

Health Effects of Fibrous Particles (CNT) vs Non-Fibrous Particles

1. Do CNT cause health effects distinct from non-fibrous particles?
 - a. NIOSH: SWCNT & MWCNT cause rapid inflammation, granulomas and interstitial fibrosis. At similar mass concentrations and similar surface area nano-sized CB did not cause any of these effects.
 - b. SWCNT & MWCNT – agglomerates vs. dispersed: agglomerates cause granulomas, dispersed cause interstitial fibrosis
 - c. What is relevancy of granulomas as a health end-point? NIOSH risk assessment looked at two end-points: granulomatous inflammation and interstitial fibrosis to determine BMD and found surprising coherence between studies (SW vs MW, long vs short, different syntheses processes, different degree of agglomeration).
2. Physico-chemical properties vs biological activity
 - a. Shape: CB vs CNT – fibrous particles more potent, two parameters changes: crystal structure and length. TiO₂ nanospheres vs short and long nanowires – nanowires were more potent with potency related to the length of the wire: same crystal structure, the same diameter.
 - b. Aspect ratio: abdominal instillation of MWCNT
 - i. Japanese study found mesotheliomas at high doses
 - ii. Scottish study found inflammation of the abdominal wall at low doses with long

fibers being potent and short fibers not potent

- iii. Japanese study was repeated at low doses and found mesothelioma.
 - iv. German study used short (less than 1 μm) MWCNT and found no mesothelioma.
 - v. NIOSH long vs short TiO_2 – long were potent bioactive, short were not, both in vitro and in vivo.
 - vi. Hypothesis for length related mesothelioma assumes that ducts in the chest wall lining (6-8 μm) clear short but not long fibers
- c. Deposition: Agglomerates deposit in the terminal bronchials and proximal alveoli while smaller structures deposit in the distal alveoli. Because of low density micrometer-sized agglomerates still have low aerodynamic diameter and can deposit in the respiratory region of the lung.
- d. Clearance: CNT are resistant to acid treatment and high temperature and thus are viewed as durable. Little evidence from NIOSH study of clearance of SWCNT 1 year post exposure. Perhaps clearance is low because CNT are encapsulated in granulomas and in the interstitial space. Kagan et al. recently reported degradation of SWCNT with peroxidase found in PMN. Question is whether this occurs in vivo.
- e. Phagocytosis: NIOSH data indicates low rate of phagocytosis for SWCNT and higher rate for MWCNT. Mechanism for asbestos induced disease involves frustrated phagocytosis (fibers too long to be completely engulfed by AM). In

general CNT are not long enough to cause frustrated phagocytosis. Question is whether this mechanism holds for CNT. CNT are being used for bone grafting because they are not rejected but form a matrix upon which the bone cells grow. Evidence indicates that lung fibroblasts grow more rapidly in the presence of CNT and produce more collagen. This suggests a distinct mechanism of action compared to asbestos that is when CNT get into the interstitial space they form a matrix upon which fibroblasts grow and lay down fibrous tissue.

- f. Translocation: Kreyling et al report slow translocation of nanospheres from the lung to systemic organs (less than 1%). Mercer et al. used labelled SWCNT and found no measureable translocation to systemic organs over 2 week period. Porter et al. has reported that MWCNT can leave the lung and enter the intra-pleural space. With co-exposure damage to the air-blood barrier could increase the rate of translocation of NP to systemic tissues.
- g. Surface reactivity: raw CNT contain catalytic metals and produce ROS while purified CNT do not. In vitro raw CNT are more toxic. However, raw vs purified CNT exhibit similar potency in vivo (inflammation, granulomas and fibrosis). Efforts are being pursued to functionalise CNT to decrease surface activity.