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**TITLE:** INFLAMMOGENIC EFFECT OF WELL-CHARACTERIZED FULLERENES IN INHALATION AND INTRATRACHEAL INSTILLATION STUDIES

**PUBLISHED:** March-10

**CITE:** Particle and Fibre Toxicology, 2010, 7:4 (18pp)

**ABSTRACT:**

We used fullerenes, whose dispersion at the nano-level was stabilized by grinding in nitrogen gas in an agitation mill, to conduct an intratracheal instillation study and an inhalation exposure study. Fullerenes were individually dispersed in distilled water including 0.1 % Tween 80, and the diameter of the fullerenes was 33 nm. These suspensions were directly injected as a solution in the intratracheal instillation study. The reference material was nickel oxide in distilled water. Wistar male rats intratracheally received a dose of 0.1 mg, 0.2 mg, or 1mg of fullerenes and were sacrificed after 3 days, 1 week, 1 month, 3 months, and 6 months. In the inhalation study, Wistar rats were exposed to fullerene agglomerates (diameter: 96+/-5 nm; 0.12+/-0.03 mg/m<sup>3</sup>; 6 hours/days for 5 days/week) for 4 weeks and were sacrificed at 3 days, 1month, and 3 months after the end of exposure. The inflammatory responses and gene expression of cytokine-induced neutrophil chemoattractants (CINCs) were examined in rat lungs in both studies. Results In the intratracheal instillation study, both the 0.1 mg and 0.2 mg fullerene groups did not show a significant increase of the total cell and neutrophil count in BALF or in the expression of CINC-1,-2alphabeta and-3 in the lung, while the high-dose, 1 mg group only showed a transient significant increase of neutrophils and expression of CINC-1,-2alphabeta and -3. In the inhalation study, there were no increases of total cell and neutrophil count in BALF, CINC-1,-2alphabeta and-3 in the fullerene group. Conclusion These data in intratracheal instillation and inhalation studies suggested that well-dispersed fullerenes do not have strong potential of neutrophil inflammation.

Non-technical Summary: This study used fullerenes, whose dispersion at the nano-level was stabilized by grinding in nitrogen gas in an agitation mill, to conduct an intratracheal instillation study and an inhalation exposure study on Wistar rats. The inflammatory responses and gene expression of cytokine-induced neutrophil chemoattractants (CINCs) were examined in rat lungs in both studies.