

AUTHORS: Sayes, C. M.; Marchione, A. A.; Reed, K. L.; Warheit, D. B.,

TITLE: COMPARATIVE PULMONARY TOXICITY ASSESSMENTS OF C60 WATER SUSPENSIONS IN RATS: FEW DIFFERENCES IN FULLERENE TOXICITY IN VIVO IN CONTRAST TO IN VITRO PROFILES

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**ABSTRACT:** It has previously been reported that the in vitro cytotoxic effects of water-soluble fullerene species are a sensitive function of their surface derivatization status. In a recent study, it was reported that doses of an aggregated form of underivatized C60, termed nano-C60, were 3-4 orders of magnitude more toxic to human dermal fibroblasts, lung epithelial cells, and normal human astrocytes when compared to identical exposures of these cell types to a fully derivatized, highly water-soluble derivative, C60(OH)24. Accordingly, the aim of this study was to test and validate these in vitro findings by comparing the in vivo pulmonary toxicity effects in rats of intratracheally instilled nano-C60 and C60(OH)24. In two combined studies, groups of rats were instilled with doses of either 0.2, 0.4, 1.5, or 3.0 mg/kg of nano-C60, C60(OH)24, or -quartz particle types using Milli-Q water as the vehicle. Subsequently, the lungs of vehicle and particle-exposed rats were assessed using bronchoalveolar lavage (BAL) fluid biomarkers, oxidant and glutathione endpoints, airway and lung parenchymal cell proliferation methods, and histopathological evaluation of lung tissue at 1 day, 1 week, 1 month, and 3 months postinstillation exposure. Exposures to both nano-C60 or water-soluble C60(OH)24 produced only transient inflammatory and cell injury effects at 1 day postexposure (pe) and were not different from water instilled controls at any other pe time periods. An increase in lipid peroxidation endpoints vs controls was measured in BAL fluids of rats exposed to 1.5 and 3 mg/kg of nano-C60 at 1 day and 3 month pe time points. In addition, no adverse lung tissue effects were measured at 3 months postinstillation exposures to the highest dose of the two types of fullerenes. In contrast, pulmonary exposures to quartz particles in rats produced dose-dependent lung inflammatory responses characterized by neutrophils and foamy lipid-containing alveolar macrophage accumulation as well as evidence of early lung tissue thickening consistent with the development of pulmonary fibrosis. The results demonstrated little or no difference in lung toxicity effects between the two fullerene samples when compared to controls, and these data are not consistent with the previously reported in vitro effects. The findings exemplify both the difficulty in interpreting and extrapolating in vitro toxicity measurements to in vivo effects and highlight the complexities associated with probing the relevant toxicological responses of fullerene nanoparticle systems.