Title *

Surface area is the biologically most relevant dose metric for nanoparticle-induced inflammation in the lung

Abstract *

As part of the EU-funded SmartNanoTox project (Horizon2020) a large body of data on short-term (1d) and intermediate-term (28d) pulmonary inflammation (PMNs in BAL) after intratracheal instillation of low-solubility (nano-)materials (NMs) was assessed in rodents. Hundreds of data points from our laboratories and from the literature were included comprising dozens of NMs consisting of spherical primary particles. A wide range of materials (e.g. polystyrene, TiO_2, carbon-based nanoparticles, transition metal oxides, crystalline/amorphous SiO_2), primary particle diameters (9-1500 nm) and mass-specific BET surface areas (5-1000 m^2/g) was included.

After proper scaling of PMN values and applied dose there was excellent agreement between data from different animal models (mice and rats) and from different laboratories. Surface area was identified as the biologically most relevant dose metric explaining about 80% of the observed variability in acute pulmonary inflammation (R^2~0.8). For comparison, mass and volume (R^2~0.5), joint length (R^2~0.4), and number of primary particles (R^2~0.2) had a much lower predictive power for particle-induced PMN influx.

Moreover, surface area was the only dose metric which allowed clustering of different types of materials into toxicity classes independent of particle size. At 1d, NMs *without intrinsic toxicity* (EC_{50}=175 cm^2/g-lung) could be clearly distinguished from materials with intrinsic toxicity such as *transition metal oxides* (here: Co, Ni, Zn, Fe; EC_{50}=15 cm^2/g-lung) and *crystalline quartz* (EC_{50}=3.5 cm^2/g-lung).

This analysis implies that mainly surface-related modes of action are driving NM-induced pulmonary inflammation at least for short-term responses (1d). Prolonged inflammation (here: 28d) was observed mainly for Printex90 and some transition metal oxides (Ni, Fe).

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