FATE AND TRANSLOCATION OF INHALED GOLD PARTICLES

DR JENNIFER B RAFTIS
MRC CENTRE FOR INFLAMMATION RESEARCH, UNIVERSITY OF EDINBURGH
Clean Air Act 1968
(Tall chimneys)

1950s

Clean Air Act 1956
(Smokeless fuels)

Particles
130mg/m³

Vehicles on
UK roads
2 million

Clean Air Act 1993
(Smoke control areas)

<20mg/m³

35 million

Traffic derived
nanoparticles

Compared to the past we now have much less particles by weight but more very small traffic-derived particles by number.
Air Pollution and the Cardiovascular System

- Exposure to diesel exhaust has widespread actions throughout the cardiovascular system
Air Pollution and the Cardiovascular System

- Increased mortality from cardiovascular diseases with long-term exposure to air pollution
- Short-term exposure to urban air pollution linked to onset of myocardial infarction
- Underlying cause for link unknown
  - How does pollution cause cardiovascular effects?
  - Which components of air pollution are responsible?
- Associations strongest for particulate matter in air pollution
Biological Mechanisms

Air pollution → Lungs → ? → Cardiovascular Disease
Where do inhaled nanoparticles deposit

From Chapter 3 Kreyling et al in Particle Toxicology Eds Donaldson and Borm
Air Pollution and the Cardiovascular System

Removal of the ultrafine particles from diesel exhaust using a high efficiency particle filter prevents the vascular dysfunction associated with exposure to whole diesel exhaust.
The current hypotheses for the cardiovascular effects of inhaled particles

Combustion Derived Nanoparticles

1. Lung Inflammation

2. Particle Translocation

3. Autonomic Regulation

Lungs

Cardiovascular Impairment

Direct vascular interaction

Regulation of parasympathetic: sympathetic balance

Inflammatory mediators
Can nanoparticles translocate into the circulation?

- Lung-blood barrier is thin
- Huge surface area
- Nanoparticle translocation is highly plausible
- Has never been shown in man due to experimental limitations
- New approach was needed

Investigating particle translocation

**Difficulties**
- Small size of particles
- Low levels of particles that translocate
- Large volume of blood in the body
- Labels for tracking can come off particles
- Detection of carbon-based particles confounded by levels of carbon in cells
Gold nanoparticles

Why use gold?

- Size similar to particles in vehicle exhaust
- Largely inert
- Specialised techniques to measure very low levels
- Low levels of gold in the body
Inhalation of gold nanoparticles

- 14 healthy male subjects
- 2-hour inhalation of gold nanoparticles during exercise
- 3.8 nm diameter primary particle size
- 18 nm mean aerodynamic diameter
- Blood samples from 15 min – 24h & 3 months
- 24-h total urine collection

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<tr>
<td>Mass concentration</td>
<td>$116 \pm 12 , \mu\text{g/m}^3$</td>
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<tr>
<td>Particle number</td>
<td>$5.8 \pm 0.3 \times 10^6$ particles/cm$^3$</td>
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HR-ICMPS analysis of blood and urine

- Gold first detected in the blood 15 min after exposure and increased slowly over the next 6 hours.
- By 24H we could detect gold in the blood of all subjects.
- Gold was also detected in the urine, suggesting that this is one of the ways the nanoparticles were cleared from the body.
- Interestingly after 3 months gold was still detectable in the blood and urine suggesting that these particles are retained in the body for a long time.

Miller & Raftis et al. (2017). ACS Nano
Is particle translocation size dependent?

Clinical exposures

Murine exposures

Mean aerodynamic diameter
Smaller particle  18.2 ±1.2
Larger Particle  54.1 ±3.4

Gold nanoparticle (2, 5, 10, 30, 200 nm) suspensions instillation 50 μg twice per week

Miller & Raftis et al. (2017). ACS Nano
Do gold nanoparticles accumulate at areas of vascular disease?

- Gold nanoparticle (5 nm) suspensions instillation (50 μg) twice per week
- Measurement of gold in tissues using HR-ICPMS
- Following translocation do ultrafine particles accumulate in atherosclerotic plaque?

Miller & Raftis et al. (2017). ACS Nano
Detection of Gold in Tissue
Do gold nanoparticles accumulate at areas of vascular disease in man?

**Inclusion criteria**
- Patients with carotid stenosis due to undergo CEA

**Exclusion criteria**
- Recent body piercing or history of gold tooth filling
- Jewellers by trade
- Psychiatric illness/social situations that would limit compliance with study requirements
- Patients with new stroke and a modified Rankin score >3
- Pregnant women
- Participation in the study would result in delay to surgery
- History of allergic reaction attributed to elemental gold or molecules including gold
Gold nanoparticles accumulate at areas of vascular disease in man

Miller & Raftis et al. (2017). ACS Nano
Summary

• Gold was detected in the blood and urine within 15 min – 24 h after inhalation, and was still detectable 3-months after exposure.

• Translocation was size dependent in man with greater levels of gold detected following inhalation of 5 nm (primary diameter) particles compared to 30 nm particles.

• Studies in mice confirmed the size dependent translocation with markedly greater translocation for particles <10 nm diameter.

• Gold nanoparticles accumulated preferentially in the inflammatory vascular lesions of ApoE-/ mice as opposed to non-diseased areas of the vasculature.

• Following inhalation, gold particles could be detected in surgical specimens of carotid artery disease from patients at risk of stroke.

• Translocation of inhaled nanoparticles into the systemic circulation and accumulation at sites of vascular inflammation provides a direct mechanistic link between environmental nanoparticles and cardiovascular disease, and has major implications for risk management in the use of engineered nanomaterials.
University of Edinburgh, UK
Dr Rodger Duffin
Prof Nick Mills
Dr Mark Miller
Prof David Newby
Prof Ken Donaldson
Prof Colin Campbell
Dr Simon Wilson
Dr Jeremy Langrish
Dr Alex Vesey
Dr Anoop Shah
Dr Amanda Hunter
Dr Patrick Hadoke
Dr Lorraine Bruce
Shea O’Connell
Ian Smith
Steve McLean
Callam Davidson
Annalise Gastaldello
Eileen Miller
Pawitrabhorn Samutrtau

RIVM, Netherlands
Prof Flemming Cassee
Paul Fokkens
John Boere
Daan Leesman

HR-ICPMS
Dr Petra Krystek

Clinical Research Facility Edinburgh Royal Infirmary

Volunteers and Patients

The Colt Foundation
Occupational & Environmental Medicine

British Heart Foundation
NHS Lothian