

Title *

Preliminary validation study of a 3D in vitro inhalation model, using cytokine and gene expression responses of copper oxide nanoparticles

Abstract *

Human 3D airway models are fully differentiated and functional models of the respiratory epithelium. They are cultured at an air-liquid interface (ALI), allowing relevant exposure via air. It is anticipated that these models may predict a more realistic bioavailability of inhaled compounds. To investigate the effects of donor, exposure unit, exposure session and insert, we performed air exposures of copper oxide nanoparticles using the MucilAir™ human 3D bronchial model.

MucilAir™ (Epithelix Sàrl) were exposed at ALI conditions in Vitrocell exposure modules to aerosolized CuO (0, 50, 224, 1000 mg/m³) for 1 hour. Donor and exposure module unit were rotated among the four different exposure sessions using a statistical experimental design.

Deposition of CuO nanoparticles was 4%. After a 24 hours post-incubation period, exposure to CuO showed a slight but significant LDH response for the highest dose. For inflammation markers MCP-1, IL-8 and IL-6 a dose-response was observed, where this was significant for IL-6. The influence of the parameters 'concentration' is the largest, followed by 'donor', 'unit' and 'session' which are in the same order of magnitude, which is then followed by the parameter 'insert'.

Gene expression analyses (using Illumina beadchip (humanHT-12v4)) showed a significant increase in regulated genes (adjusted p-values <0.05) in a concentration dependent way. For the highest dose up to 5852 genes were up- and down regulated. PCA showed clearly distinct groups for 'concentration', as well for 'donor'. Statistical analyses showed that differences in 'concentration' were larger than those among 'donors', while donor differences were more substantial than differences between sessions.

We conclude that the MucilAir model can be used to assess the effects of nanoparticles, as long as donor-, session- and chip differences are taken into account of the experimental design and subsequent statistical analyzes.

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