Particle physicochemical property and exposure condition effects on pulmonary toxicity of titanium dioxide nanoparticles: Results from a machine-learning-based meta-analysis of animal studies

Jeremy Gernand[1], Elizabeth Casman[2], Samantha Frady[3], Keith Houck[3], Qingyu Meng[4], Amy Wang[3, +]

[1]Energy and Mineral Engineering, Penn State University, University Park, PA
[2]Engineering and Public Policy, Carnegie Mellon University, Pittsburgh, PA
[3]Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
[4]School of Public Health, University of Medicine and Dentistry of New Jersey, Piscataway, NJ
+ Currently at Toxicology and Health Services, Syngenta Crop Protection, Greensboro, NC

Abstract

Tuneability of physicochemical properties and consequently the function accounts for much of the interest in nanomaterials. For instance, small adjustments of size and surface coatings can have significant impact on the particles' functions but may also alter their toxicities. The variety of potential adjustments to nanomaterial physicochemical properties results in a large number of ENM types. Accordingly, regulators are considering whether and how to group different types of nanomaterials for human and environmental health regulations. Currently, high-accuracy methods to quantitatively predict toxicity from physicochemical properties for nanomaterials are lacking, so grouping materials is very difficult. Here we quantitatively determine the influence from titanium dioxide nanoparticle (nano-TiO_2) physicochemical properties and exposure conditions on observed pulmonary toxicity by conducting a meta-analysis of 25 studies in which animals were exposed through the respiratory tract (inhalation or instillation). Machine learning models, including regression trees and random forests, revealed that size has the most influence on toxicity. Compared to 1000 nm nano-TiO_2, exposure to similar doses of the 3.5 nm nano-TiO_2 (the smallest in our analysis) resulted in 45% higher concentrations of lactate dehydrogenase in bronchoalveolar lavage (BAL) fluid, an indicator of cytotoxicity. Most other particle characteristics—including crystalline phase (anatase fraction), size of aggregates, surface property/coating, shape, and purity—had negligible effect on toxicity indicators. We conclude that the present information supports treating nano-TiO_2 materials as one class in considering pulmonary effects and setting regulatory health and safety inhalational exposure limits.