosphere and is scalable in terms of exposure concentration, time, and particle size.

These advances provide viable, human-relevant alternative methods for acute inhalation toxicity studies.