Multiscale Mechanistic Modeling of the Respiratory Toxicodynamics of Engineered Nanoparticles

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Respiratory Effects of Silver and Carbon (RESAC) Project 3 efforts continued towards implementing, testing and evaluating a prototype, biologically-based modular modeling system describing the toxicokinetics and toxicodynamics of engineered nanoparticles (with focus on silver nanoparticles - nAg) in the mammalian lung. A major development that took place during this past seven month period has been the extension and implementation of the modeling framework, originally formulated and tested for the mouse lung, to a second species (rat). Parallel efforts have focused on the systematic sensitivity analysis of the mammalian pulmonary toxicodynamics model; on the refinement of particle dynamics modules accounting for processes affecting cellular particle dosimetry, such as particle dissolution and agglomeration; and on refining and testing modules describing inflammatory responses of the lung resulting from exposures to nanoparticles.

The overall modeling system being developed by RESAC Project 3 to describe and quantify mammalian pulmonary processes and function, accounts for biophysical and biochemical events occurring at multiple biological scales, linking changes of cellular and surfactant dynamics, that are caused by the presence of nanoparticles, to associated changes in alveolar surface tension and lung function. The modeling system accounts for the cellular and biochemical dynamics involved in the regulation of breathing processes and the control of inflammatory and immune responses to inhaled (or instilled) nanoparticles. Type I and Type II cells, alveolar macrophages, inflammatory cells (neutrophils, T-cells, etc.), surfactant constituents (phospholipids and surfactant proteins) that interact with the nanoparticles of concern, and intercellular signaling involving cytokines, are all explicitly considered. Multiple “cell level event” modules provide their outputs to an “organ level” module that simulates resulting lung response, in terms of changes to pulmonary resistance and elastance across the spectrum of breathing frequencies.

The cross-species extension of the in vivo pulmonary toxicodynamics model, originally developed by RESAC Project 3 for the mouse, to the rat, involved the mechanistic adjustment of relevant physiological and biochemical processes and parameters to account for inter-species differences. Model predictions for rats were compared with in vivo measurements of cellular endpoints such as total cell count, macrophage count, immune cell count and of biochemical endpoints such as surfactant lipids and protein concentrations provided by RESAC Project 2. Efforts are also on-going towards utilizing preliminary pulmonary measurements performed on rats after receiving inhaled nanoparticle (nAg) doses, in order to compare and assess pulmonary endpoints (for mice and rats) observed following intratracheal instillation. The multi-species
pulmonary toxicodynamics model was also subjected to systematic global sensitivity analysis in order to assess the influence of different inputs and parameters on modeled pulmonary endpoints.

Other work during this past period includes characterizing and estimating the effects of particle properties on measureable cellular endpoints \textit{in vitro}, through modeling explicitly processes of particle sedimentation, diffusion, agglomeration, and dissolution (with focus on nAg for the present application). The modeling has been implemented by considering particle-particle and particle-medium attractive and repulsive interactions. The predictions from particle process modeling are being compared to \textit{in vitro} measurements of particle dissolution and size distribution available from the RESAC Science Core. These particle-specific processes have been used to refine \textit{in vitro} system dosimetry modeling for relating overall particle dose to actual cellular dose, which is required in order to mechanistically quantify predictions of cellular endpoints such as cell viability, LDH, and ROS production measured in \textit{in vitro} cell cultures by RESAC Project 1. The particle dynamics modules will be subsequently adapted and incorporated into the models for \textit{in vivo} processes, to refine the description of events taking place in biological tissues and improve mechanistic predictions of biological endpoints.