The effect of ultrafine or nanoparticles on lung cells

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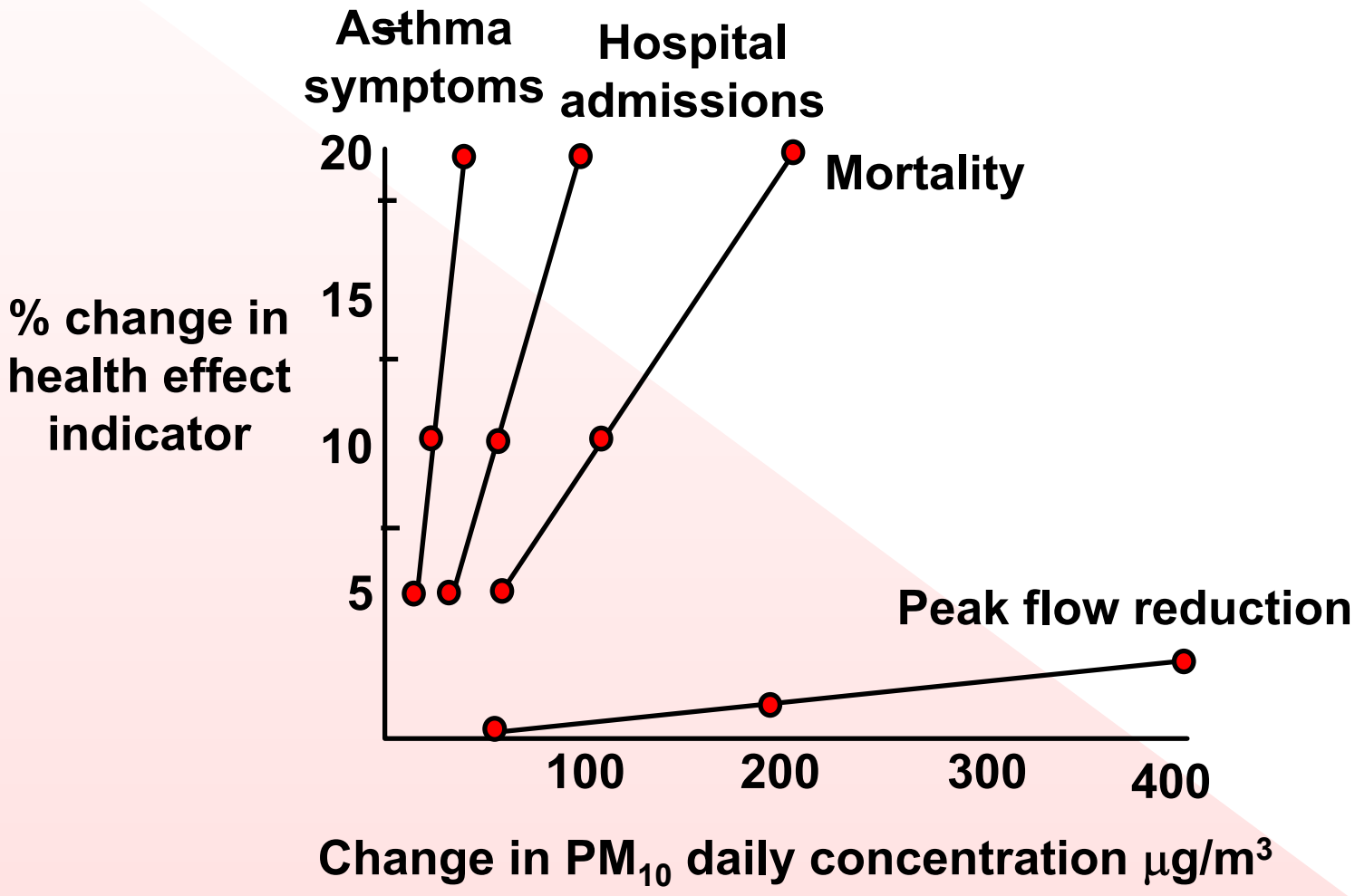
ELEGI

Institute of Occupational Medicine

Adverse health effects of PM_{10}

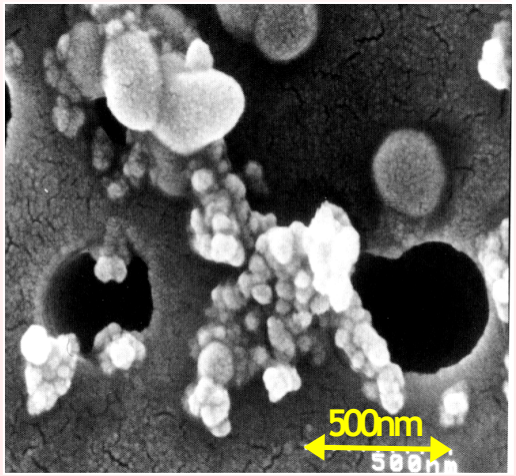


DoE 1995 and Richards 1997

PM_{10} Composition

Combustion derived carbon-centred
e.g. nanoparticles

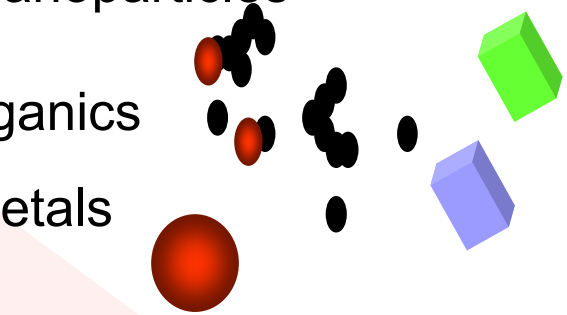
Secondary atmospheric chemistry eg ammonium nitrate

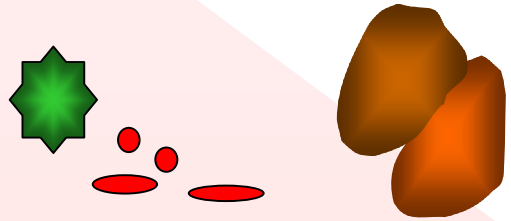


QUARG

Organics

Metals



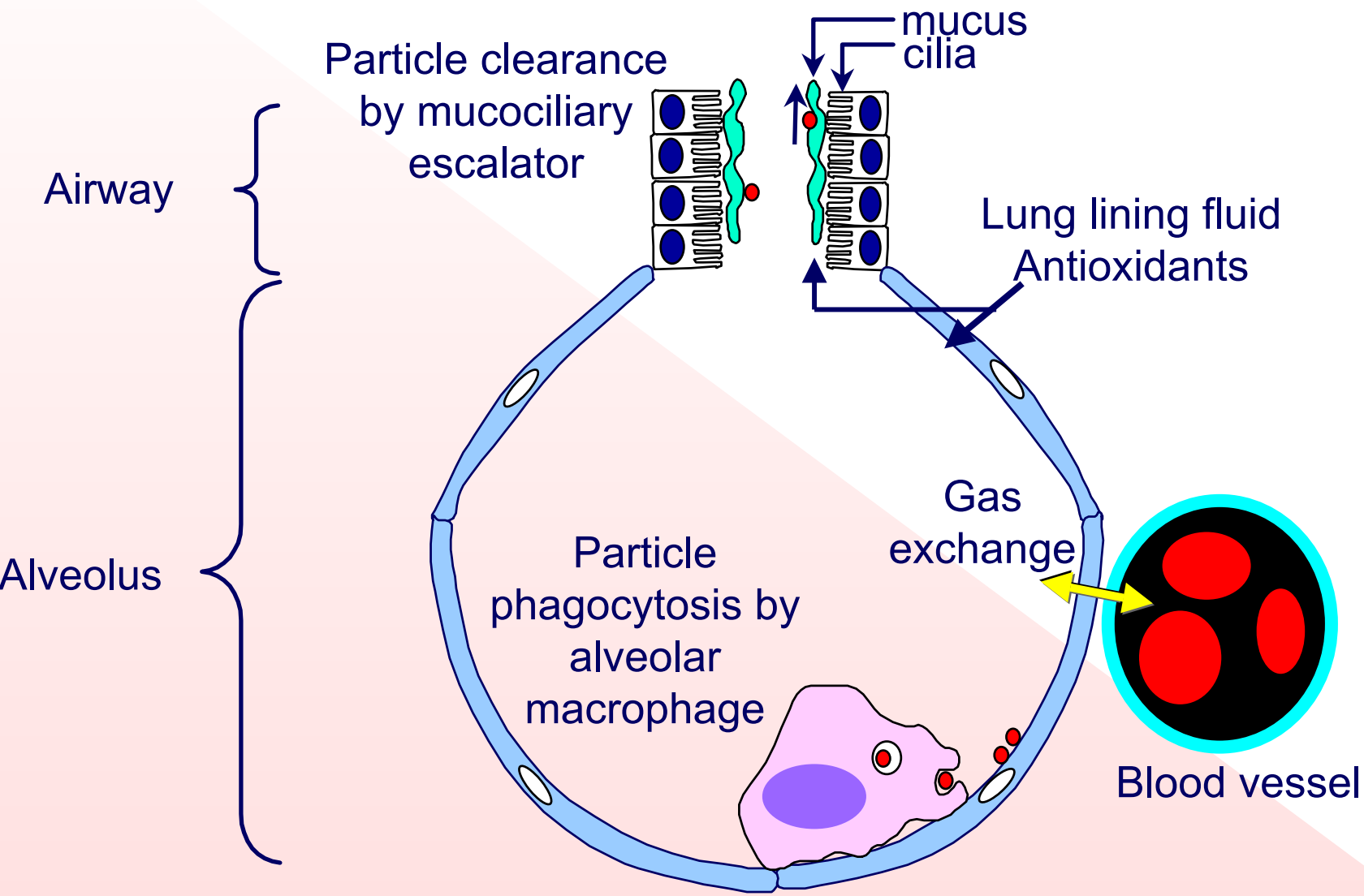


Biological
e.g. spores, bacteria

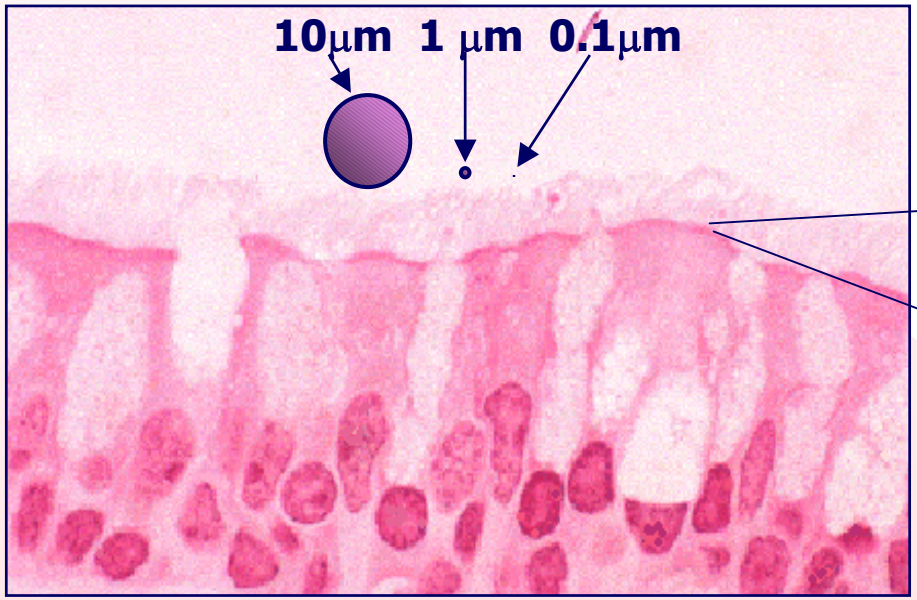
Natural minerals
e.g. soil, wind-blown

Which component is responsible for driving the adverse health effects?

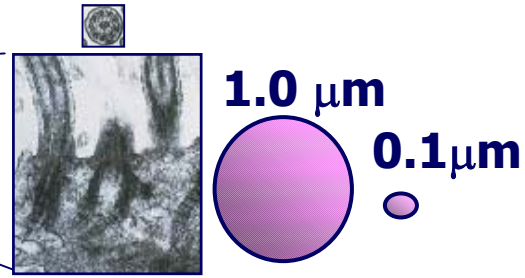
Investigating particle and cell interactions



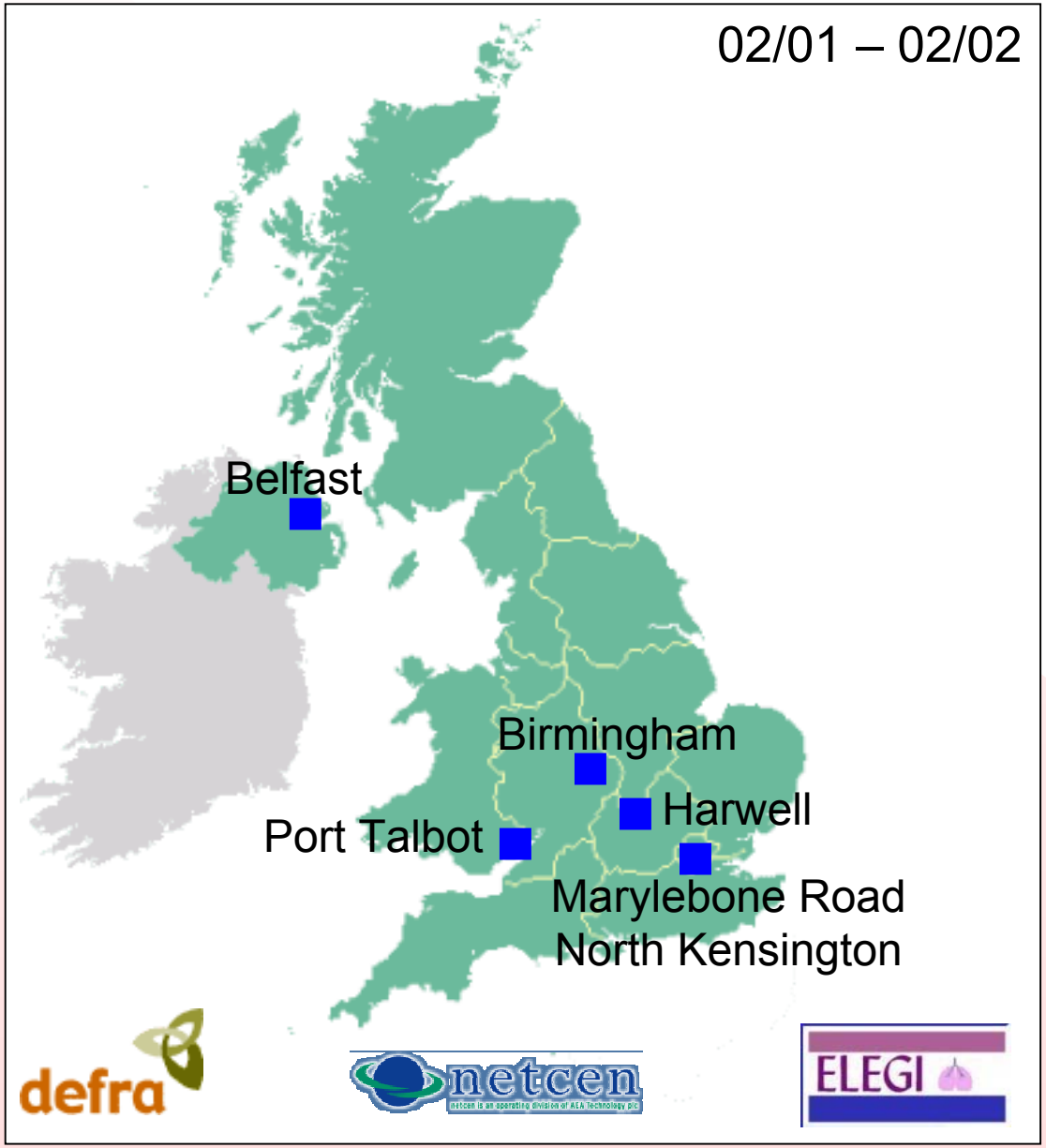
The relative size of nanoparticles to cells



Bronchial epithelium



UK sampling locations

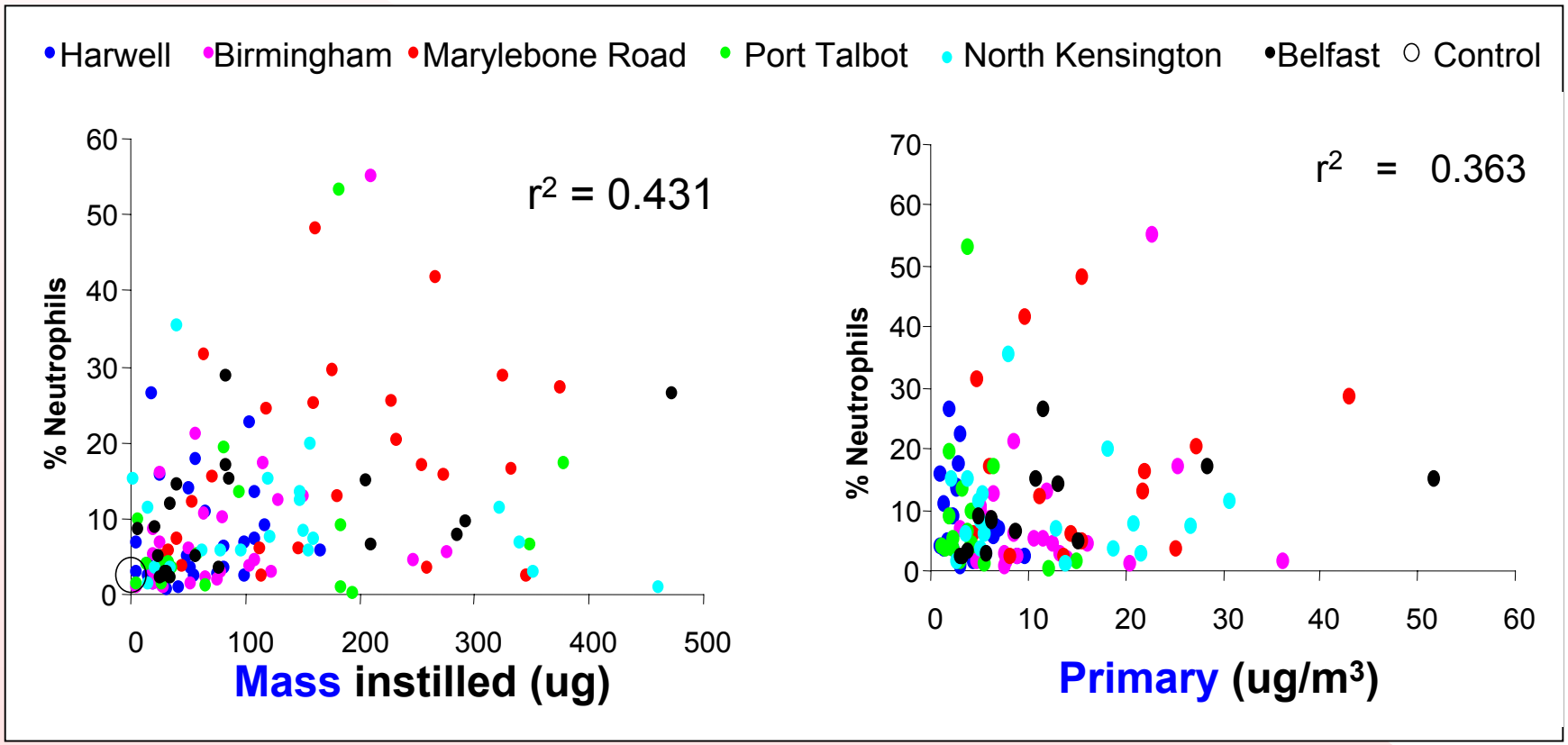


Samples collected for 24h
- 12 months for toxicology
  - *In vivo* inflammation
  - *In vitro*
- 6 months for metals analysis
  - Water soluble
  - Acid digest
  - ICP-MS

Source apportionment model
- Primary
- Secondary
- Coarse

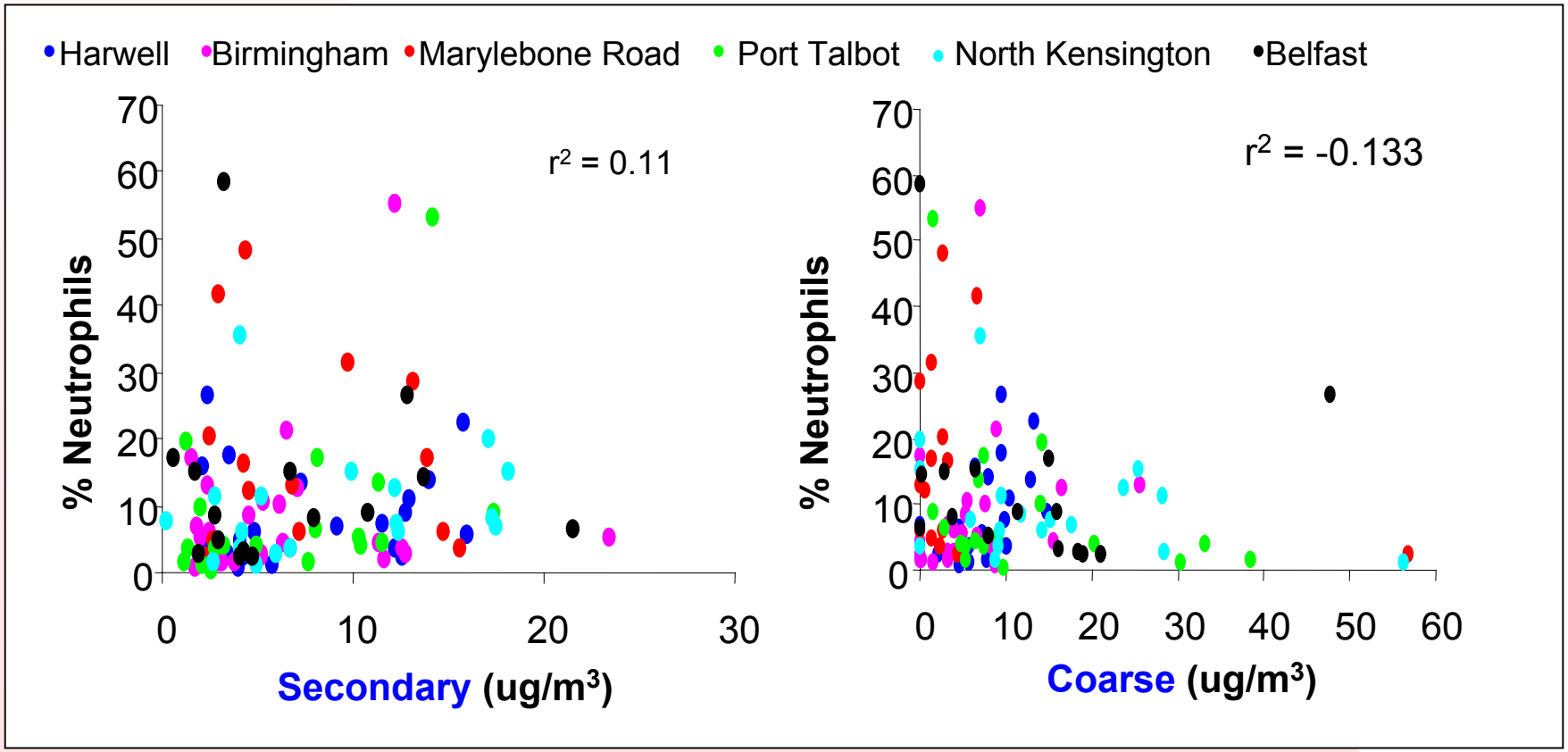
Endotoxin
- *Limulus* Amebocyte Lysate (LAL) assay

Relationship between PM_{10} mass, primary dose instilled and % neutrophils



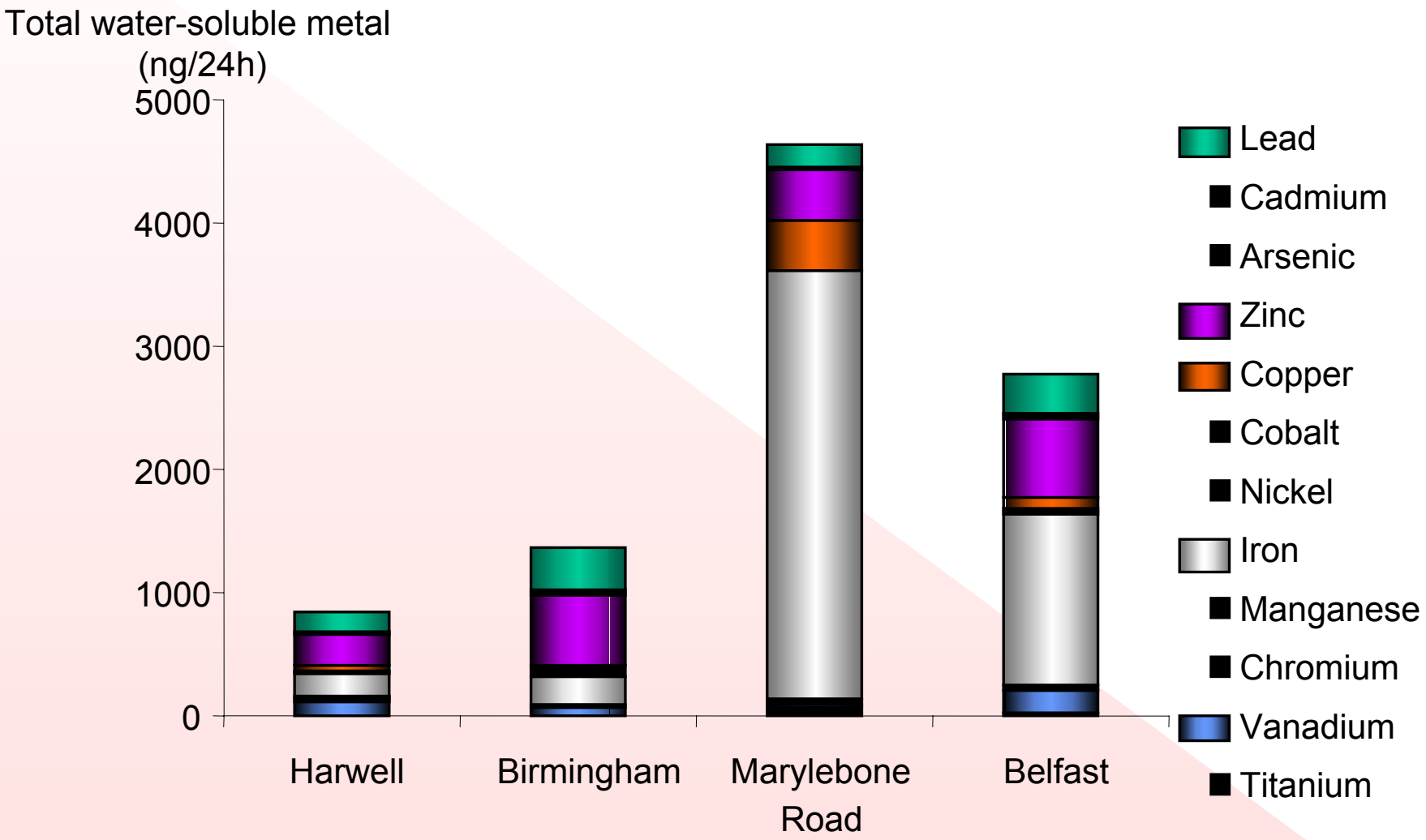
Lightbody *et al.*, 2003 Manuscript in prep

Relationship between PM_{10} composition and % neutrophils

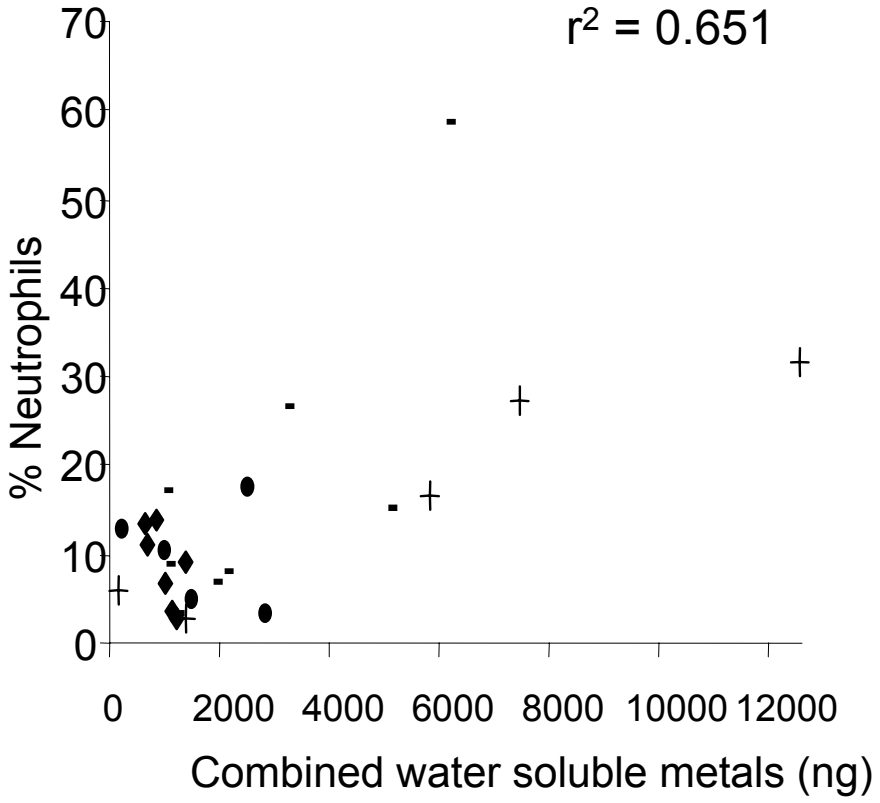


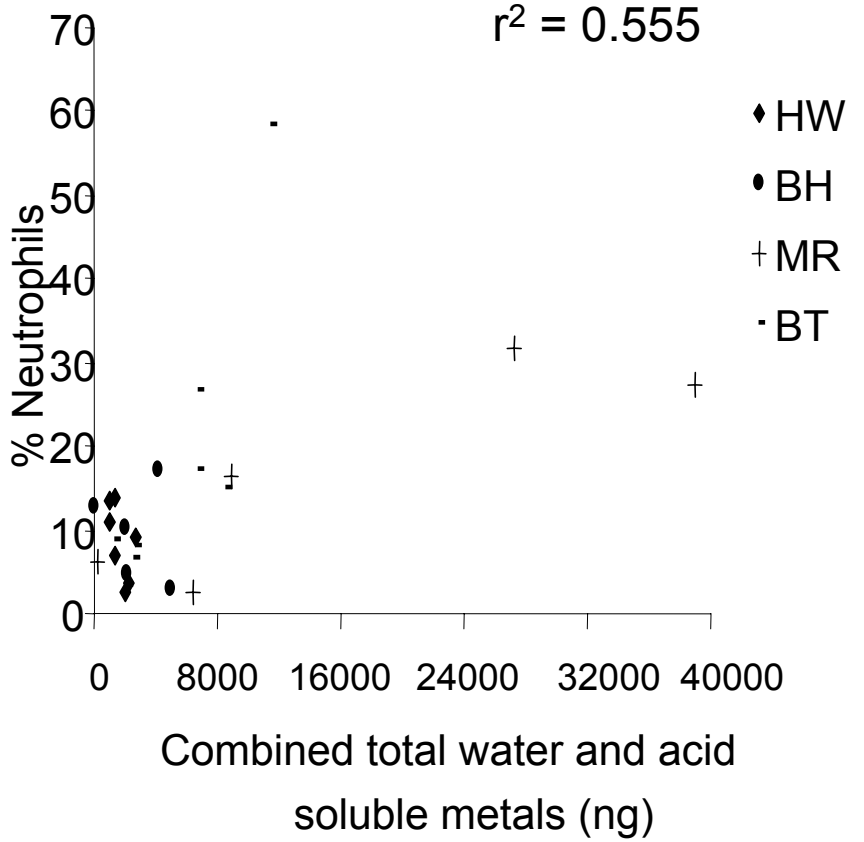
Lightbody *et al.*, 2003 Manuscript in prep

Metals analysis of PM_{10}

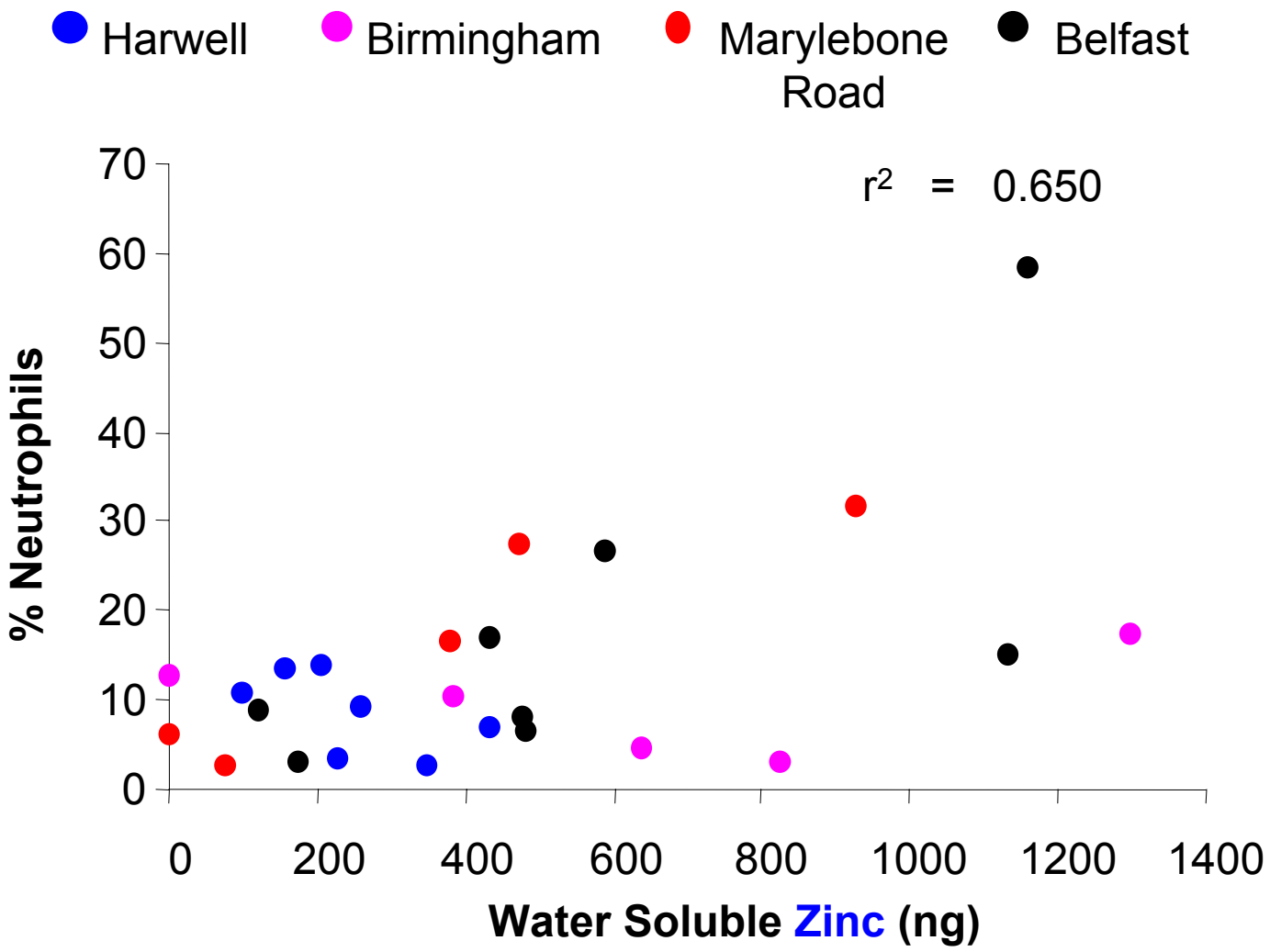


Relationship between PM_{10} metal composition and % neutrophils

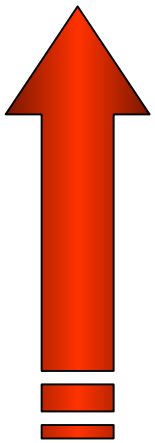




Relationship between PM_{10} water soluble zinc content and % neutrophils



Ranking of PM_{10} dose parameters driving inflammation



Increasing importance

Mass dose

Zinc (and nickel)

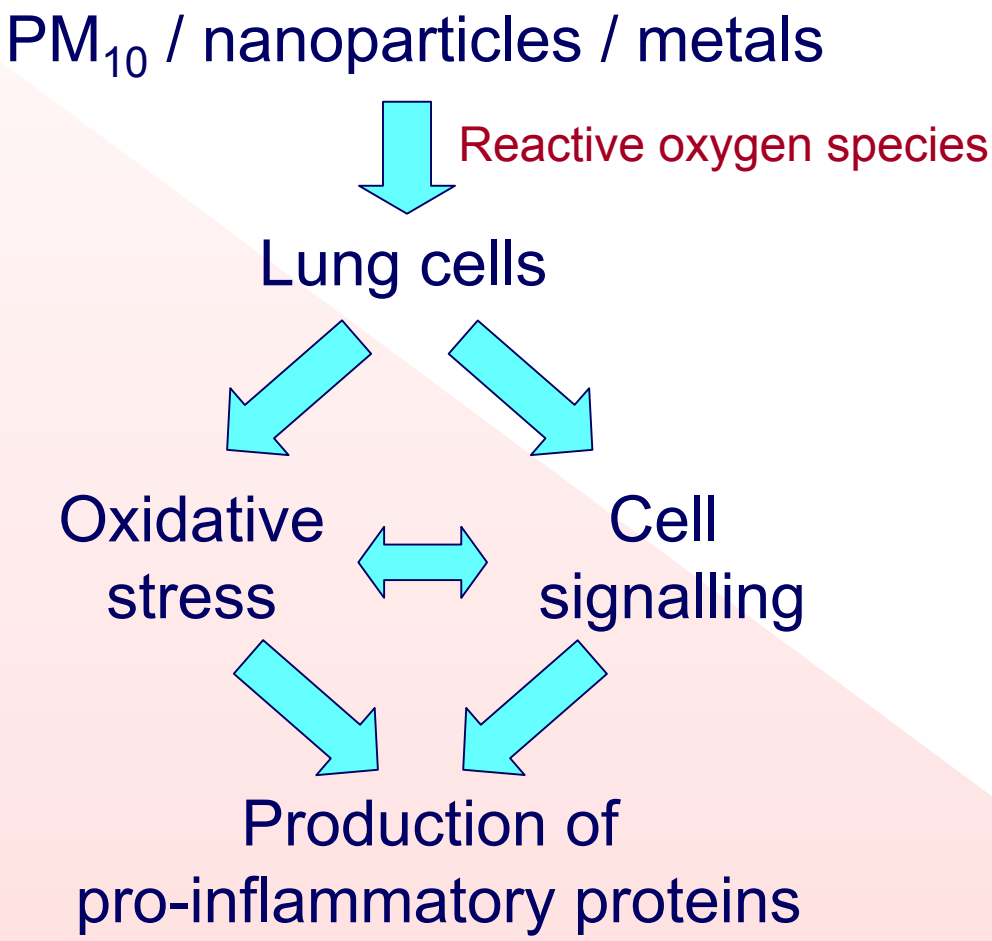
Primary

Secondary particles?

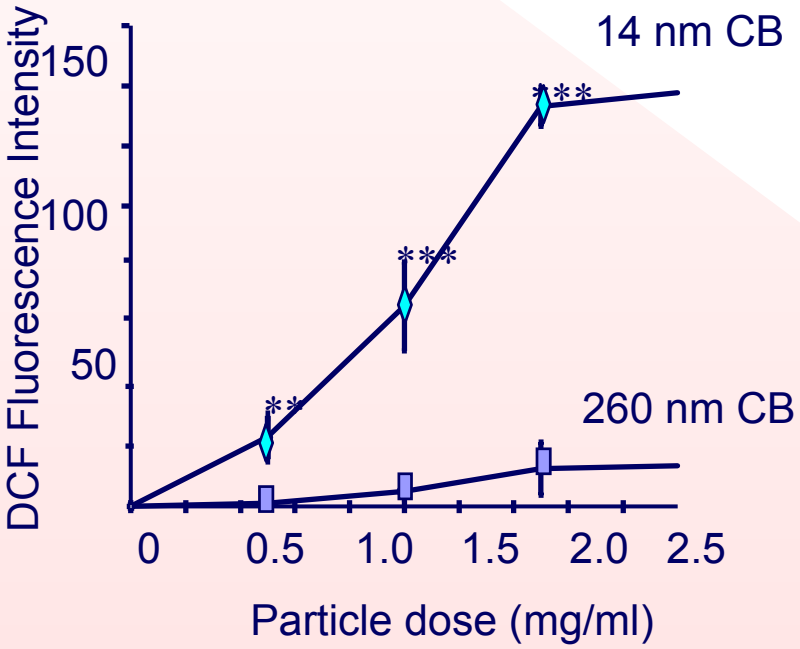
Endotoxin Coarse

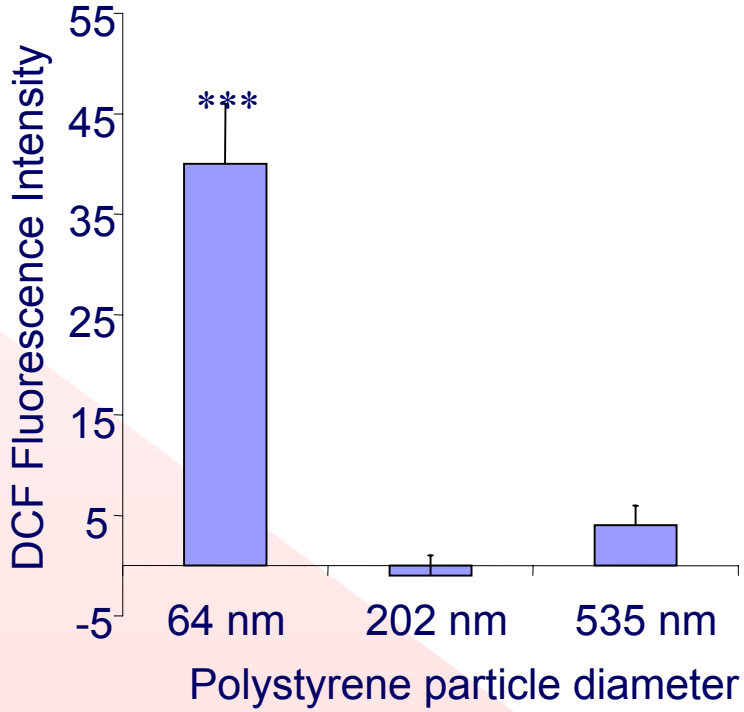
No clear relationship with inflammation

Mechanism


PM_{10} / nanoparticles / metals
Reactive oxygen species
Lung cells
Oxidative stress
Cell signalling
Production of pro-inflammatory proteins

Reactive oxygen species produced by nanoparticles

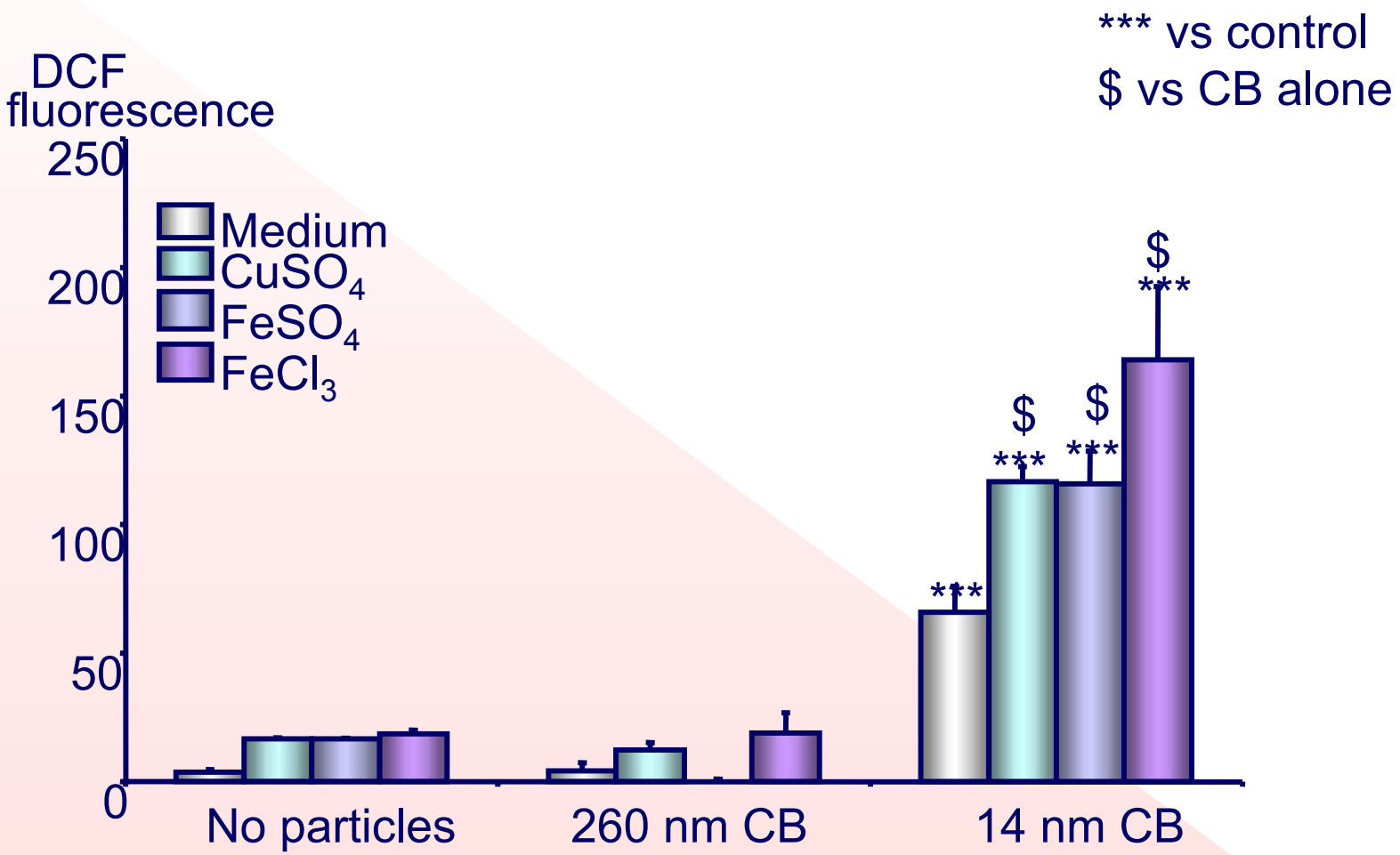




Wilson *et al.* 2002 TAP 184: 172-179.

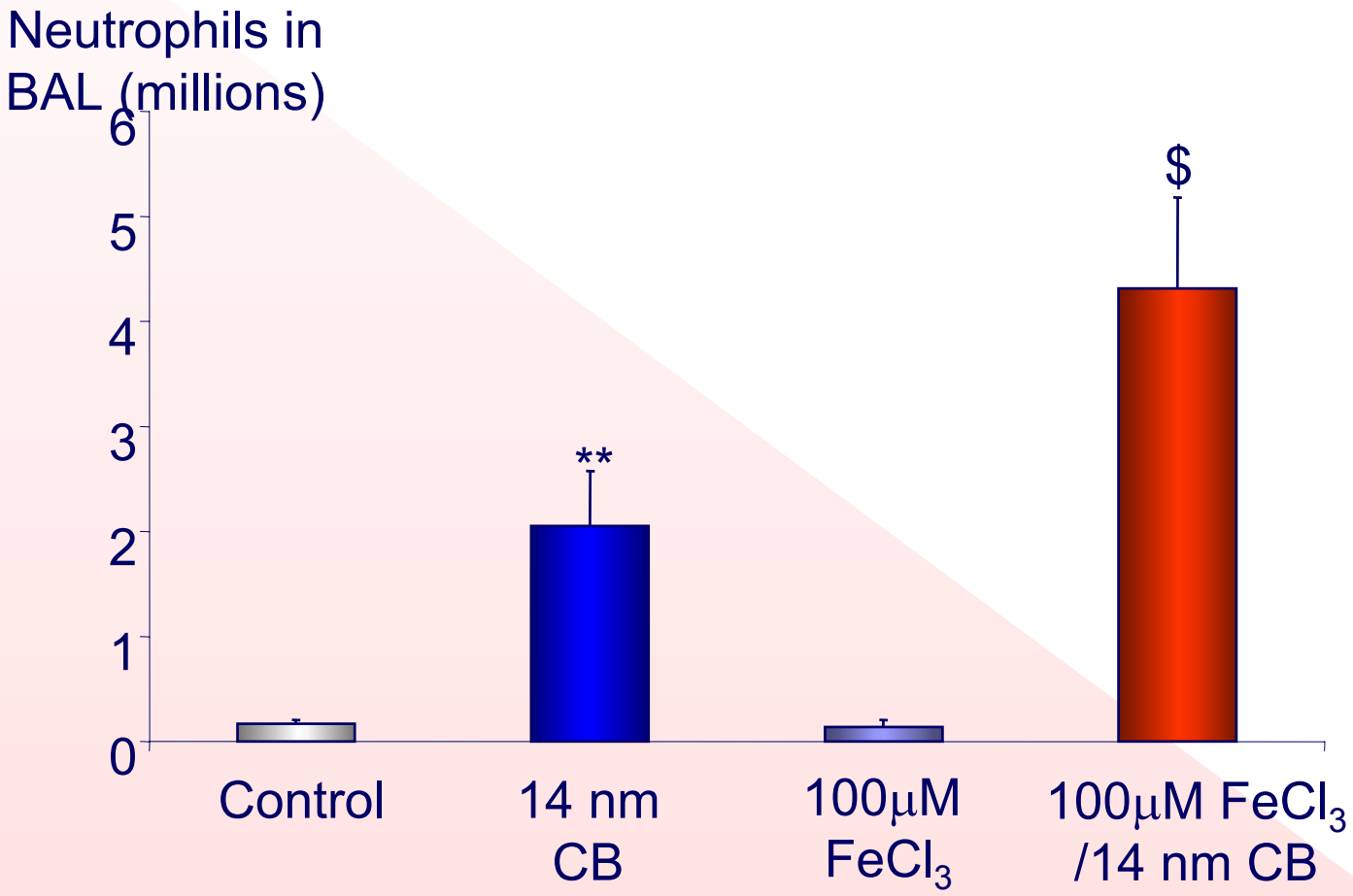
Brown *et al.* 2001 TAP 175: 191-199.

Reactive oxygen species production by particles and metals



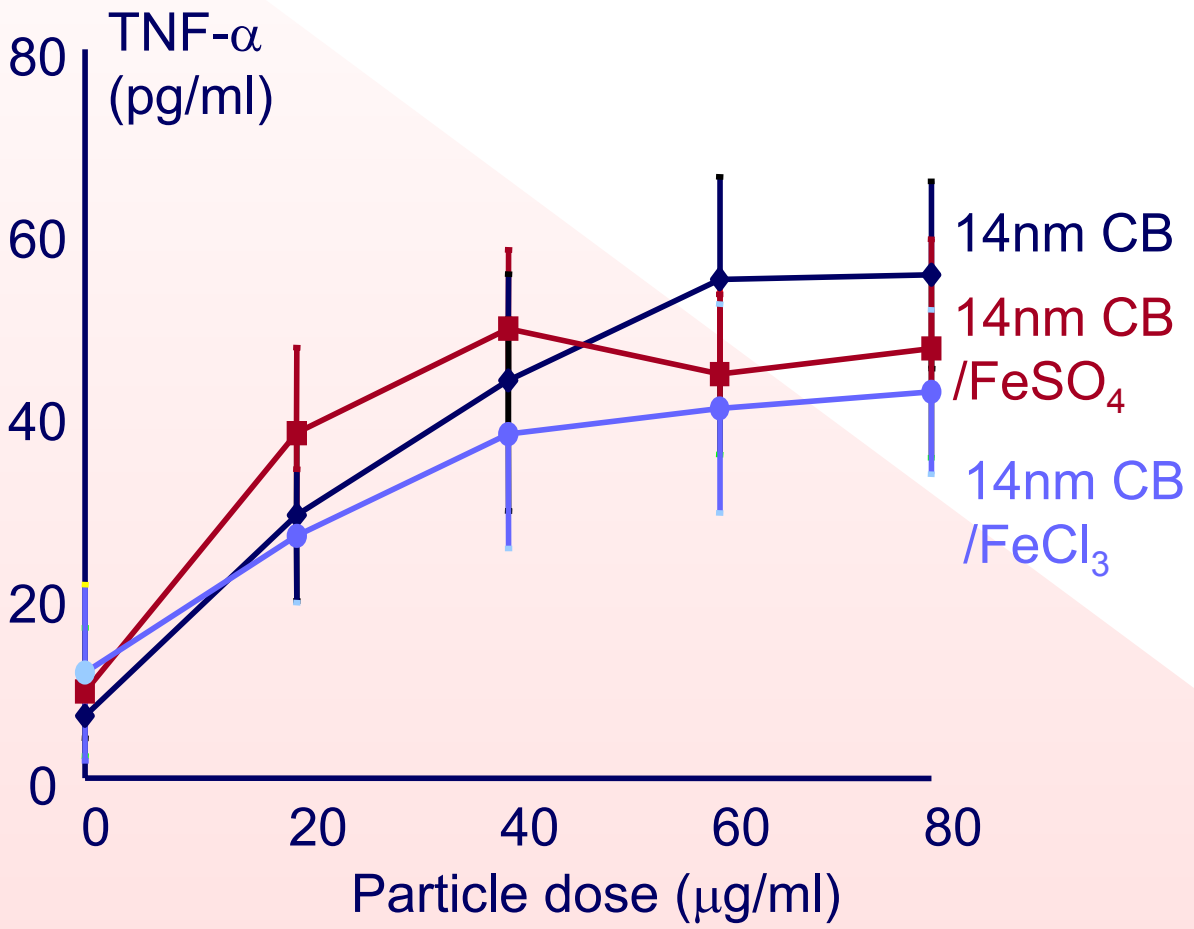
Wilson *et al 2002 TAP 184; 172-179*

Interactions between particles and metals *in vivo*



Wilson *et al 2002 TAP 184; 172-179*

Induction of ROS production in macrophages by particles and transition metal salts

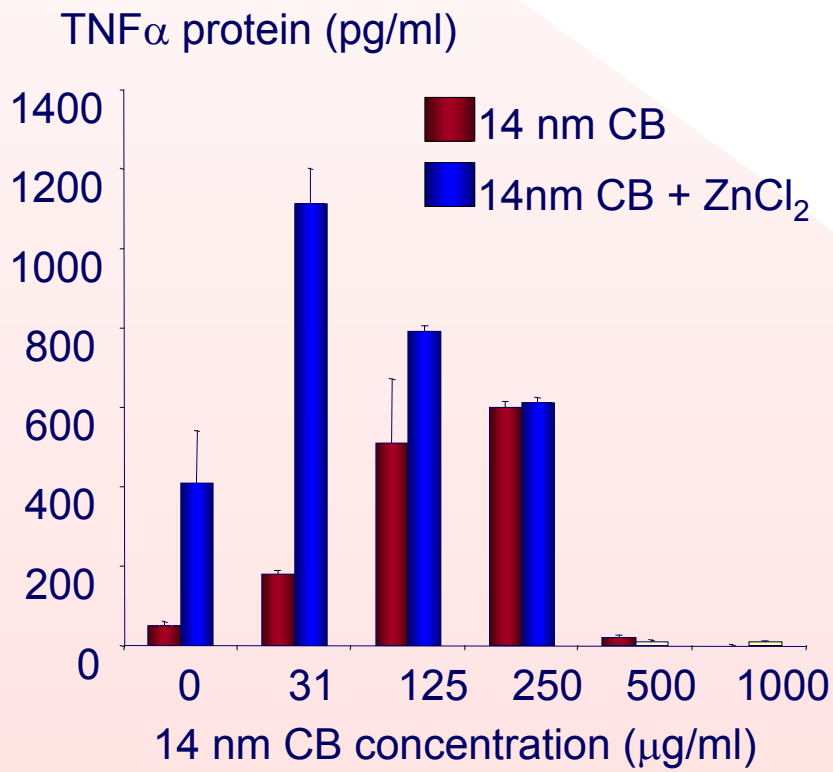


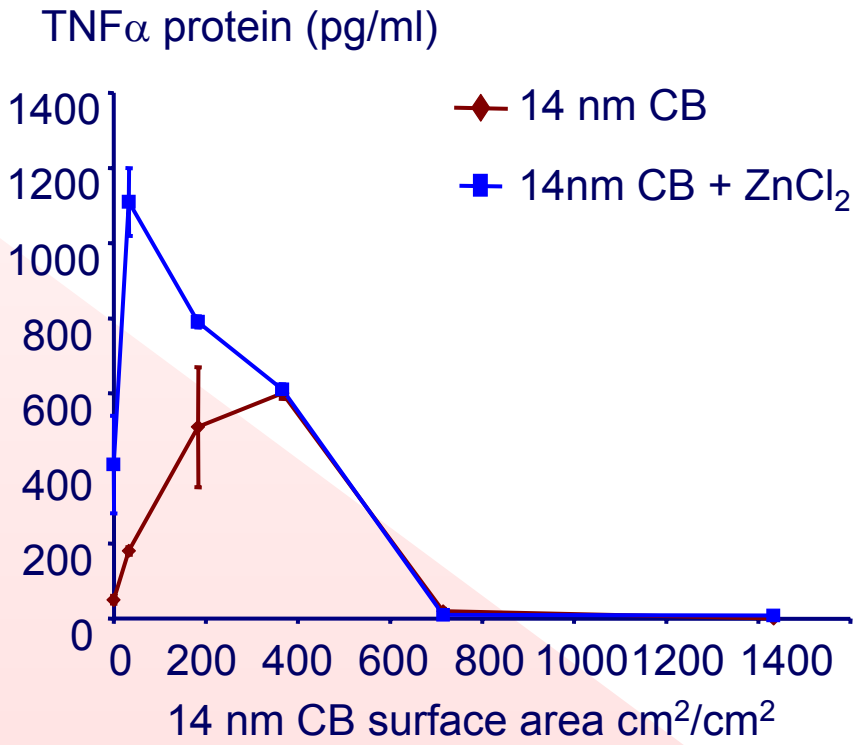
No interactions:

- TNFα protein
- GSH depletion
- ATP depletion

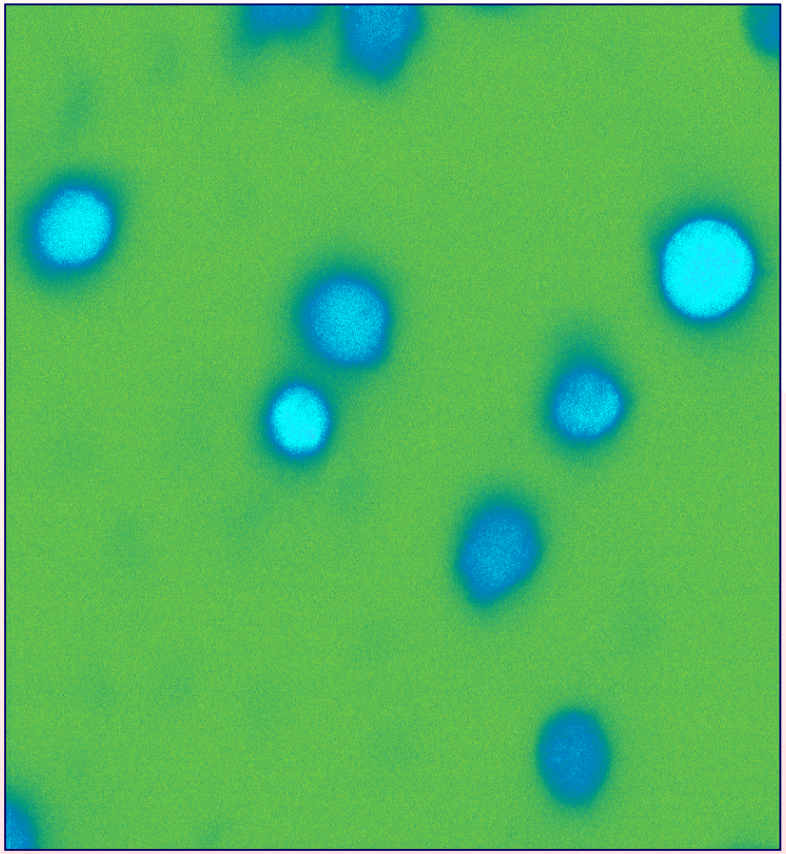
Wilson *et al* TAP (2002) 184; 172-179.

Interactions between particles and metals *in vitro*

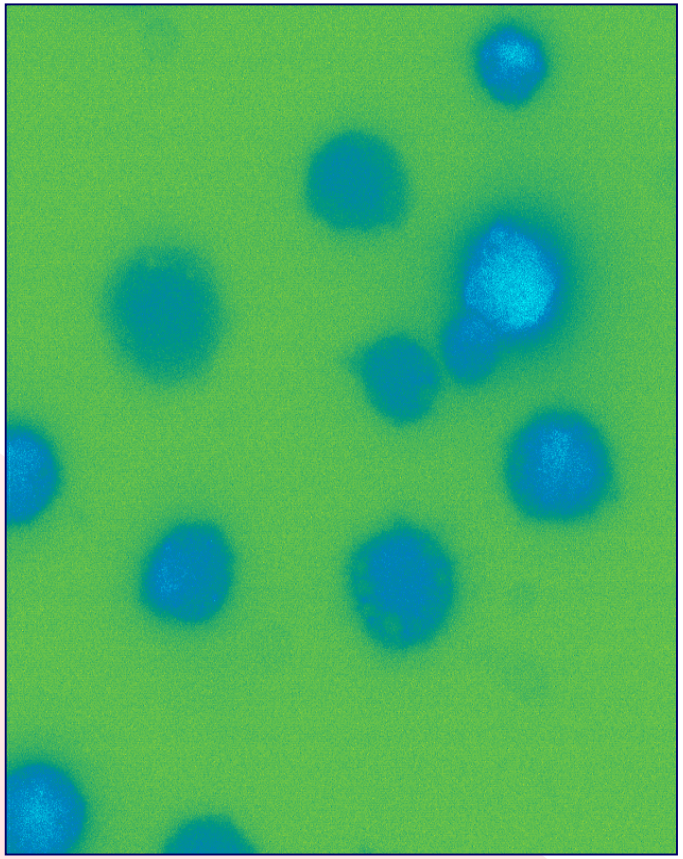




Calcium imaging of particle treated rat alveolar macrophages

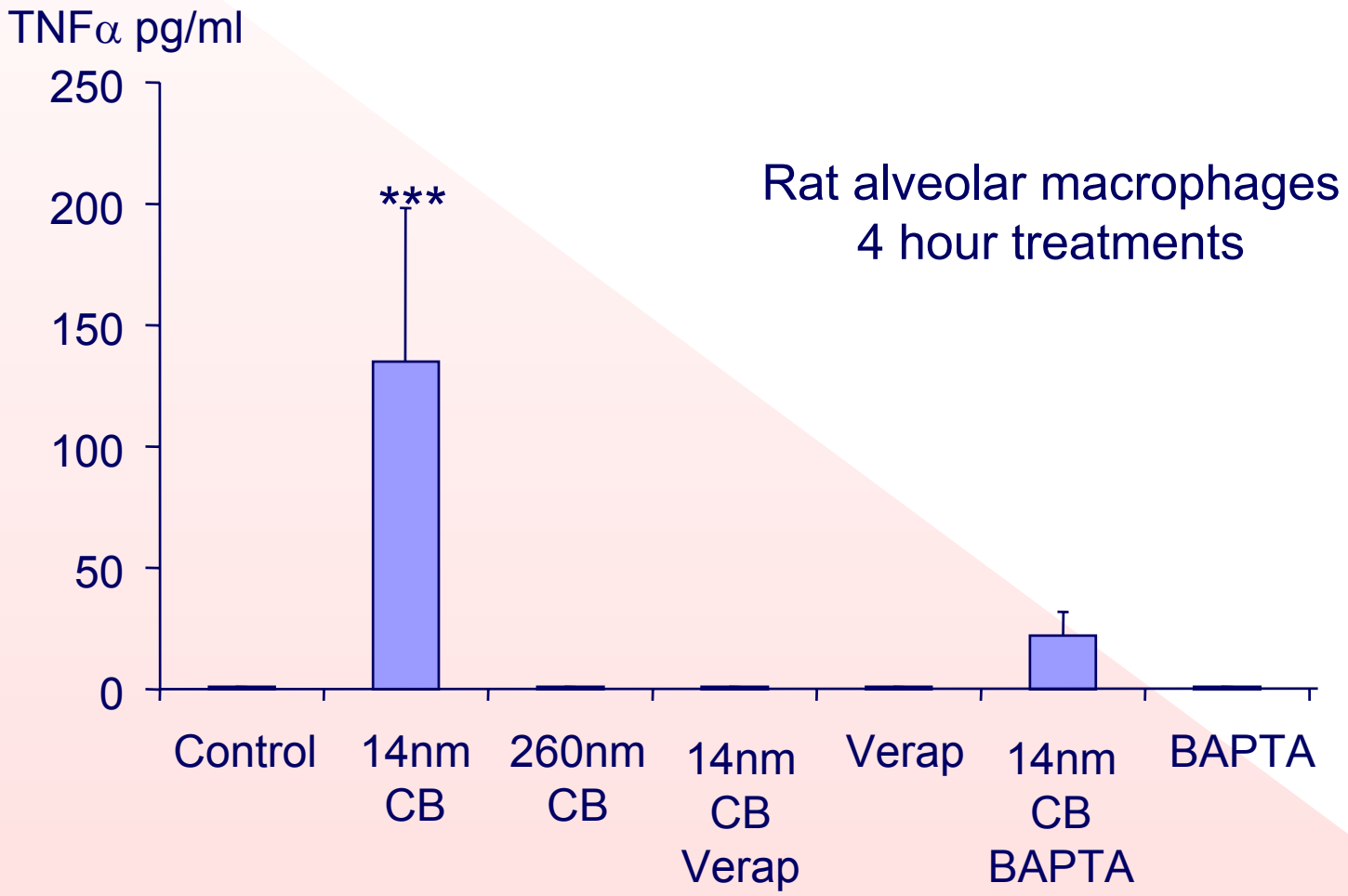


Control



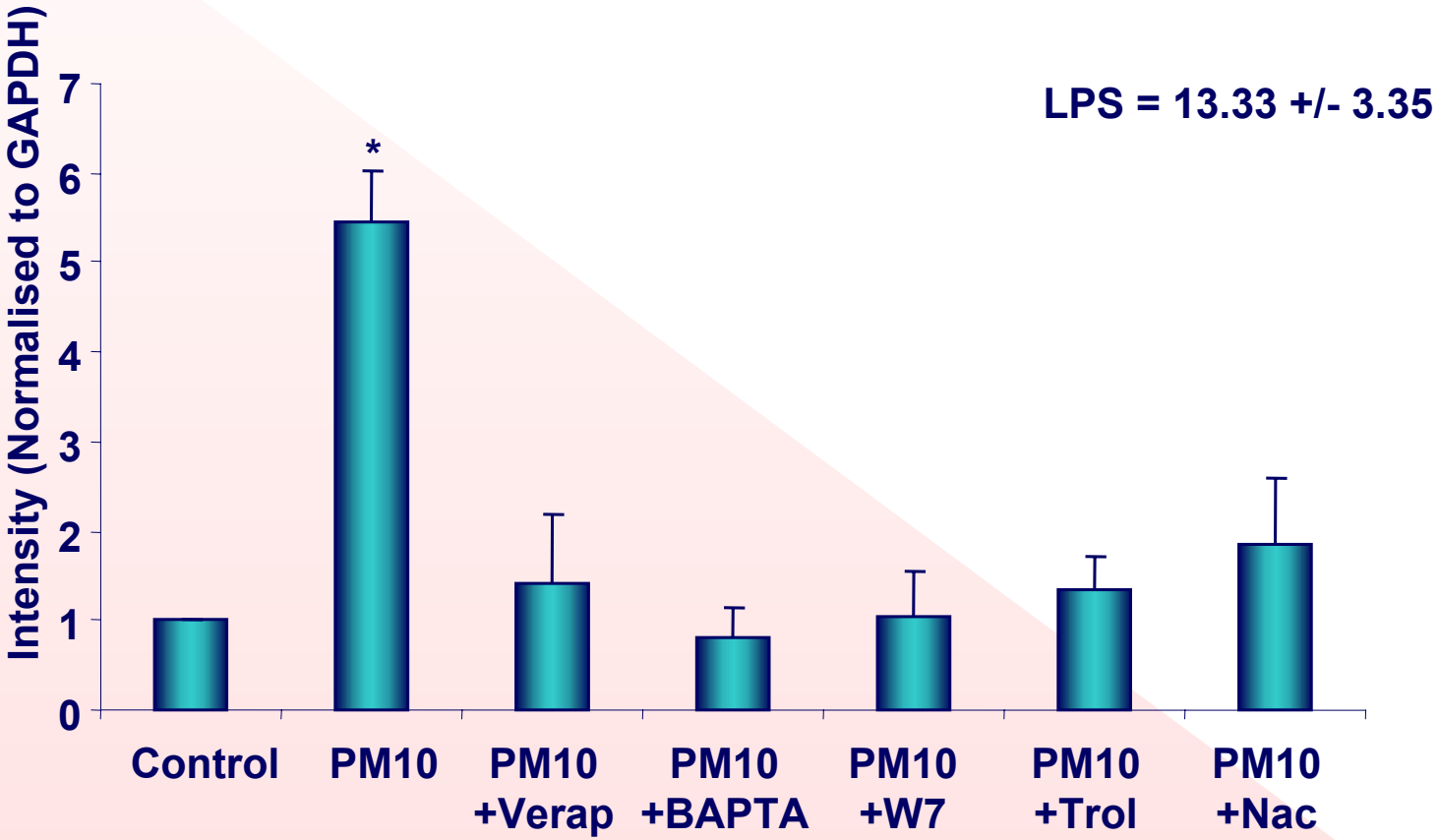
14 nm CB

The role of Ca^{2+} in the induction of TNFα protein expression by carbon nanoparticles



Brown *et al.* 2004 AJP 286: L344-L353

Inhibition of PM_{10} induced IL1α expression by calcium antagonists and antioxidants



Brown *et al.* manuscript in preparation

Summary

- The relationship between PM_{10} mass dose and inflammation was highly variable. Some of this variation was explained by composition, in particular metals and primary particles.

- Nanoparticles generate ROS, and this is enhanced by iron and copper salts.

- Nanoparticles induce inflammation and this is enhanced by iron.

- Nanoparticles stimulate macrophages to make TNFα. This is enhanced by zinc, but not iron.

- Nanoparticles stimulate TNFα production via ROS and calcium signalling.

Acknowledgements

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