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Poorly soluble particulates: Searching for a unifying denominator of nanoparticles and fine particles for DNEL estimation

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ABSTRACT

Under the new European chemicals regulation, REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) a Derived No-Effect Level (DNEL), i.e., the level of exposure above which humans should not be exposed, is defined. The focus of this paper is to develop a weight-of-evidence-based DNEL-approach for inhaled poorly soluble particles. Despite the common mode of action of inhaled insoluble, spherical particulate matter (PM), a unifying, most appropriate metric conferring pulmonary biopersistence and toxicity has yet not been demonstrated. Nonetheless, there is compelling evidence from repeated rat inhalation exposure studies suggesting that the particle displacement volume is the most prominent unifying denominator linking the pulmonary retained dose with toxicity. Procedures were developed to analyze and model the pulmonary toxicokinetics from short-term to long-term exposure. Six different types of poorly soluble nano- to submicron PMs were compared: ultrafine and pigmentary TiO_2, synthetic iron oxide (Fe_3O_4, magnetite), two aluminum oxyhydroxides (AlOOH, Boehmite) with primary isometric particles approximately of either 10 or 40 nm, and MWCNT. The specific agglomerate densities of these materials ranged from 0.1 g/cm^3 (MWCNT) to 5 g/cm^3 (Fe_3O_4). Along with all PM, due to their long retention half-times and associated biopersistence in the lung, even short-term inhalation studies may require postexposure periods of at least 3 months to reveal PM-specific dispositional and toxicological characteristics. This analysis provides strong evidence that pulmonary toxicity (sustained inflammation) is dependent on the volume-based cumulative lung exposure dose. Lung toxicity, evidenced by PMN in BAL occurred at lung doses exceeding 10-times the overload threshold. Furthermore, the conclusion is supported that repeated inhalation studies on rats should utilize an experimental window of cumulative volume loads of respirable PM in the range of 1 μl/lung (no-adverse-effect range); however, not exceeding ≈10 μl/lung that would lead to retention half-times increasing 1 year. This can be targeted best by computational toxicology, i.e., the modeling of particle deposition and lung retention biokinetics during the exposure and recovery periods. Inhalation studies exceeding that threshold volume may lead to meaningless findings difficult to extrapolate to any real-life scenario. In summary, this analysis supports a volume-based generic mass concentration of 0.5 μl $PM_{respirable}/m^3$ × agglomerate density, independent on nano- or submicron-sized properties, as a generic no-adverse effect level in both rats and humans.

1. Introduction

Results from numerous short-term inhalation/aspiration/instillation studies with various types of carbon nanotubes (CNT) have been published (for reviews see Donaldson et al., 2006; Madl and Pinkerton, 2009; Maynard, 2007; Oberdörster et al., 2005, 2007). The degree and kind of aggregation of CNT structures is determined by the rigidity and pliancy of nanotubes and whether their diameters are thin enough to allow their buckling and self-aggregation into low-density, particle-like, intertwined, and often coiled assemblages (Pauluhn, 2009a). Given the differences in the physical shape of agglomerate structures, a categorization into rigid and flexible CNT appears to be among the most straightforward discriminative variable. In addition, the type of assemblage structure and whether it is stabilized by mere agglomeration or some kind of inter-tubular aggregation (physical entanglement) needs to be appreciated. Hence, depending on these characteristics, agglomerate structures of nanotubes may differ appreciably from thin-walled to thick-walled, rigid MWCNT. These properties may be decisive for hazard assessment as the critical toxic principle may either emerge from the individual tube structure (e.g., fiber) or the collective behavior of inhalable assemblages of nanotubes.

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