Environmental transformation and biological fate of fresh and aged cerium oxide nanoparticles

EPA STAR Program: No. RD-83486001

Dingsheng Li[1], James Barres[1], Ethan Eagle[1], Claude Emond[2], Masako Morishita[1], James G. Wanger[3], Margaret Wooldridge[1], Olivier Jolliet[1]*

[1] University of Michigan [2] University of Montreal [3] Michigan State University

* ojolliet@umich.edu

1. Introduction

The overall objective is to improve our understanding of environmental exposure-dose pathways of CeO_2 NPs. Our Specific Aims are:

(1) **Environmental transformation and uptake of freshly-combusted and aged CeO_2:** characterize environmental transformation and physicochemical properties of aged CeO_2 NPs using their interactions with UV radiation and ambient air co-pollutants, and compare them to freshly-combusted CeO_2 NPs.

(2) ***In vivo* biological fate:** determine the biological fate of freshly-combusted and aged CeO_2 NPs, comparing the concentrations in blood and target organs resulting from animal inhalation and IV exposures.

(3) ***In silico* PBPK modeling:** develop and evaluate a Physiologically Based Pharmacokinetic (PBPK) model of CeO_2 NPs to identify the main factors affecting translocation and distribution of CeO_2 NPs in the body.

2. Methods

Generation and exposure experiment settings

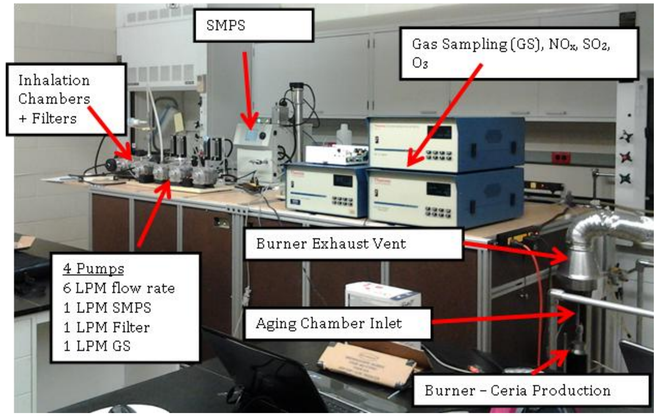

Fig 1: Image of the nanoparticle generation system integrated with the particle aging and inhalation systems.

Exposure test conditions

- Concentrations for fresh and aged CeO_2 NPs: 12.9±0.4 and 2.0±0.5 mg/m^3.
- Rats were exposed for 5 hours and sacrificed 15 min, 1 day, 7 days, and 14 days after exposure. Two rats per time point.
- Lungs, blood, liver, spleen, brain, kidneys, heart, and feces were analyzed for CeO_2 content with ICP-MS.

PBPK model conceptual framework

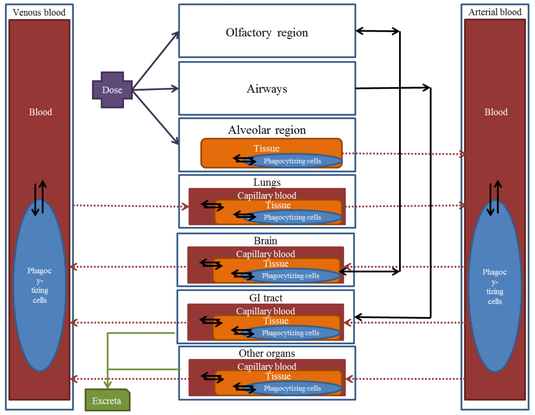

Fig 2. Conceptual framework of the PBPK model.

- Adapted from Li et al., 2013 (*6*).
- With a novel model and specific subcompartments for the NPs capture by phagocytizing cells.

3. Results

Characterization of nanoparticles

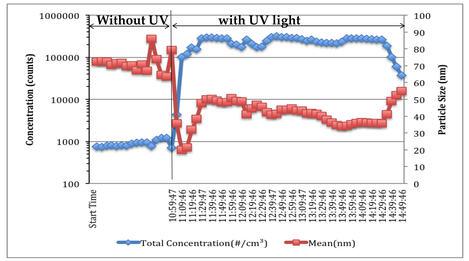

Fig 3. Nanoparticle concentration and size during a 4 hour SMPS characterization study with ultraviolet lights applied in the aging chamber at 11am. These conditions represent a high particle loading case.

The ultraviolet light led to a substantial reduction in particle size of up to a factor 3.

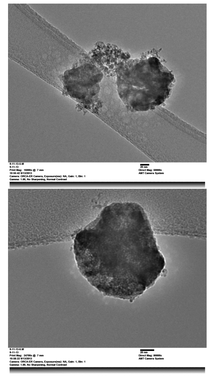

Fig 4. TEM photos of fresh CeO_2 nanoparticles

Observed Nano CeO_2 masses

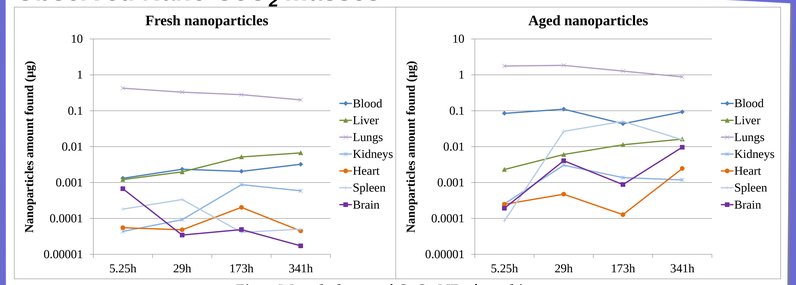

Fig 5. Mass balance of CeO_2 NPs found in rats

- Lungs contained the highest amount of CeO_2 NPs. Concentrations in other organs were three to four orders of magnitude lower.
- High concentrations of CeO_2 NPs were also found in feces after one day (7300 mg/kg against 1900 mg/kg in the lung), but sharply decreased afterwards (178 mg/kg in feces after 4 days)

PBPK model results

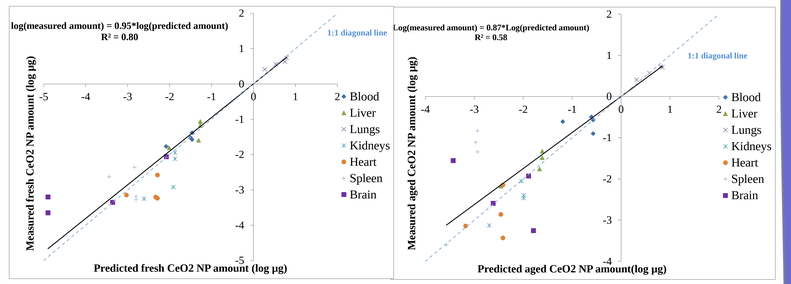

Fig 6. PBPK modelled fit for the measured data

- The alveolar region in the lungs takes up the majority of NPs.
- NPs are slowly released into the blood and distributed to other organs.
- Parts of the dose may deposit in the upper airway and are transferred into the GI tract before being quickly excreted via feces.

4. Conclusions

- Nanoparticle generation and aging system is established and stable.
- Conditions for animal exposure study are optimized by the test runs.
- PBPK model can be applied to this study with limited adaptation.
- Future work:
  - ➢ Increase animal sample size.
  - ➢ Additional measurements from GI tract, feces, and the rest of the body.
  - ➢ Conduct *in vitro* studies with macrophages.

References

1. US EPA, 2009. Report number EPA/635/R-08/002F.
2. HEI (Health Effects Institute), 2001. HEI communication 9, North Andover, MA; Flagship Press.
3. Brunner et al., 2006. *Environmental Science & Technology*, **40**, 4374-4381.
4. Lin et al., 2006. *International Journal of Toxicology*, **25**, 451-457.
5. Park et al., 2008. *Toxicology*, **40**, 220-227.
6. Li et al., 2013. *Nanotoxicology*, in press.