National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

The influence of redox activity of inhaled nano-sized cerium dioxide on respiratory, immune and cardiovascular effects in multiple mouse models

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Introduction

For a successful safe by design approach and safety evaluation, knowledge on the influence of the physicochemical characteristics of nanomaterials on their toxic potential and the underlying biological mechanisms of action is needed. We assessed the influence of redox activity by modification of cerium dioxide nanoparticles (CeO_2 NPs) via zirconium dioxide (ZrO_2) doping on respiratory, immune and cardiovascular effects in mice following subacute inhalation.

Materials and methods

- Animals: Healthy C57BL/6J, Western-diet fed ApoE$^{-/-}$ (Apolipoprotein E knockout mice, prone to the development of atherosclerotic plaques) and ovalbumin (OVA) sensitised BALB/c mice.
- Exposure: 4 weeks to clean air or CeO_2 NPs with 0%, 22% or 78% ZrO_2-doping (4 mg/m^3, 3 hours/day, 5 days/week).
- Effects: assessed 2 or 4 weeks after exposure.

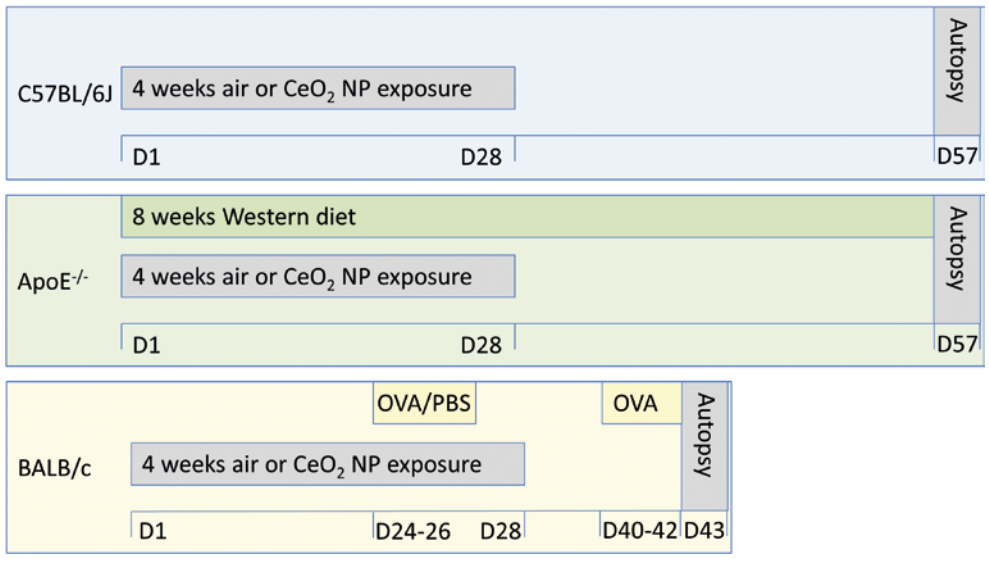

Figure 1: Schematic overview of the study design

Conclusions

- Inhalation of CeO_2 NPs caused minimal toxicological effects.
- Redox modification via ZrO_2-doping has limited effect on these responses.
- Further studies with nanomaterials of greater inherent toxicity or a wider range of redox activities are needed to fully assess the influence of redox activity on the toxicity of nanomaterials.

Results

CeO_2 NPs caused modest inflammatory lesions in the lung (increased incidence in minimal chronic inflammation, alveolar inflammation and alveolar macrophages), which were not related to the % of ZrO_2-doping.

CeO_2 NPs did not alter the size of atherosclerotic plaques in the brachiocephalic arteries of the ApoE$^{-/-}$ mice, although there was a trend towards an increased inflammatory cell content in plaques with increasing ZrO_2–doping of the NPs (see Figure 2). Heavily inflamed plaques in humans are vulnerable to rupture, that can trigger a cardiovascular event, e.g. heart attack.

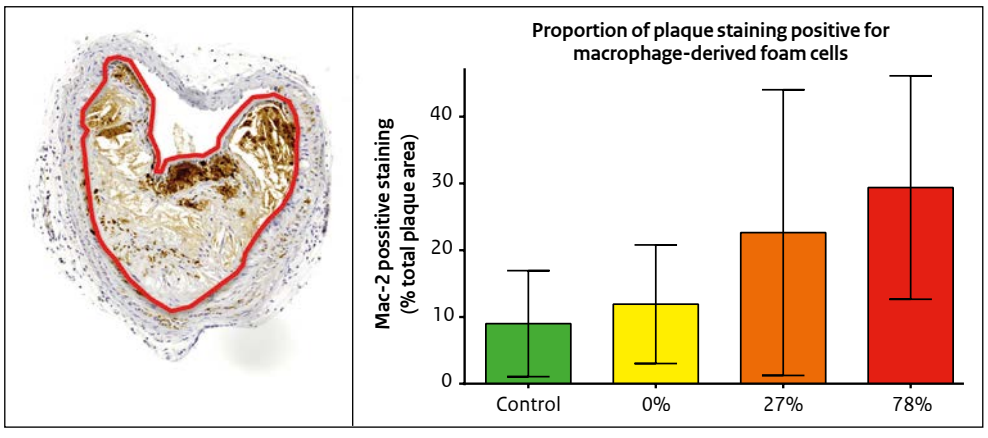

Figure 2: Atherosclerotic plaque (red outline on the left) and inflammatory cell content of the plaques (right graph) in the brachiocephalic arteries of ApoE$^{-/-}$ mice

CeO_2 NPs increased serum OVA-specific IgG_1 (see Figure 3a), but not IgE levels in BALB/c mice, suggesting a mild adjuvant effect of CeO_2 NPs. In addition, ZrO_2-doping related differences in IL-5 (see Figure 3), IL-4 and TNF-α induction in isolated spleen and lymph node cells were observed.

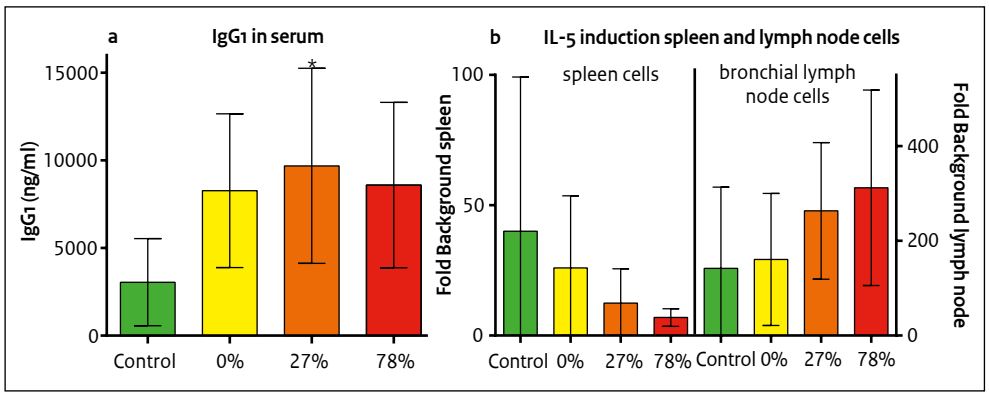

Figure 3: IgG1 concentration in serum and IL-5 induction in isolated spleen and bronchial lymph node cells in BALB/c mice

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National Institute for Public Health and the Environment
P.O. Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

009513

Acknowledgements

The work leading to these results has received funding from the European Union's Seventh Framework Programme for research, technology development and demonstration under grant agreement n° 310451 (NanoMILE) and the Netherlands Food and Consumer Product Safety Authority (NVWA).