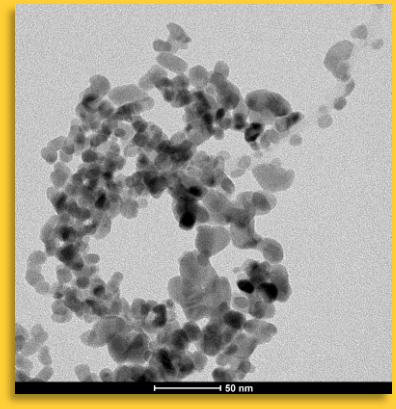
SUN

Sustainable Nanotechnologies Project

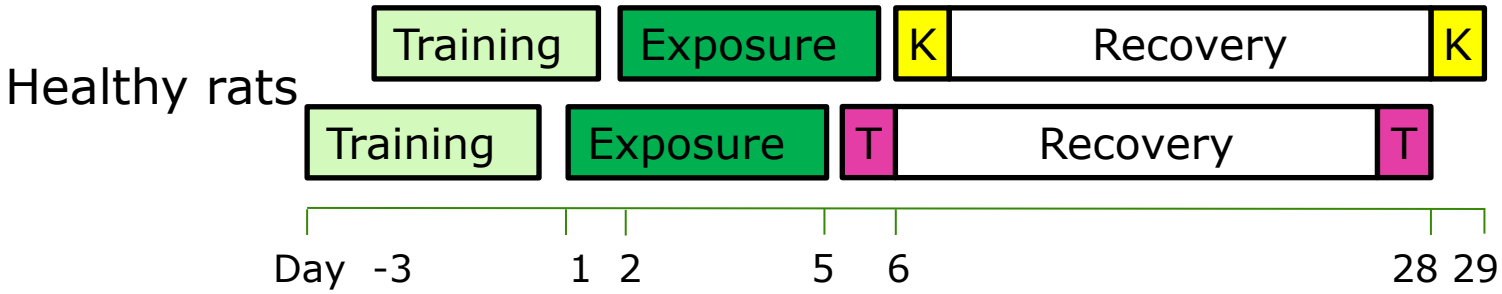
National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Pulmonary toxicity of surface modified copper oxide nanoparticles

Flemming R. Cassee



Short term inhalation study CuO



Training for adaptation to nose-only tubes

Exposure to CuO or filtered air during 5 days

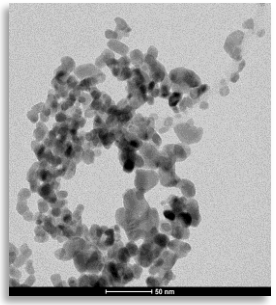
The dose is expressed as 6 h-concentration equivalents of 0, 0.6, 2.4, 3.3, 6.3, and 13.2 mg/m^3

Recovery period of three weeks

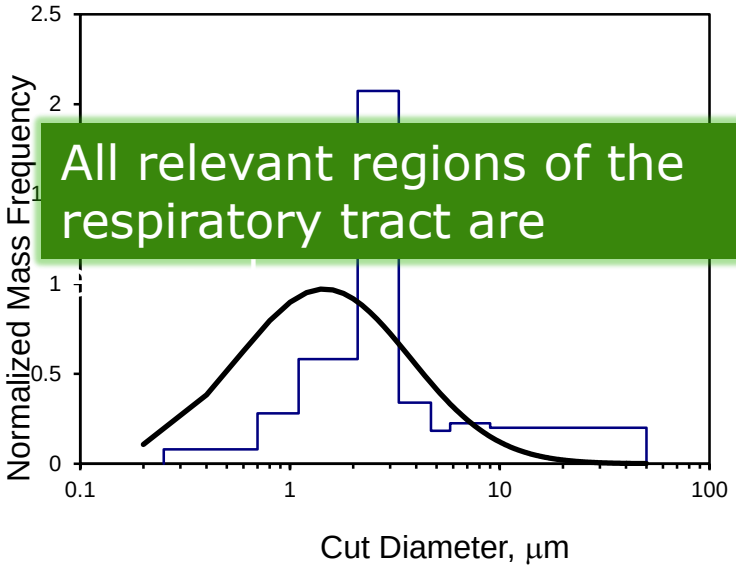
K is kinetic analysis

T is toxicological assessment

Nose-only inhalation CuO exposure

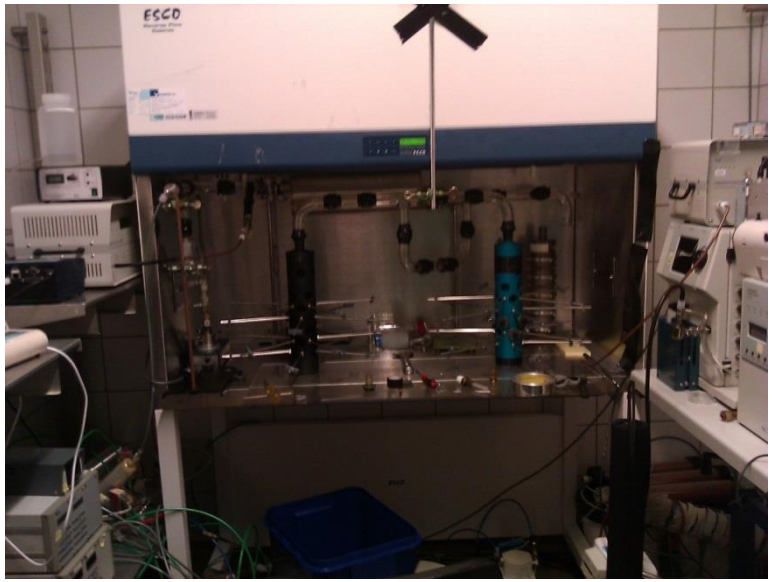


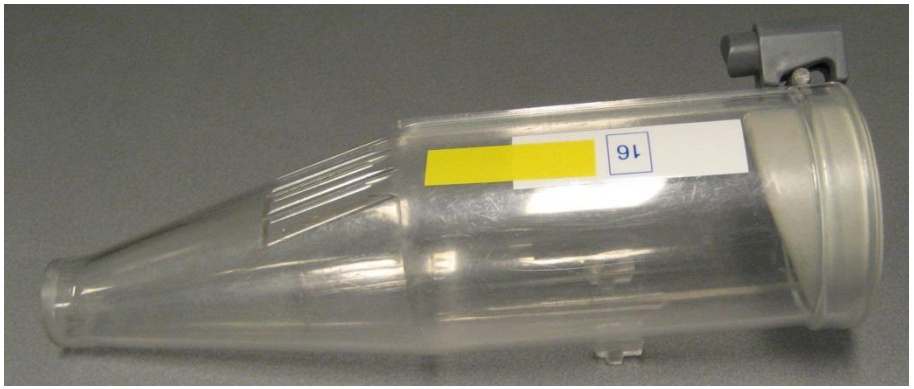
TEM CuO nanoparticles: 10 nm



All relevant regions of the respiratory tract are

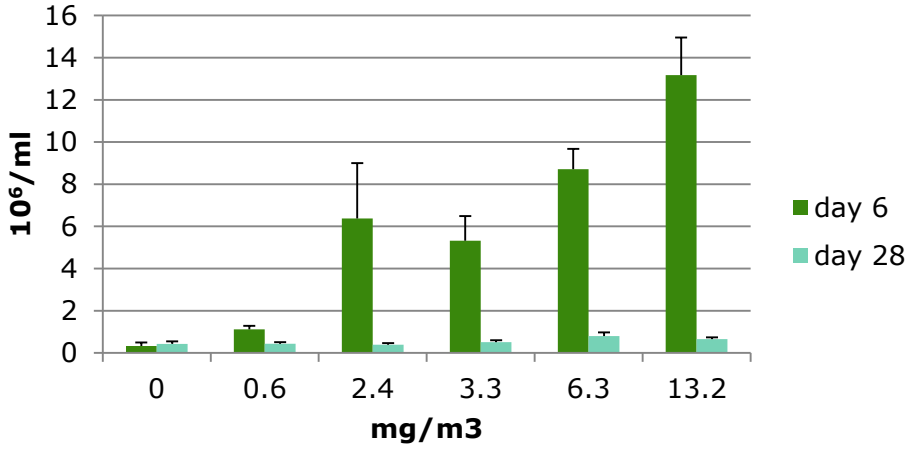
MMAD: 1.45 µm , GSD: 2.57 µm



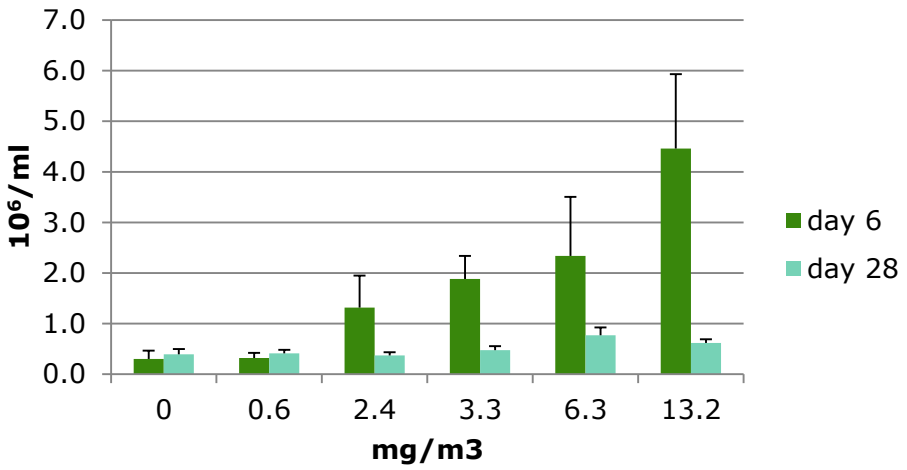


Lung inflammation and cell damage

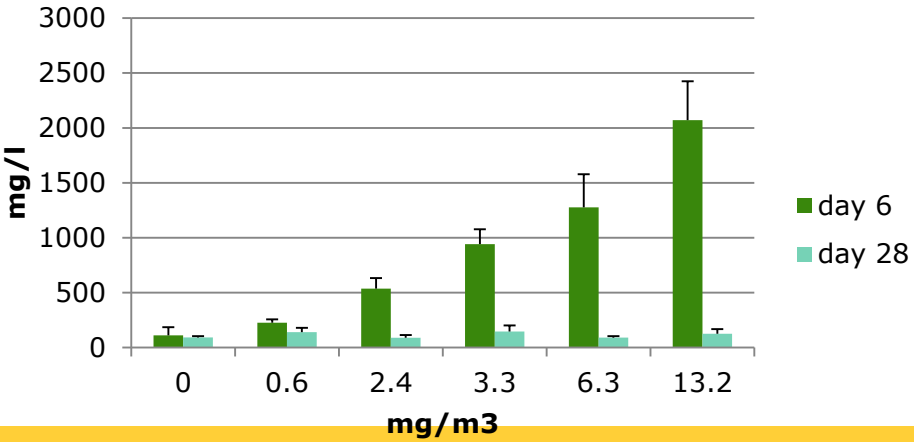
Total cell number BALF



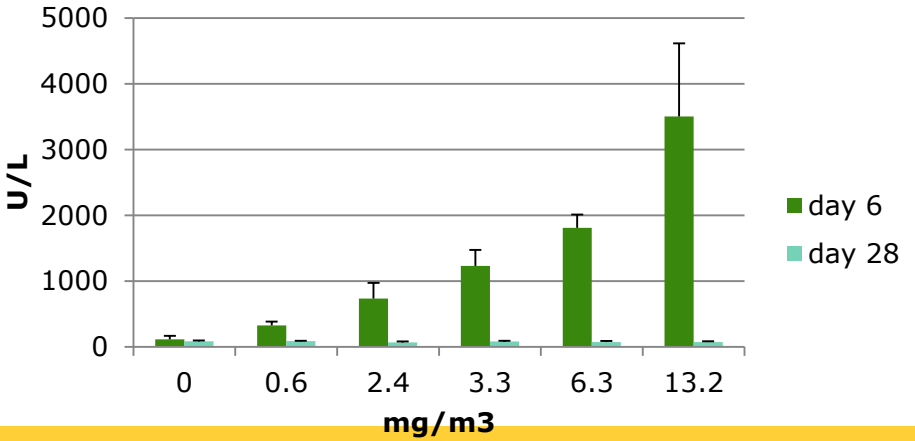
macrophages BALF



total protein

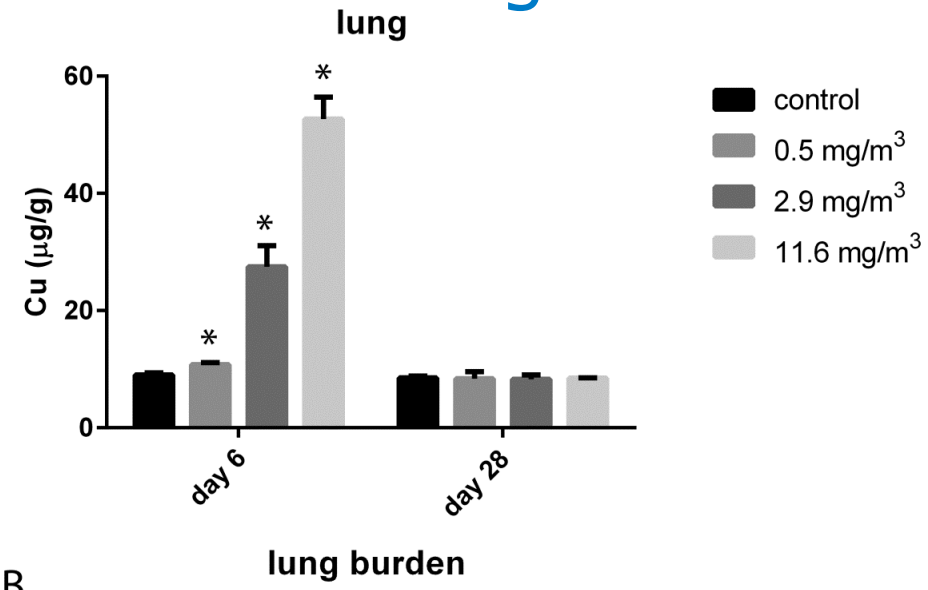


LDH



Lung burden

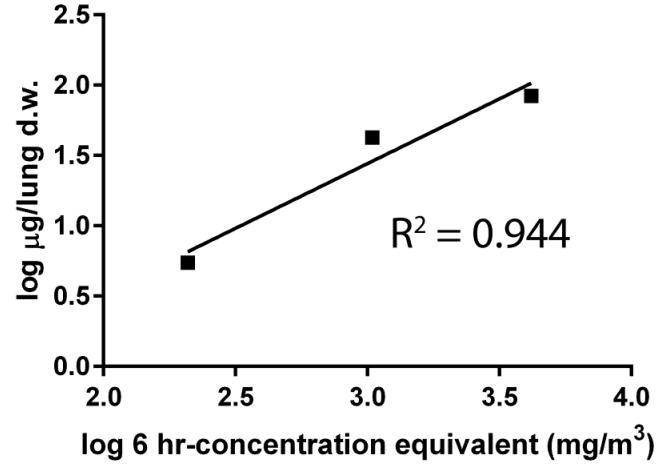
A



Retained lung burden

Measured load: 0.085 mg (43% of modeled deposited dose including clearance at day 6)

B



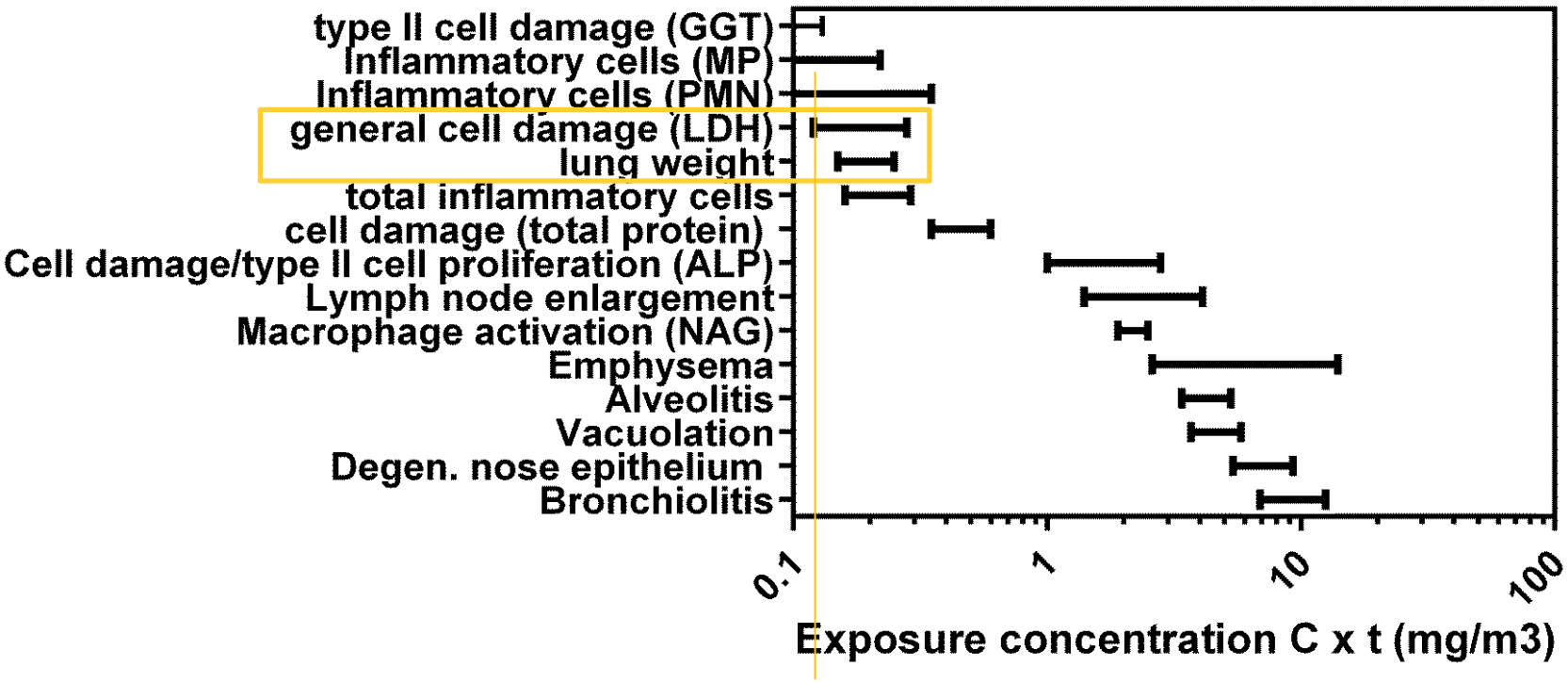
Linear relationship for measured lung burden

Clearance kinetics not similar as for poorly soluble particles

from Gosens et al. (2016) Nanotoxicology

Bench mark dose for risk assessment

dose needed to induce a certain effect



Cellular damage was completely reversible, while inflammatory response was not completely reversible 3-weeks post exposure

Summary prestine CuO

- Dose-dependent inflammatory response with cellular damage in the lung at day 6
- Linear increase in lung burden with increasing exposure at day 6 and no Cu levels above detection limit after the recovery period
- Although no Cu levels are detected at day 28, some remnants of inflammation present in lung
- Activation of draining lymph nodes as expected
- Degeneration of olfactory epithelium that completely recovers
- No inflammation or degeneration of other organs and no Cu levels detected in other organs.

Nanotoxicology

Nanotoxicology, 2016; 10(8): 1084–1095
 DOI: 10.3109/17435390.2016.1172678

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

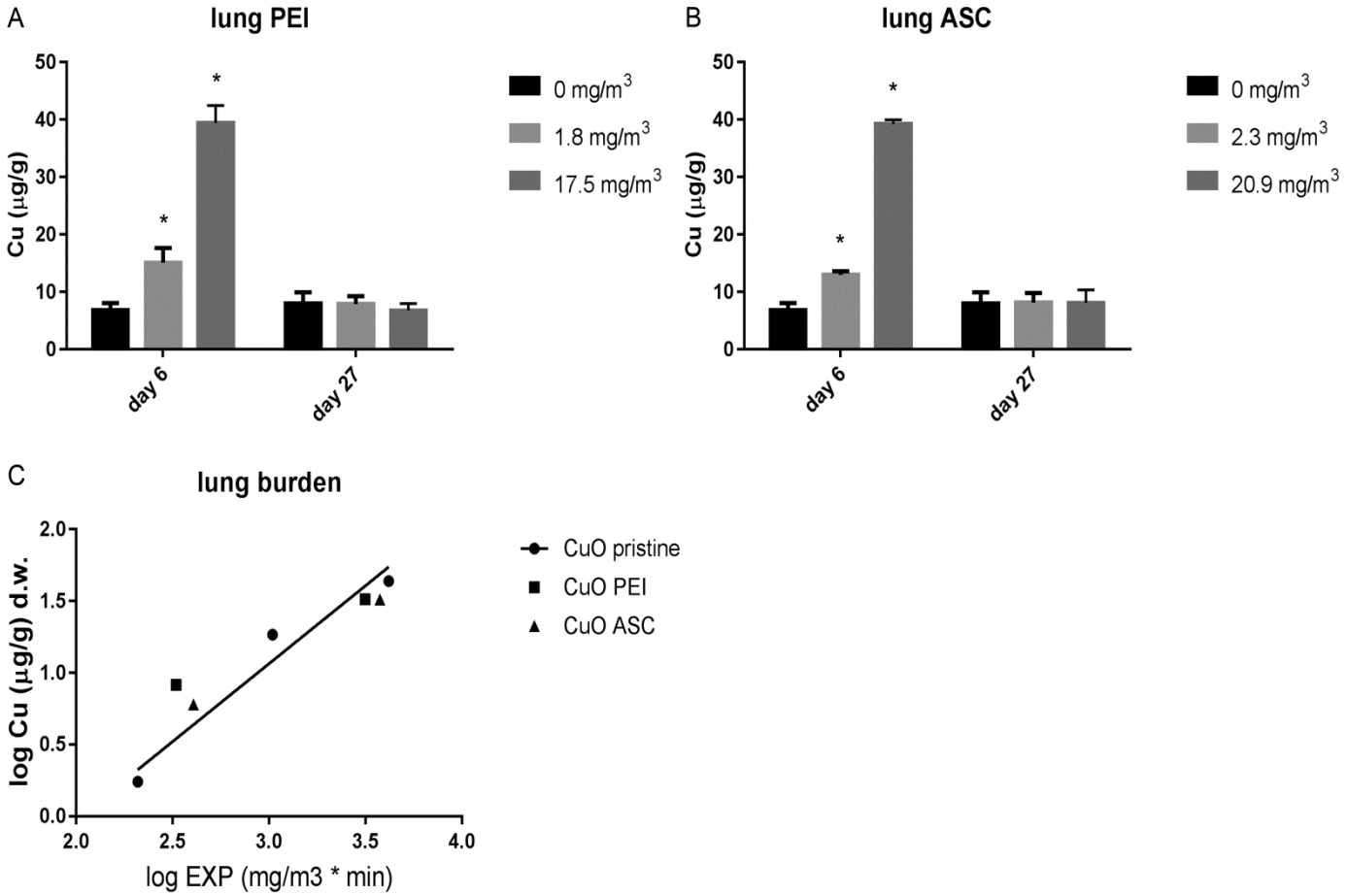
Organ burden and pulmonary toxicity of nano-sized copper (II) oxide particles after short-term inhalation exposure

Ilse Gosens[1], Flemming R. Cassee[1,2], Michela Zanella[3], Laura Manodori[3], Andrea Brunelli[4], Anna Luisa Costa[5], Bas G. H. Bokkers[1], Wim H. de Jong[1], David Brown[6], Danail Hristozov[4], and Vicki Stone[6]

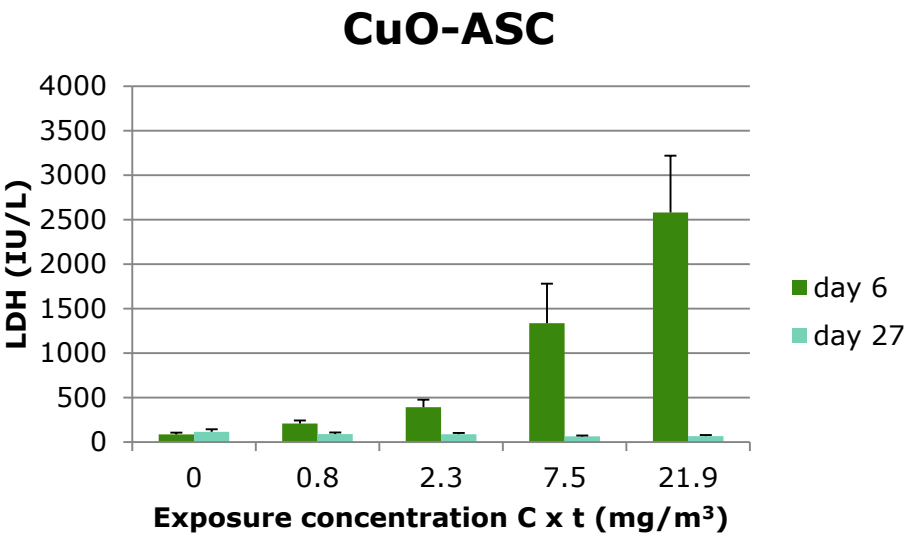
Can the toxicity of CuO NPs be decreased? (safer-by-design)

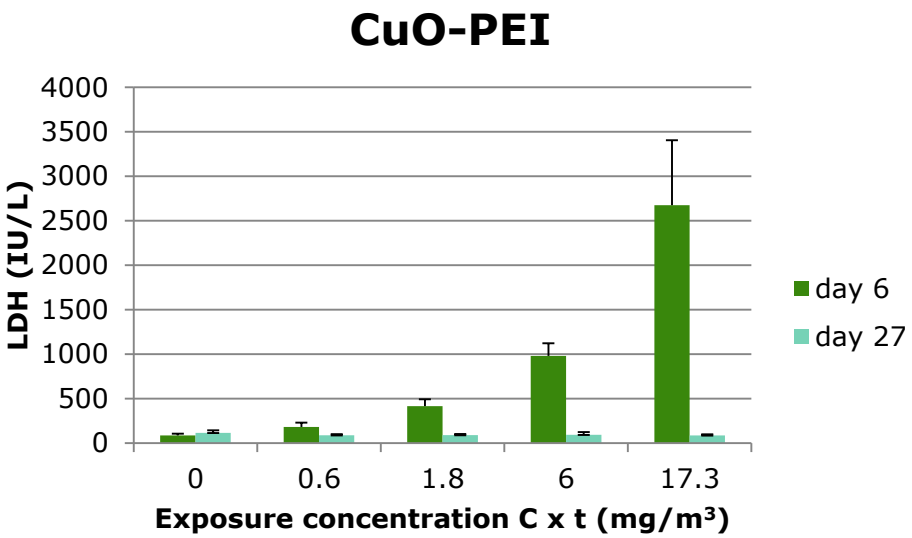
- Positively charged NPs have been shown to be more toxic compared to negatively charged NPs partly due to enhanced macrophage recognition (Bhattarcharjee et al 2010).
- 10 nm CuO NPs were modified with either a polyethylenimine (PEI, positive charge) or ascorbate (ASC, negative charge) coating.
- Ascorbate might protect against free radicals that are generated during inflammatory reactions.
- We hypothesize that negatively charged CuO-ASC NPs contribute to a **safer design** by inducing less pulmonary toxicity compared to postitively charged CuO-PEI NPs.

Lung burden – 5 day inhalation, 3 weeks recovery



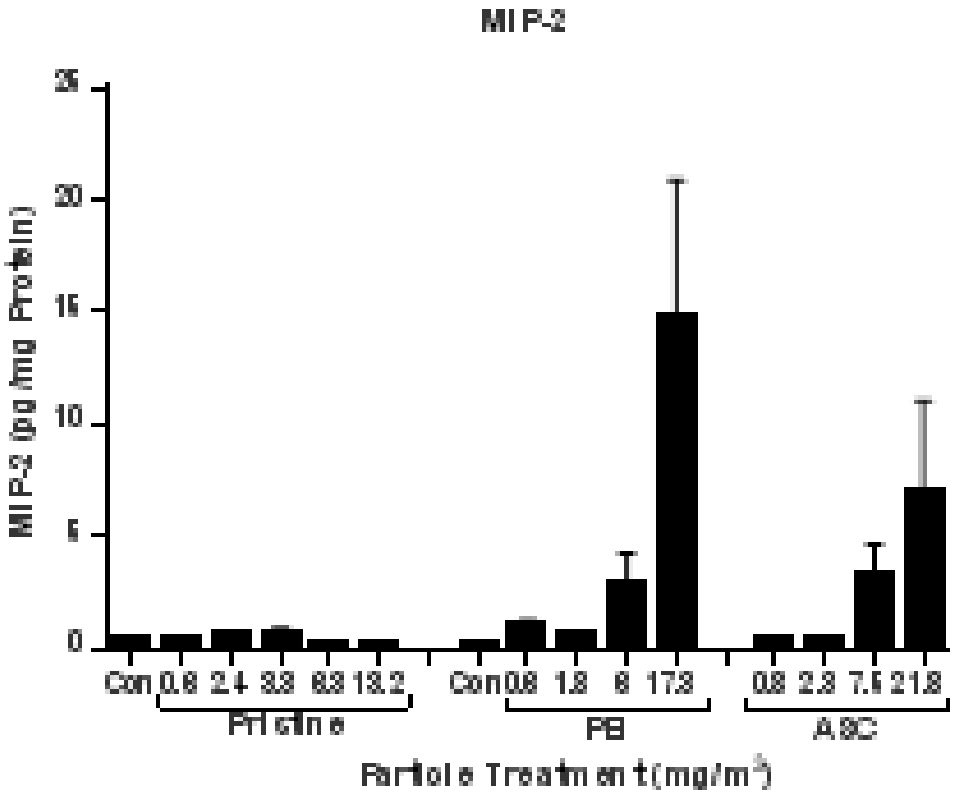
LDH release in lung





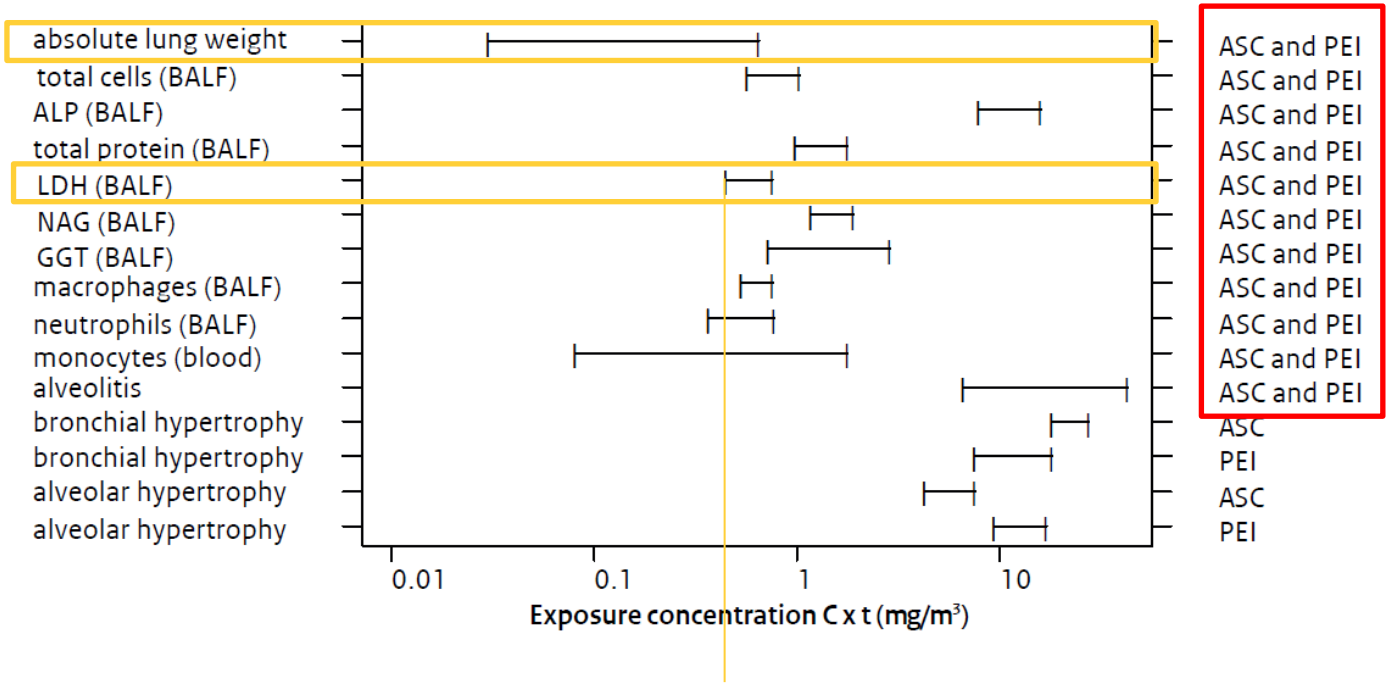
Levels return to baseline values 3-wk post-exposure

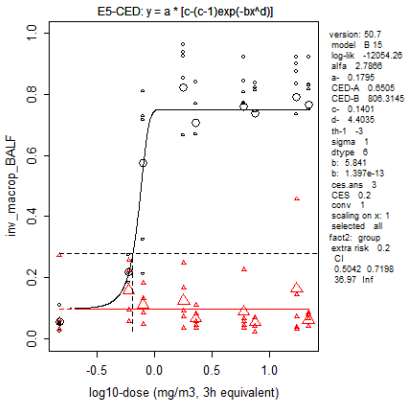
Comparing pristine and modified CuO



Modified seem slightly more potent inducing inflammation

Results modified CuO NPs





- Both positively charged and negatively charged CuO NPs lead to lung inflammation and cellular damage
- No differences were found after exposure to CuO-ASC and CuO-PEI except for histopathological markers bronchiolar and alveolar hypertrophy.

Conclusion modified CuO NPs

- In contrast to our hypothesis, the **ascorbate coating does not** protect against the pulmonary effects.
- Additional microarray analysis: might reveal a difference in pathway activation? → Karolinska – Bengt Fadeel and Health Canada – Sabina Halappanavar

Acknowledgements

RIVM
Ilse Gosens
Paul Fokkens
John Boere
Daan Leseman
Harm Heusinkveld
Wim de Jong
Liset de la Fonteyne
Piet Beekhof
Christiaan Delmaar
Bas Bokkers

Heriot Watt University
Vicki Stone
Daniele Pantano
David Brown

Karolinska Institutet
Lucian Farcal
Pedro Costa
Bengt Fadeel

University of Venice
Andrea Brunelli

VenetoNanotech
Michela Zanella
Laura Manodori

ISTEC
Anna Louisa Costa

Health Canada
Sabina Halappanavar

SUN coordination: Danail Hristozov and Antonio Marcomini

SUN

Sustainable Nanotechnologies Project

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

Pulmonary toxicity of surface modified copper oxide nanoparticles

Flemming R. Cassee