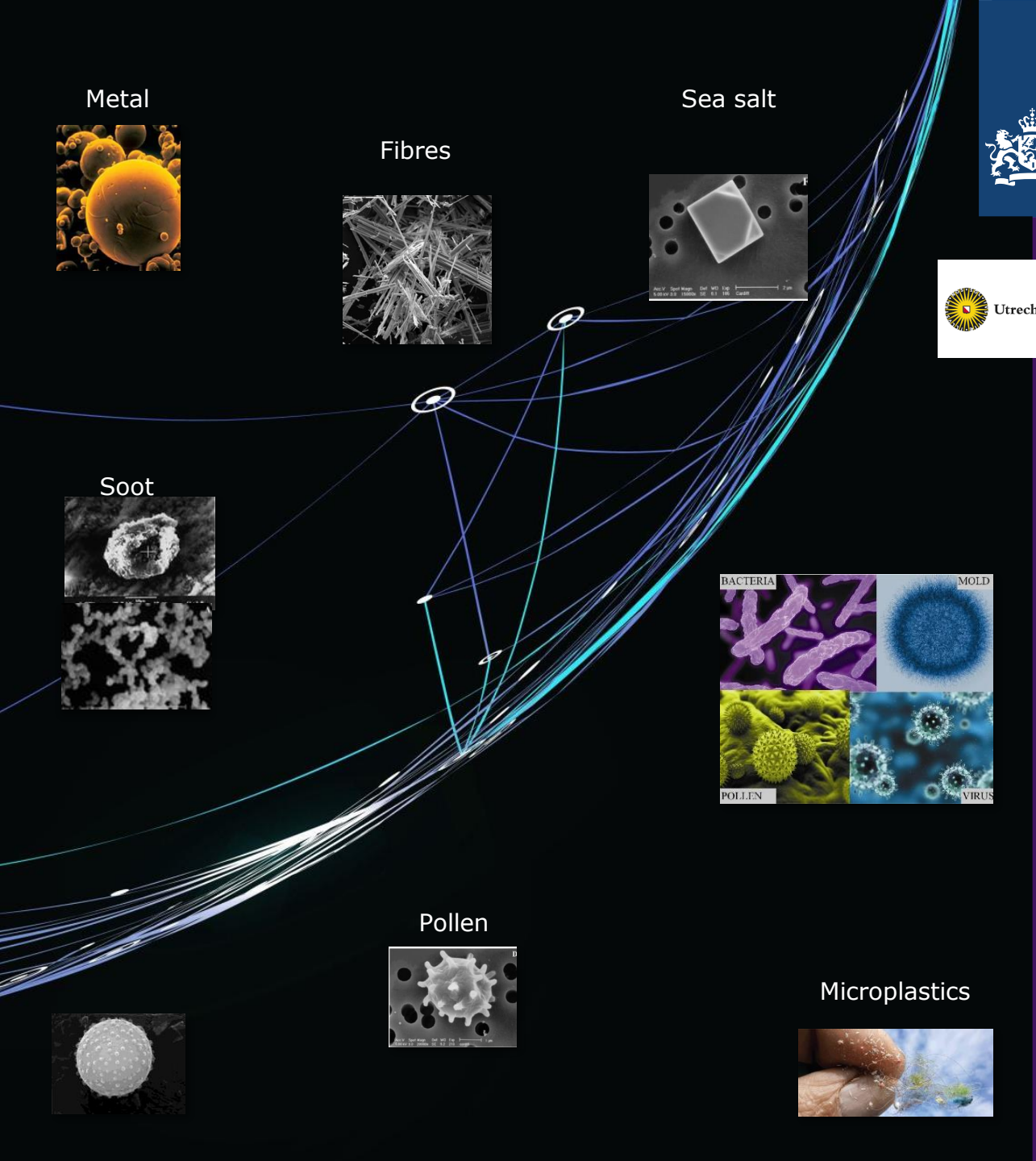
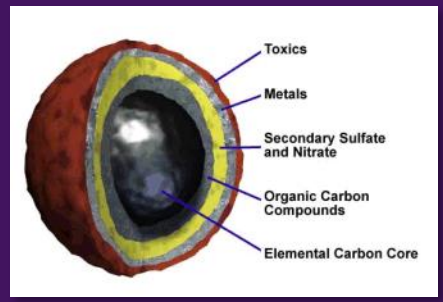


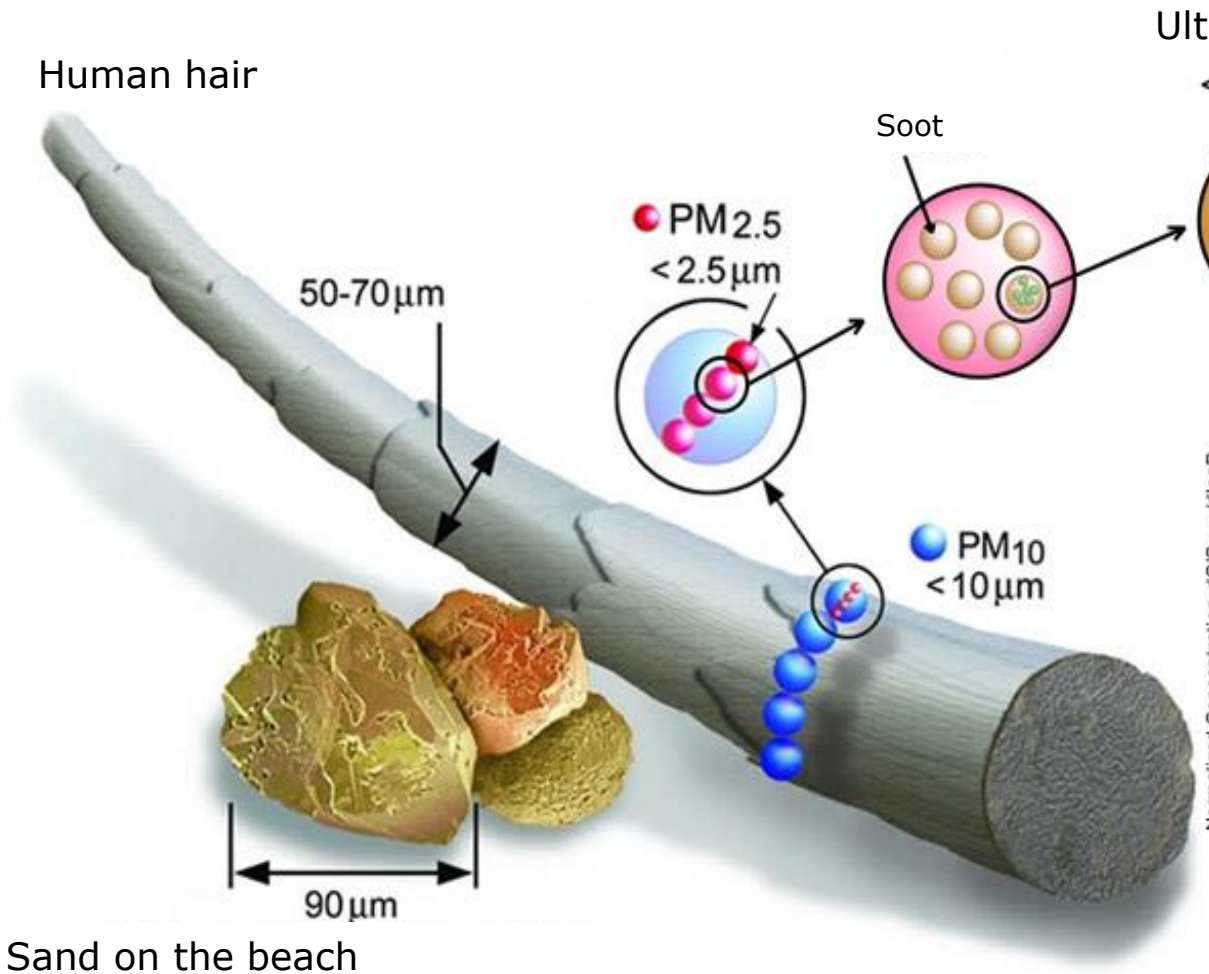
National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

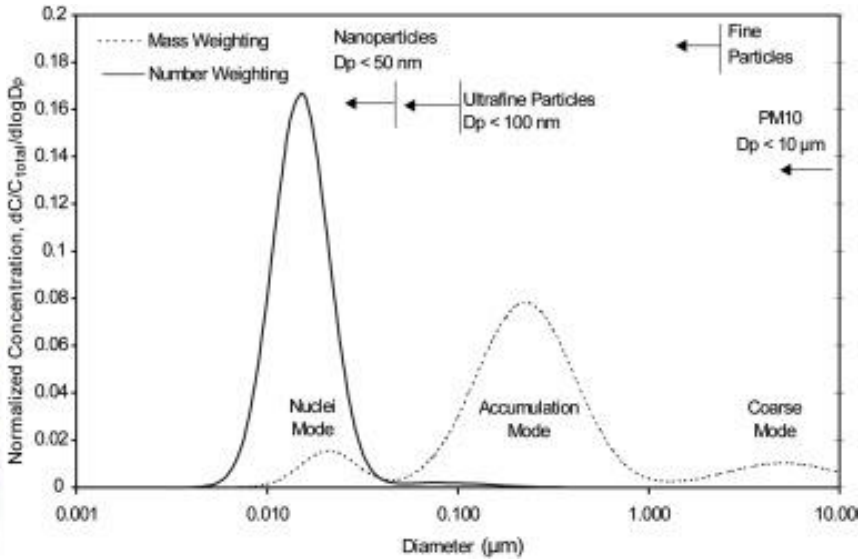
Utrecht University



Health effect due to ultrafine solid particles of increasing concern?

Flemming R. Cassee, PhD ERT

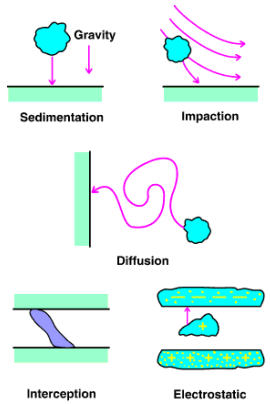


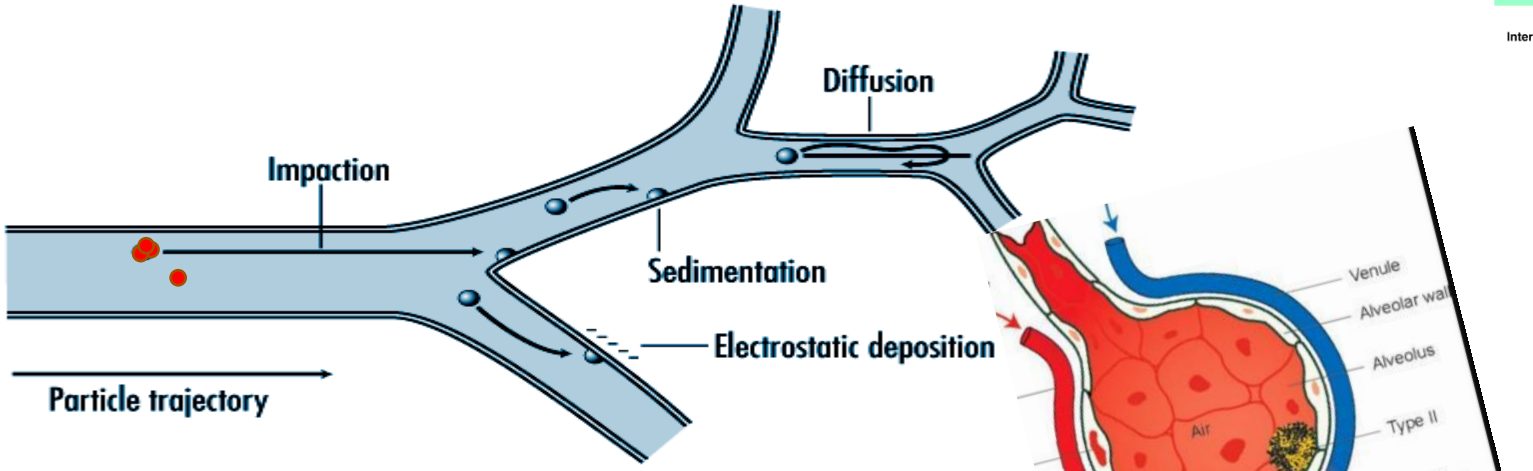


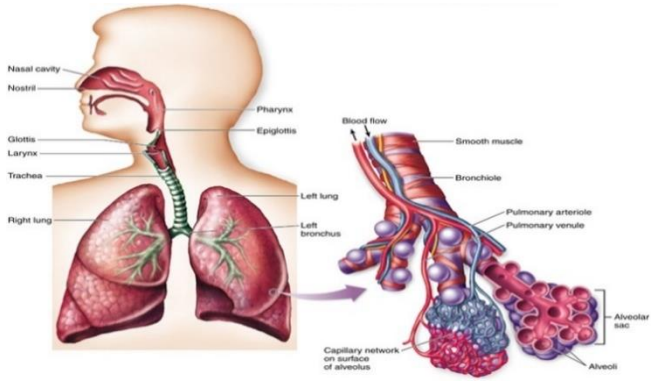
1 µm is 0.000001 meter is 0.001 millimeter

Basis figuur:EPA (USA)

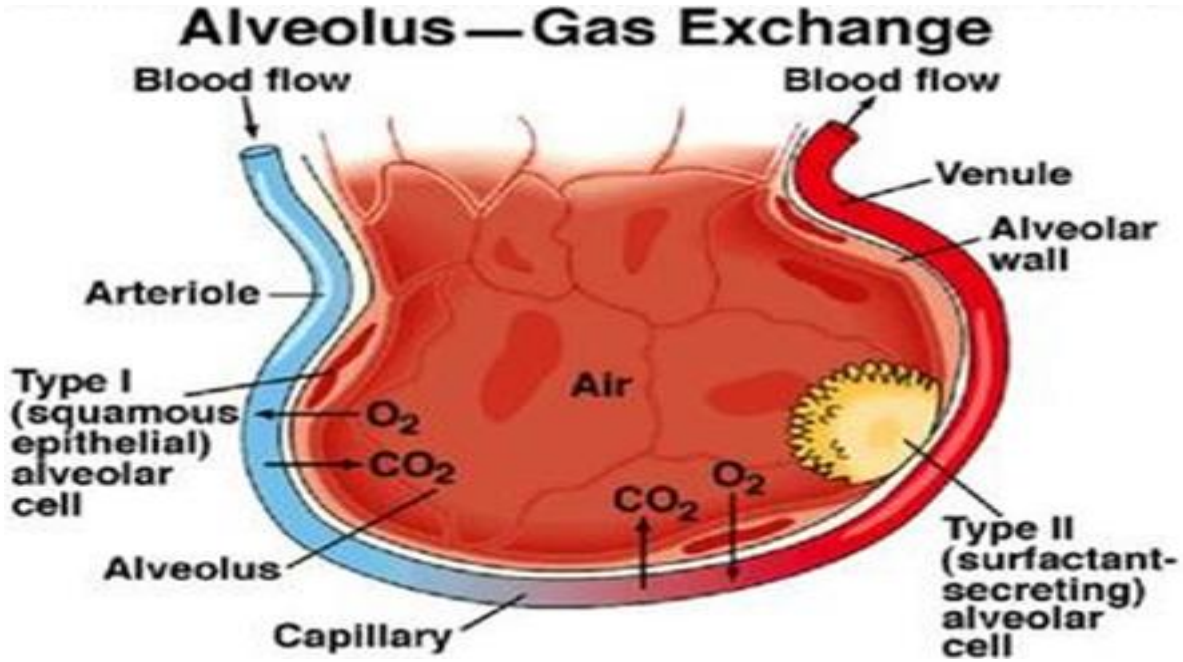
Mechanisms of particle deposition

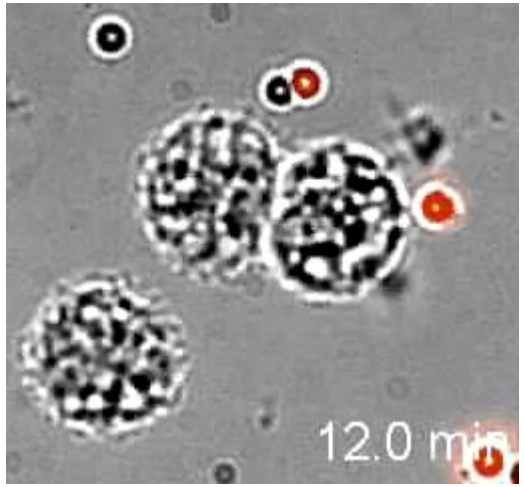






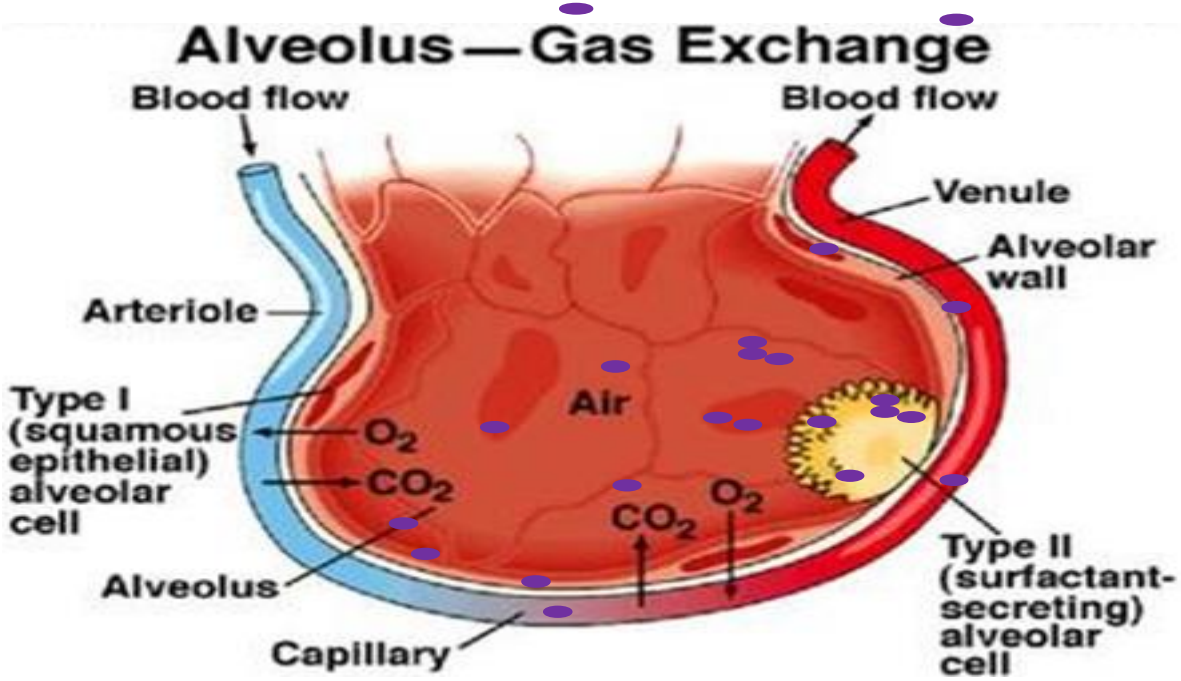
Size matters: micro particle external concentration x mg/m^3





Clearance micro-size particles within 6-14 hr

Size matters: nanoparticle: also external concentration x mg/m^3



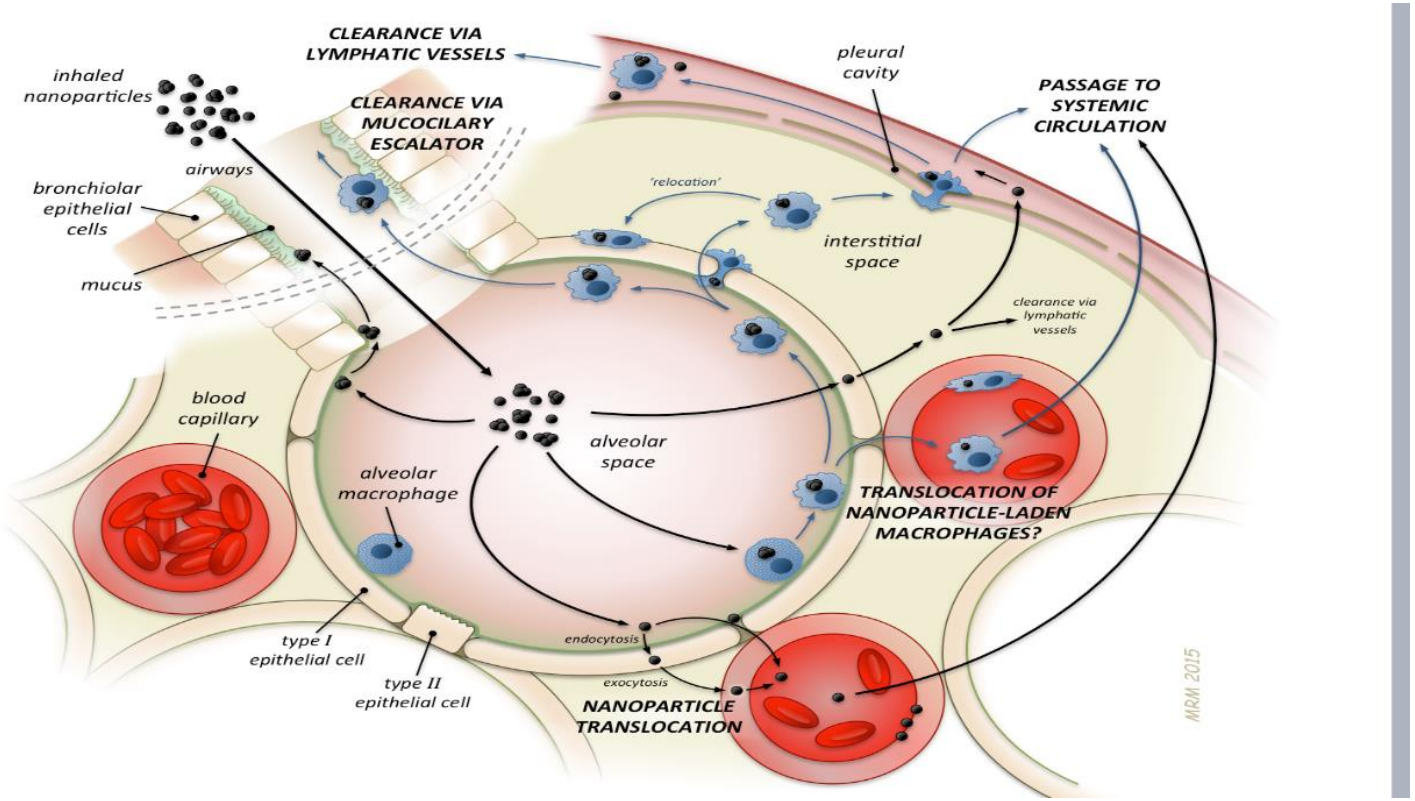
Ultrafine particle uptake by epithelial cells + interstitial translocation + lack of macrophage recognition

Size matters in terms of

- Deposition
- Clearance
- Retention
- Biodistribution

- Smallest particles can reach other organs explaining sytemic effects

- They come from different sources



Stone, Cassee et al, EHP, 2017

Diesel, particle trap and thrombus formation
A study in volunteers

Increase thrombus

Decrease thrombus

Particle Traps Prevent Adverse Vascular and Prothrombotic Effects of Diesel Engine Exhaust Inhalation in Men

Andrew J. Lucking, MD*; Magnus Lundbäck, MD, PhD*; Stefan L. Barath, MD; Nicholas L. Mills, MD, PhD; Manjit K. Sidhu, MD; Jeremy P. Langrish, MD; Nicholas A. Boon, MD; Jamshid Pourazar, PhD; Juan J. Badimon, MD, PhD; Miriam E. Gerlofs-Nijland, PhD; Flemming R. Cassee, PhD; Christoffer Boman, PhD; Kenneth Donaldson, PhD; Thomas Sandstrom, MD, PhD; David E. Newby, MD, PhD; Anders Blomberg, MD, PhD

1726 Circulation April 26, 2011

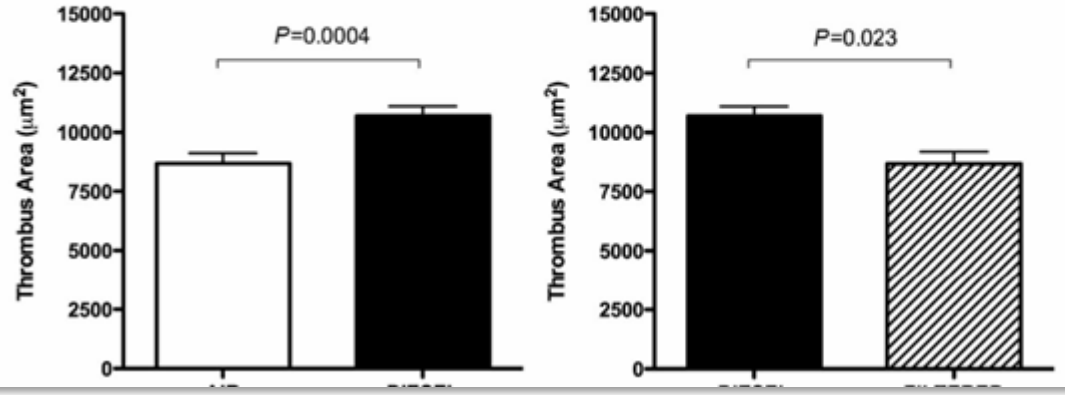
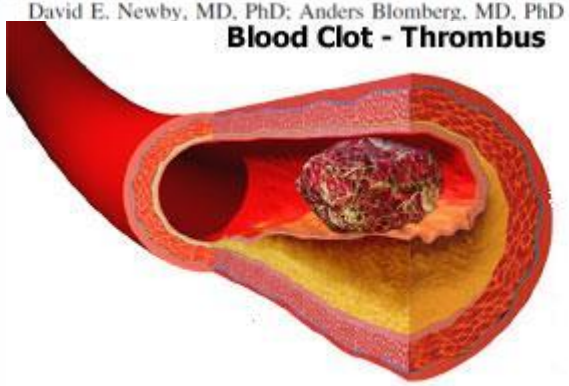
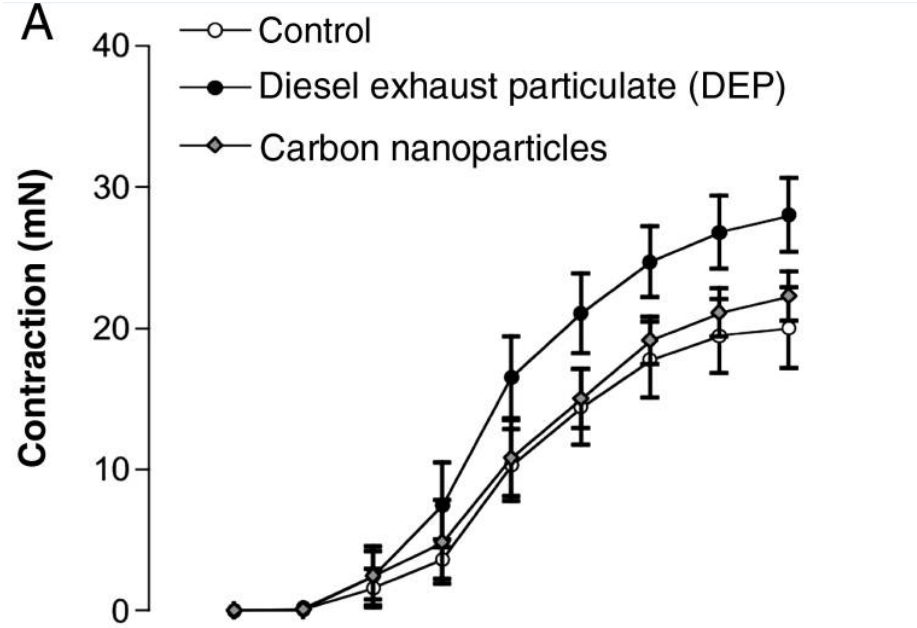


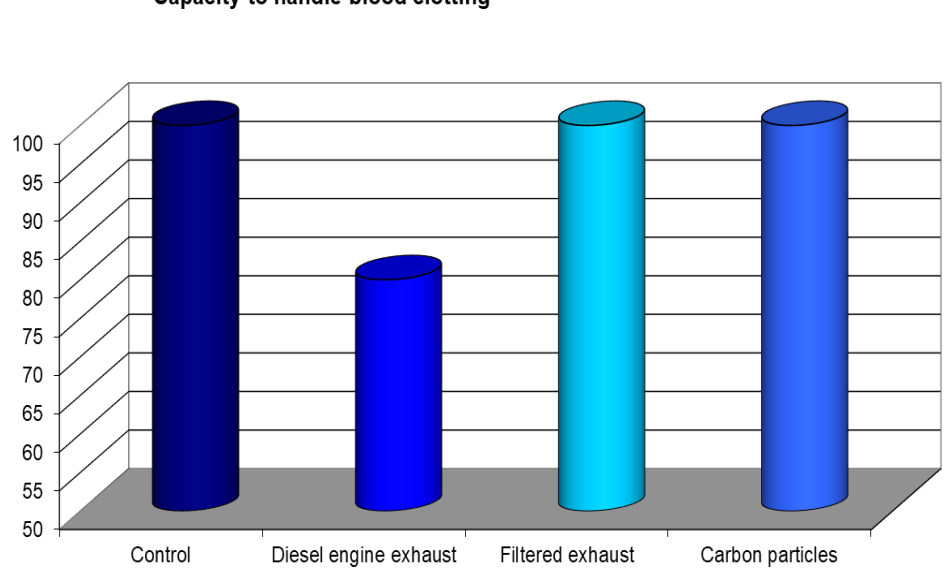
Figure 4. Ex vivo thrombus formation assessed with the Badimon chamber at 2 hours after exposure. Data from the low-shear chamber are shown in the top



Clean air Diesel Diesel Filtered

Contraction of blood vessel (ex vivo)





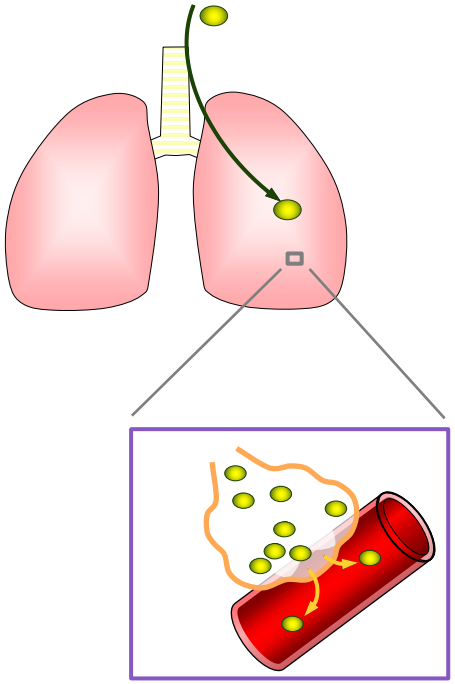
Absorbed components on ultrafineparticles seem to drive the response

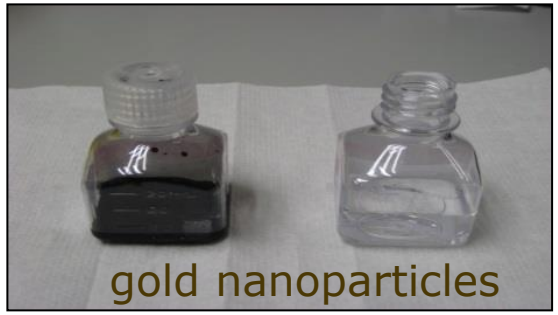
Characterization of exposure conditions

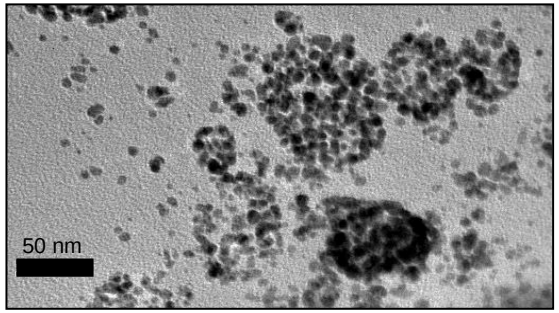
	Filtered air	Diesel exhaust	Filtered exhaust	Carbon
PM (teflon filter), $\mu g/m^3$	<1	348 ± 64	6 ± 16	70 ± 28
Particle number, $\times 1000/cm^3$	<1	1198 ± 204	2 ± 4	3865 ± 424
Particle diameter, nm	–	67 ± 4	–	37 ± 4

Mills et al., Eur Heart J. 2011 Nov; 32(21): 2660–2671.

Investigating particle translocation using gold particles



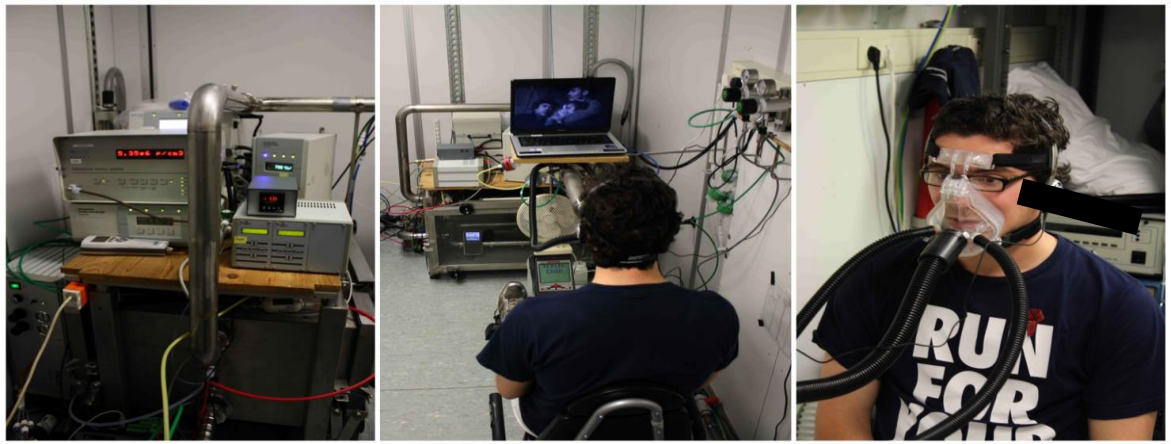


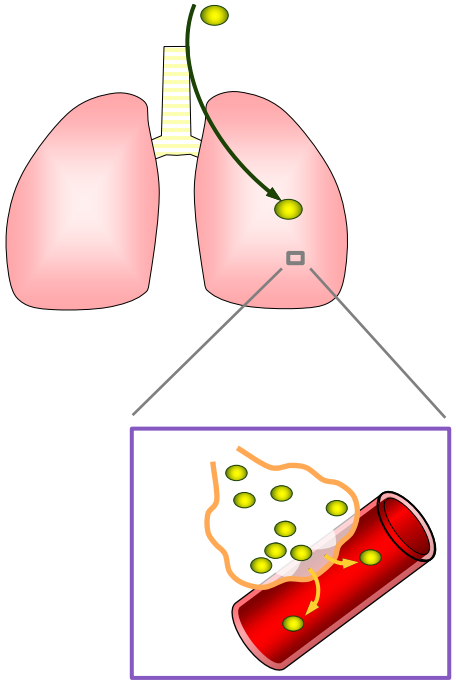


Why use gold?

- Very small size available
- Safe to use
- Techniques to measure very low levels
- Low levels of gold in the body (background)

Inhalation of gold nanoparticles





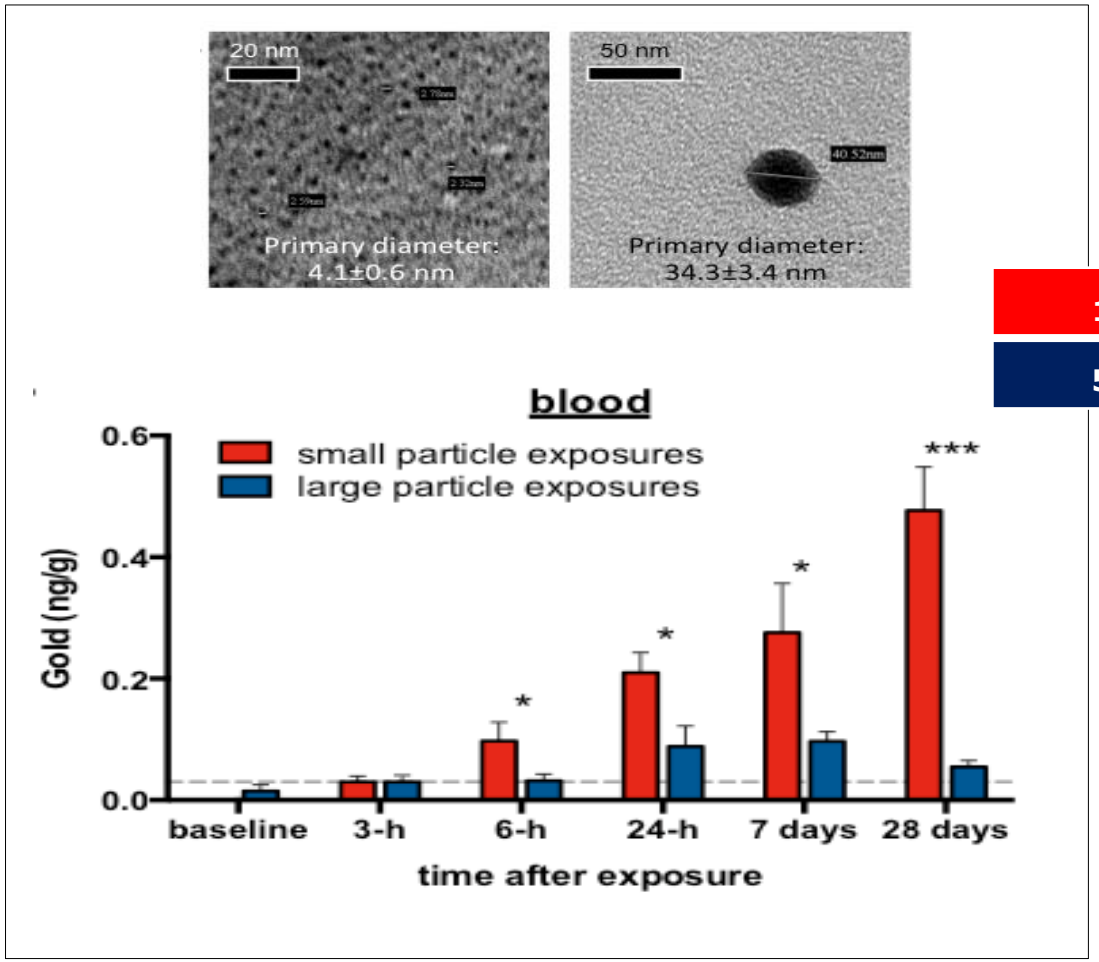
5-15 nm; 5. 10^6 per cc

GOLD!

- 16 healthy volunteers
- 2-hour inhalation of gold nanoparticles
- Measure gold in blood after the exposure

Translocation: particle size

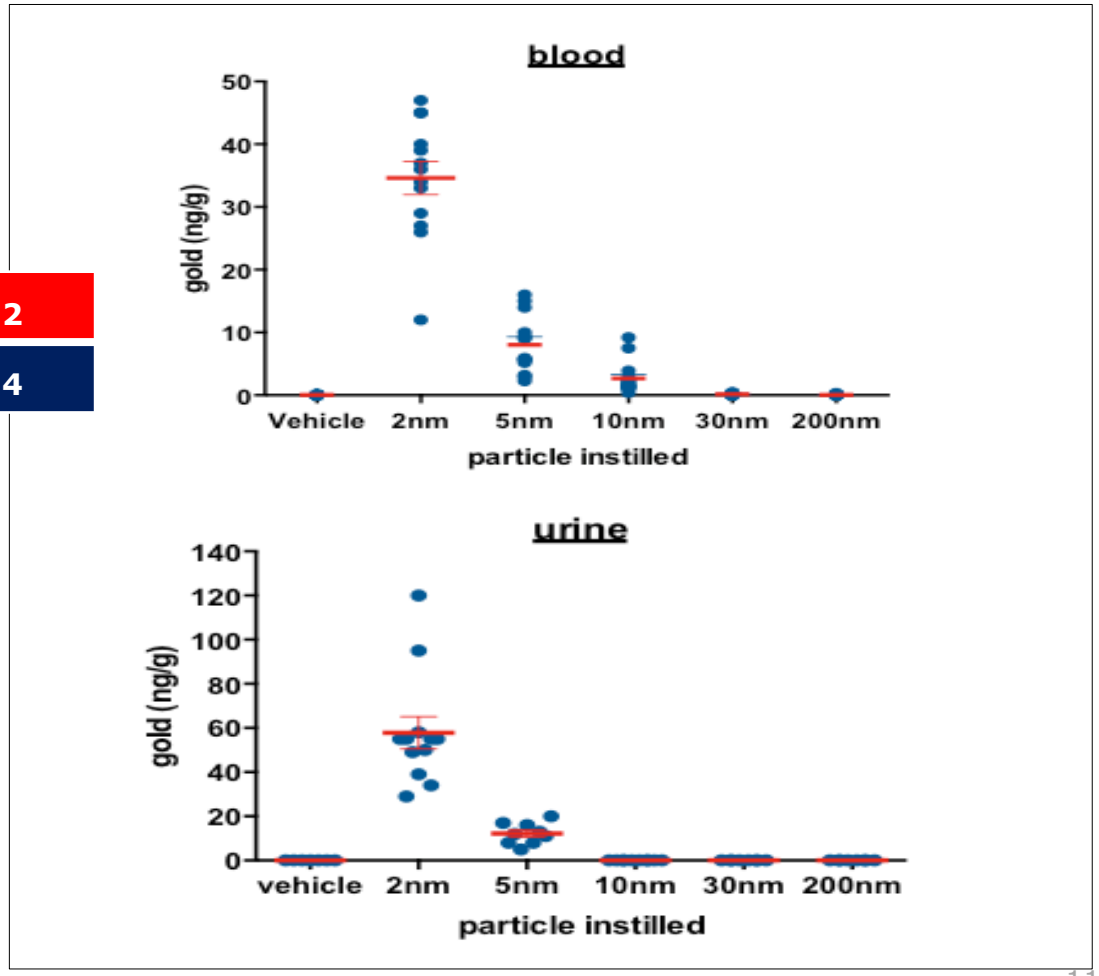
Clinical exposures



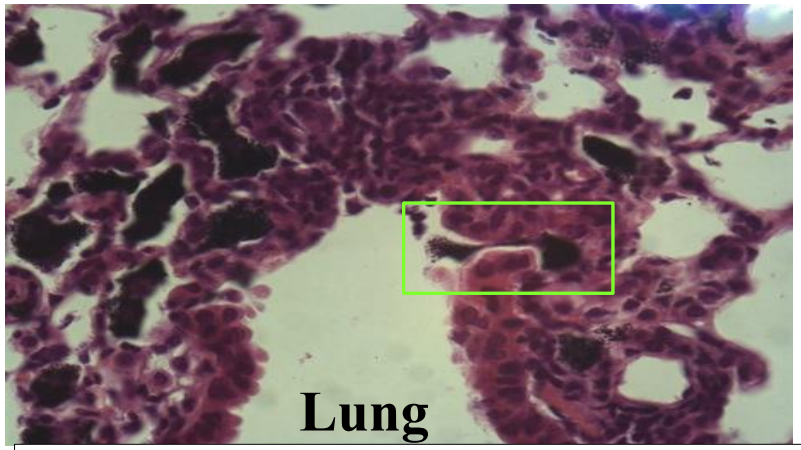
17.8 ± 1.2

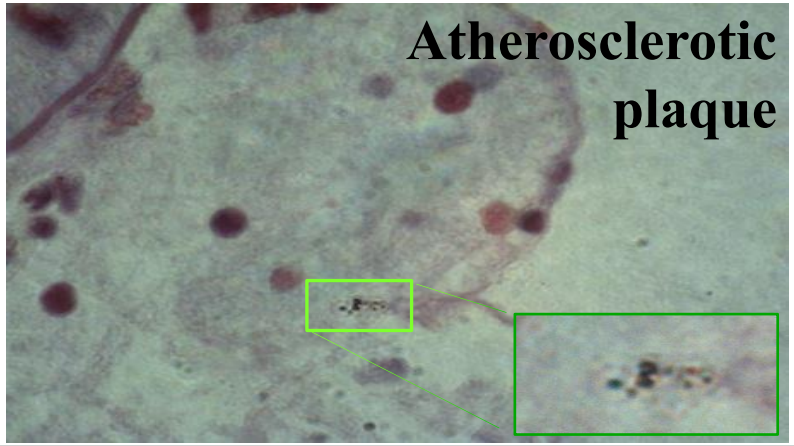
52.4 ± 1.4

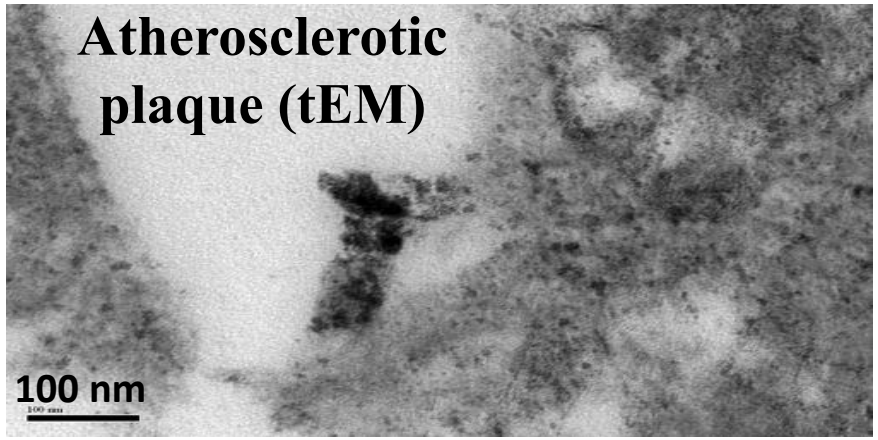
Murine exposures



Visualising translocated nanoparticles

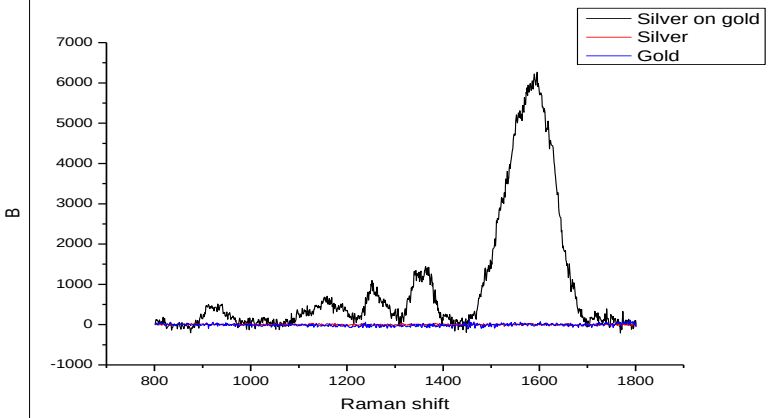






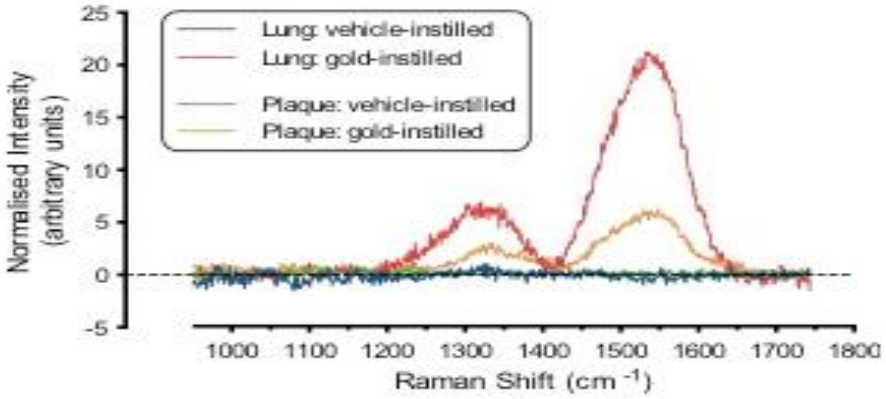
Raman spectroscopy

Gold particles on a glass slide

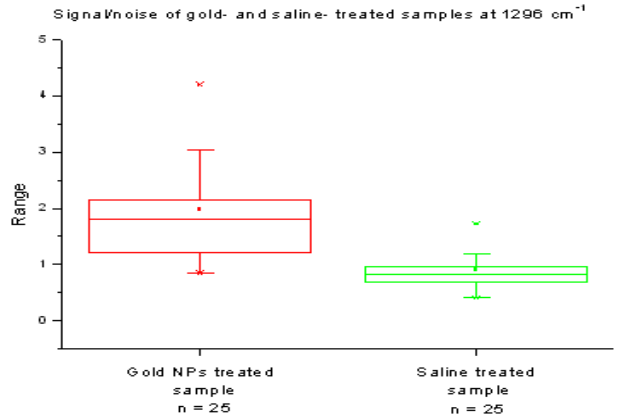


Artery from gold-treated mouse

Raman Spectra from lung and arteries from gold-instilled mice

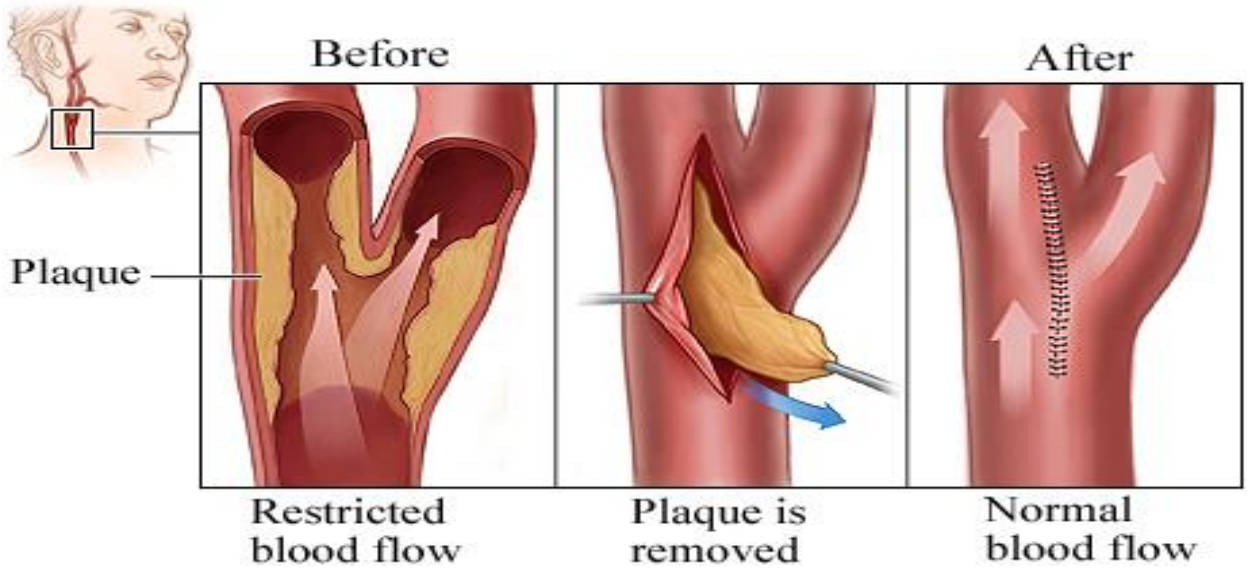


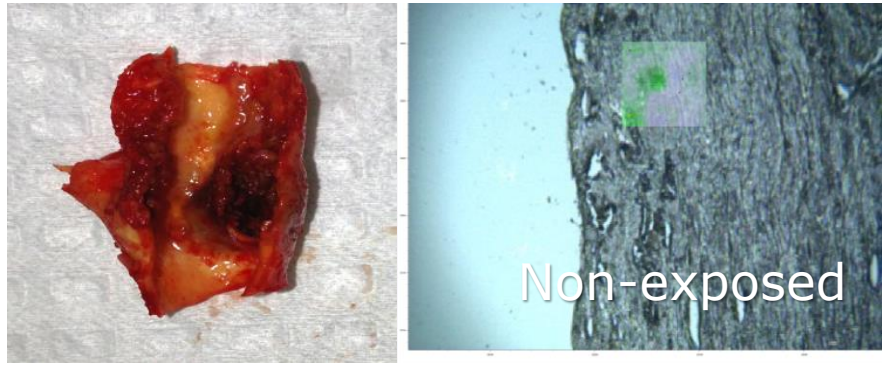
Scans on atherosclerotic plaque

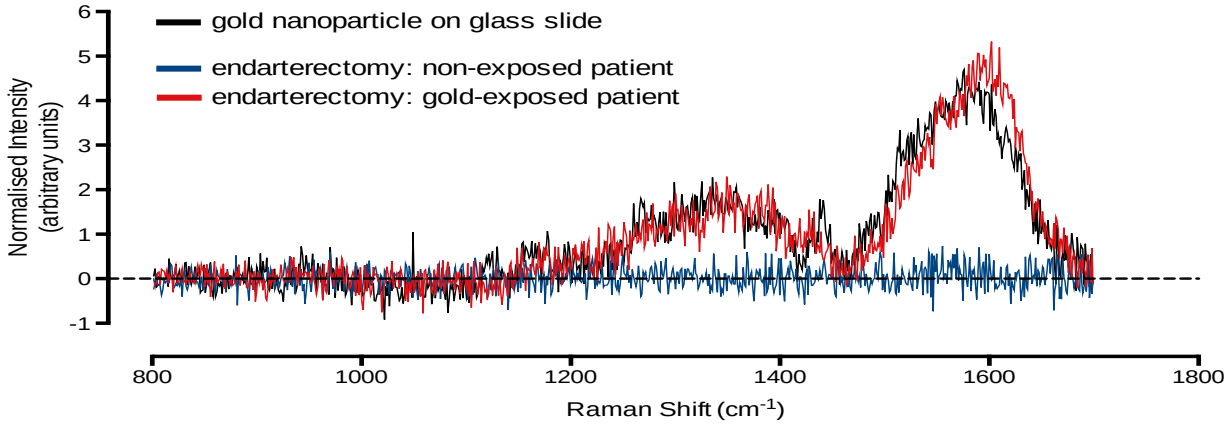


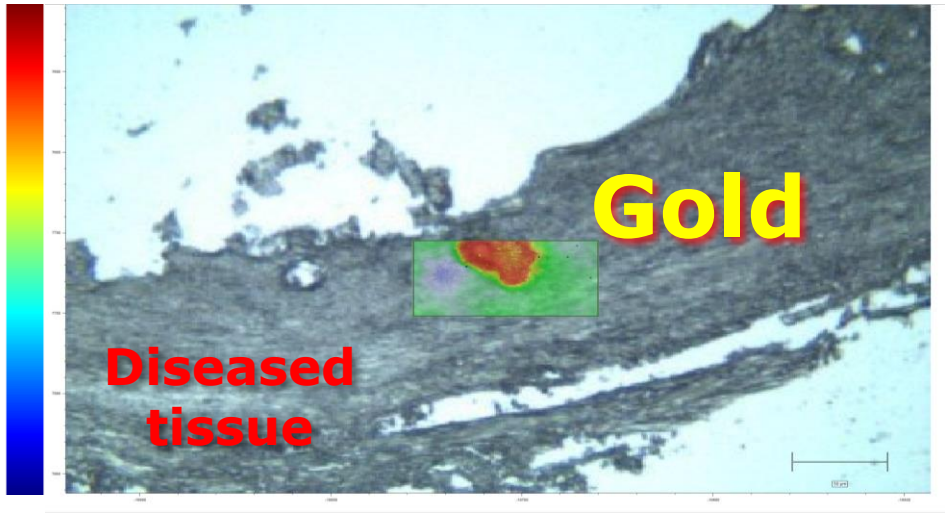
gold **saline**

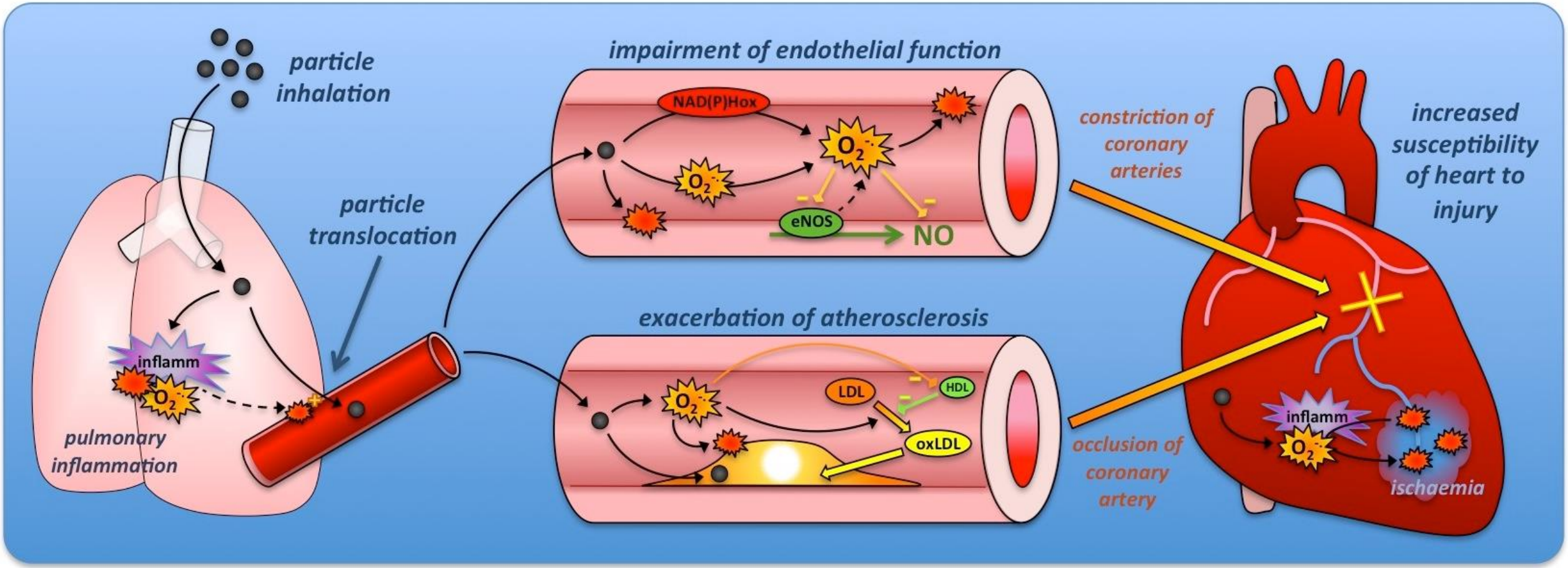
Gold nanoparticles reach areas of vascular disease





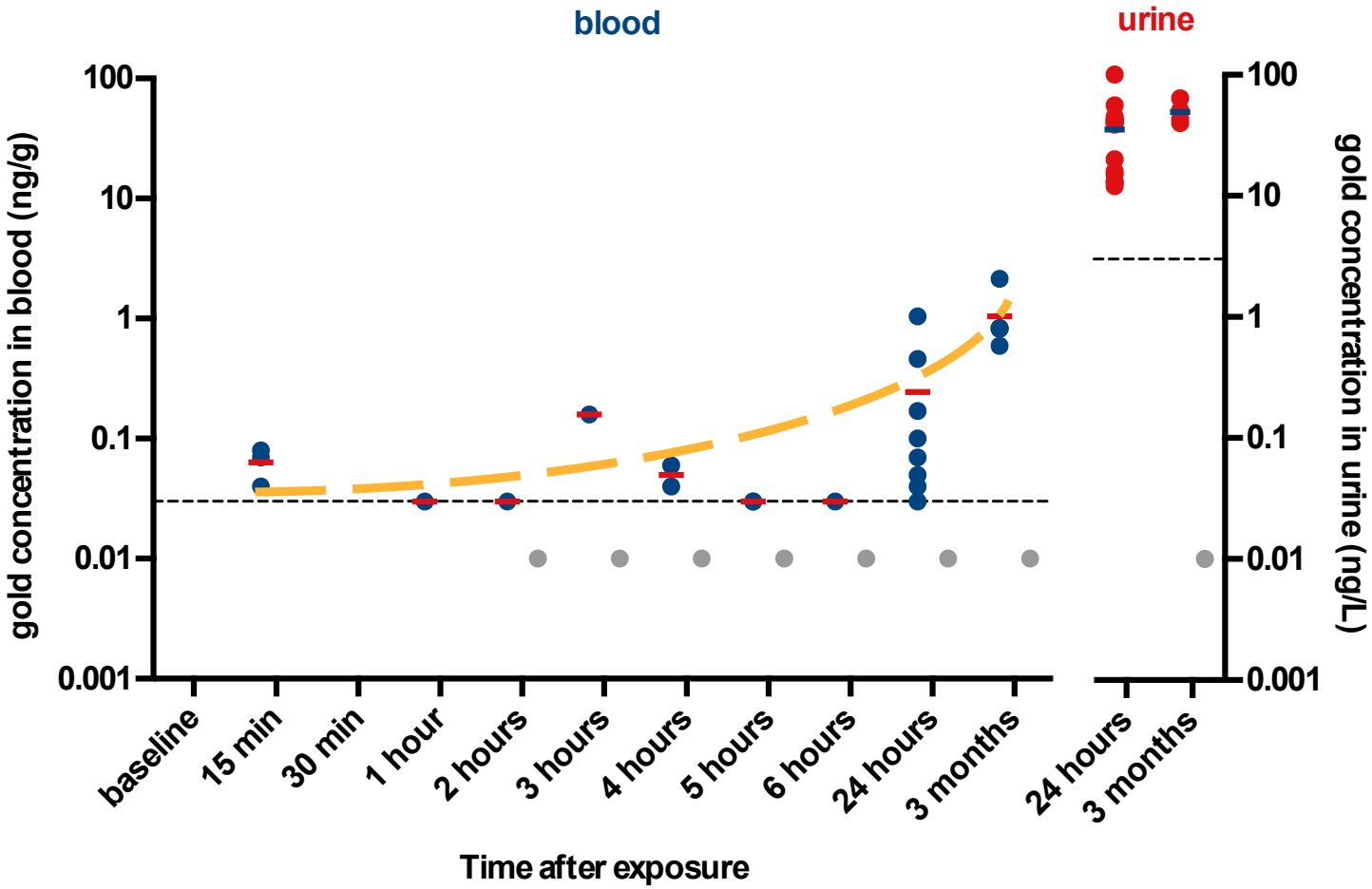






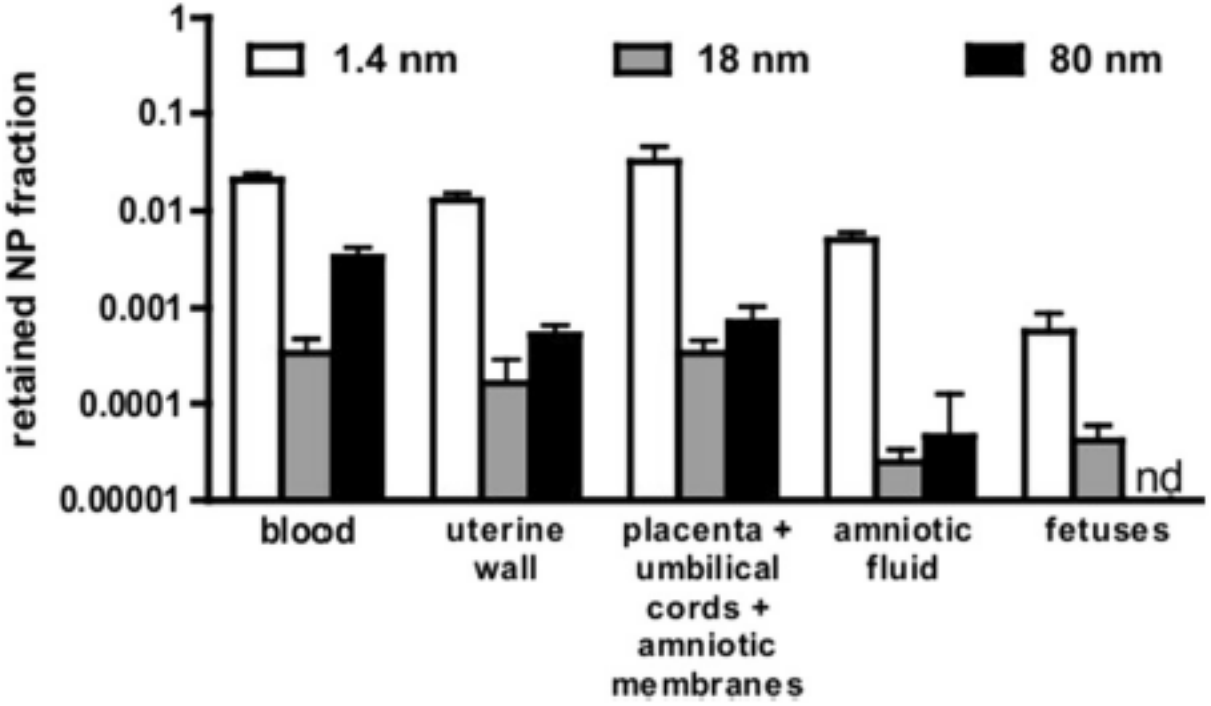
Courtesy Mark Miller,
Miller (2014). Biochem Soc Trans 42:1006-11

Gold nanoparticles reach the systemic circulation



Maternal Exposure and Translocation of AuNP

- Intravenously injected monodisperse, negatively charged, 1.4 nm, 18 nm and 80 nm gold particle 198AuNP (5, 3 and 27 µg/rat)
- Translocation from maternal blood into the fetus is NP-size dependent



Semmler-Behnke *et al. Particle and Fibre Toxicology* 2014, **11**:33
http://www.particleandfibretoxicology.com/content/11/1/33

PARTICLE AND FIBRE TOXICOLOGY

RESEARCH Open Access

Size dependent translocation and fetal accumulation of gold nanoparticles from maternal blood in the rat

Aviation emissions

Globally, air transport has been growing rapidly

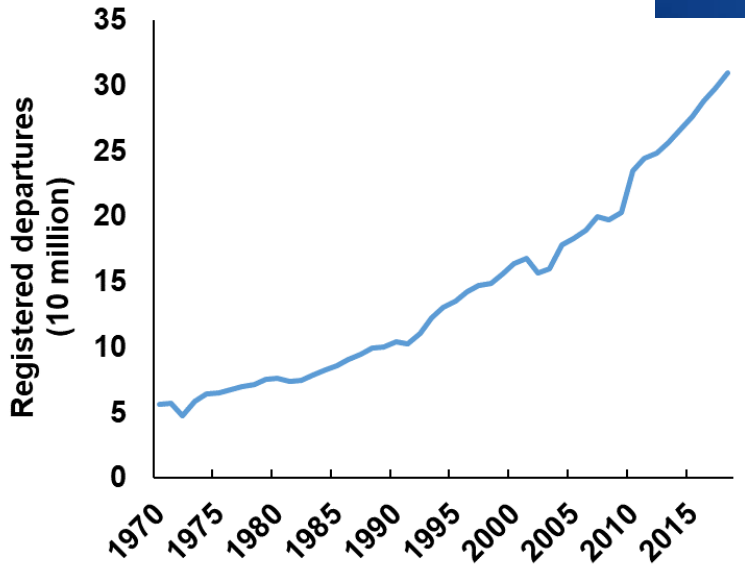
- Both passengers and freight

This results in huge increases in emissions of:

- Gases: CO, NO_x, SO_x, O_3
- Fine and ultrafine particulates (UFPs)

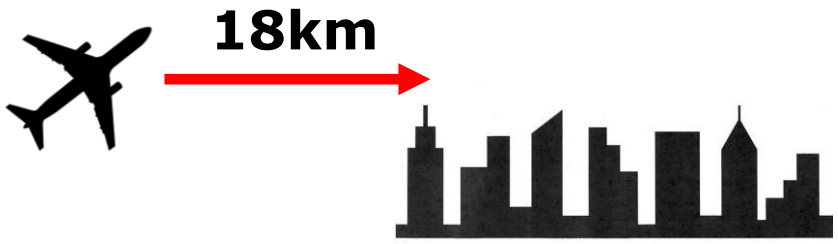
As well as those produced by:

- Ground service vehicles
- Passenger vehicles



Exposure is concerning for airport staff but also those living and working near by

- Aviation UFPs detected 18km away
- Including indoors



Airport study

- All participants received a 5-hour exposure to ambient air nearby Schiphol Airport,
  - a runway intersection and the city of Amsterdam
- Health assessment before and after every exposure

Summary of exposure variables. Values are averages for a 5-hr period as measured in the exposure cabin.

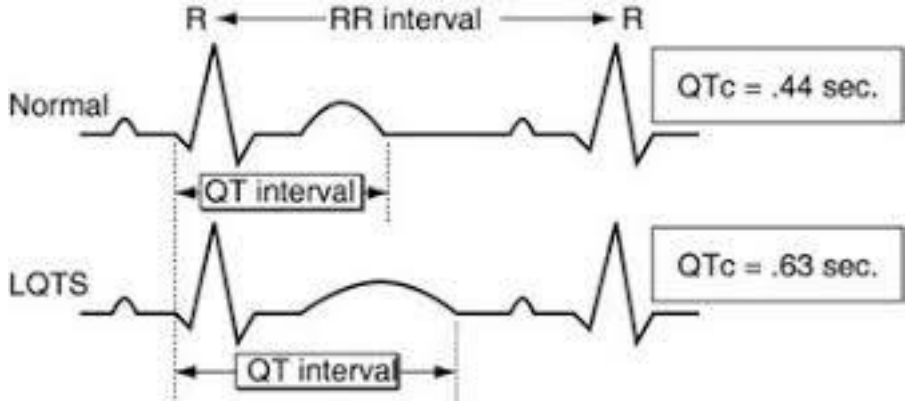
Exposure day	Mass	PNC	BC	NO_2	CO	SO_2	O_3	Temperature	rH
	(µg/m³)	(#/cm³)	(µg/m³)	(µg/m³)	(µg/m³)	(µg/m³)	(µg/m³)	(°C)	(%)
Average	23.1	53,469	0.6	28.2	638	2.0	35.7	23.3	54
SD	8.3	43,776	0.4	12.2	83	0.9	14.4	2.7	7
Highest	47.5	173,187	1.9	60.2	830	3.2	78.6	28.6	66
Lowest	10.6	10,520	0.1	12.4	494	1.2	8.8	15.7	40

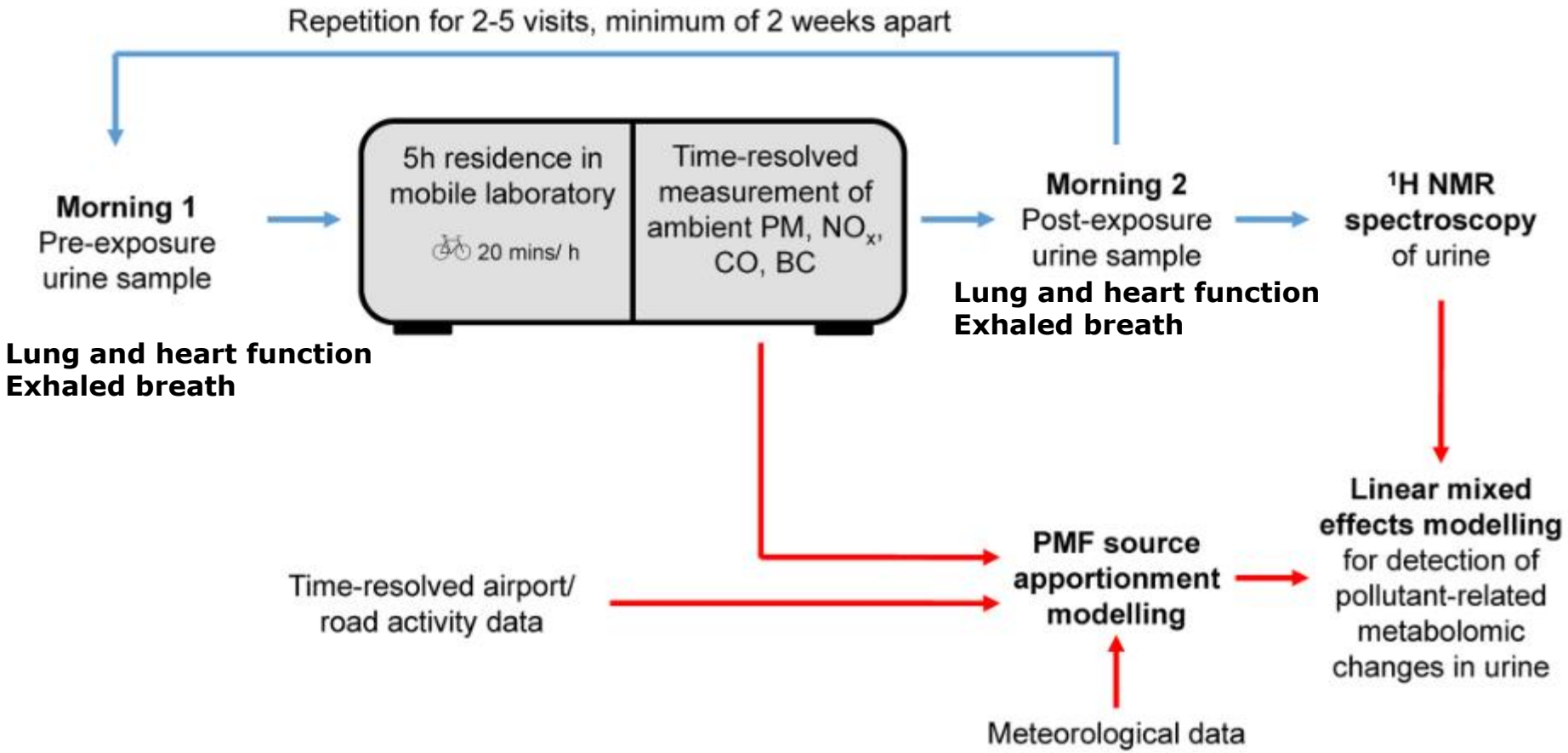
Mass concentrations are based on Filter measurements. PNC = particle number counts. See Method section for more details

DL= Below the detection limit of the instrument

Measure health indicators

- Spirometry (lung function)
- fractional exhaled nitric oxide (inflammation)
- ECG (heart function) & blood pressure
- Metabolome (oxidative stress) in urine




Repetition for 2-5 visits, minimum of 2 weeks apart
Morning 1
Pre-exposure
urine sample
Lung and heart function
Exhaled breath
5h residence in
mobile laboratory
20 mins/ h
Time-resolved
measurement of
ambient PM, NOx,
CO, BC
Morning 2
Post-exposure
urine sample
Lung and heart function
Exhaled breath
1H NMR
spectroscopy
of urine
Linear mixed
effects modelling
for detection of
pollutant-related
metabolomic
changes in urine
PMF source
apportionment
modelling
Time-resolved airport/
road activity data
Meteorological data

BOLD = statistically significant

Single-pollutant models

Outcome	PNC[a] N = 86			BC[b] N=86			NO_2[c] N = 86		
	Est.	95%CI		Est.	95%CI		Est.	95%CI	
FVC (mL)	**-5.88**	**-11.06**	**-0.03**	38.96	-23.67 – 101.60		0.57	-20.78	21.92
FEV1 (mL)	-4.04	-9.33	2.38	27.68	-28.96 – 100.50		-11.09	-30.77	16.78
FEV1/VC	0.00	0.00	0.00	0.00	-0.01 – 0.01		0.00	0.00	0.00
PEF (L/s)	-0.01	-0.03	0.02	0.16	-0.08 – 0.42		-0.05	-0.12	0.05
FeNO (ppb)	0.02	-0.09	0.14	0.24	-0.96 – 1.61		0.28	-0.12	0.72
$HR_{sitting}$ (bpm)	-0.09	-0.37	0.19	-1.39	-4.43 – 2.39		-0.40	-1.46	0.82
Saturation (%)	0.00	-0.04	0.05	0.08	-0.47 – 0.57		-0.04	-0.21	0.14
BP_{sys} (mmHg)	-0.14	-0.38	0.08	**3.18**	**0.49**	**5.74**	0.81	-0.12	1.72
BP_{dia} (mmHg)	-0.14	-0.37	0.10	**2.90**	**0.22**	**5.55**	**1.12**	**0.23**	**2.05**
ECG - HR (bpm)	0.27	-0.03	0.61	0.78	-2.98 – 4.61		0.04	-1.18	1.33
ECG - PR (ms)	-0.17	-0.58	0.15	**4.81**	**1.37**	**10.25**	0.99	-0.36	2.54
ECG - QRS (ms)	0.10	-0.10	0.30	-1.20	-3.53 – 1.13		0.06	-0.73	0.86
ECG - QTc (ms)	**0.79**	**0.16**	**1.52**	0.43	-7.26 – 9.01		-0.04	-2.64	2.82

outcome	PM2.5[c] N=86			CO[d] N=86			O_3[c] N=86		
	Est	95% CI		Est.	95%CI		Est.	95%CI	
FVC (mL)	22.74	-6.96	52.44	10.47	-345.99 – 366.92		2.98	-17.74	23.71
FEV1 (mL)	26.32	-2.39	58.27	7.67	-355.71 – 377.43		6.72	-15.37	26.76
FEV1/VC	0.00	0.00	0.01	0.00	-0.04 – 0.04		0.00	0.00	0.00
PEF (L/s)	0.02	-0.10	0.14	-0.37	-1.86 – 0.93		0.03	-0.05	0.11
FeNO (ppb)	-0.30	-0.88	0.30	-0.54	-7.34 – 6.65		-0.36	-0.75	0.04
$HR_{sitting}$ (bpm)	0.17	-1.32	1.59	2.78	-15.05 – 20.25		**1.16**	**0.11**	**2.09**
Saturation (%)	0.00	-0.25	0.23	0.52	-2.34 – 3.27		-0.09	-0.27	0.07
BP_{sys} (mmHg)	-0.21	-1.48	0.96	10.61	-4.72 – 24.36		-0.22	-1.09	0.61
BP_{dia} (mmHg)	0.05	-1.22	1.24	11.60	-3.50 – 25.64		**-1.09**	**-1.94**	**-0.29**
ECG - HR (bpm)	0.36	-1.48	1.91	8.66	-11.50 – 28.33		-0.01	-1.18	1.12
ECG - PR (ms)	0.13	-1.94	1.79	2.26	-20.51 – 23.68		-0.12	-2.03	1.05
ECG - QRS (ms)	0.10	-0.99	1.19	1.04	-11.97 – 14.05		-0.23	-0.98	0.51
ECG - QTc (ms)	0.60	-3.16	4.02	16.24	-24.94 – 61.48		0.83	-1.75	3.25

Results of the single pollutant models were corrected for room temperature and relative humidity respiratory symptoms, age, gender and BMI. a = per 10.000 particles/cm³ ; b = per 1 µg/m³; c = per 10 µg/m³; d= per 1000 µg/m³. Numbers in bold are significant (p<0.05)

Environment International 141 (2020) 105779

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Environment International

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Effects of short-term exposures to ultrafine particles near an airport in healthy subjects

A. Lammers[a], N.A.H. Janssen[b], A.J.F. Boere[b], M. Berger[a], C. Longo[a], S.J.H. Vijverberg[a], A.H. Neerincx[a], A.H. Maitland - van der Zee[a], F.R. Cassee[b,c,*]

risk of ventricular dysrhythmia and sudden death.

$$QTc = \sqrt{\frac{QT\ measured}{RR\ \text{(in seconds)}}}$$

Toxicological impact of exposure

Inflammation (pulmonary and systemic)

- Infiltration of mouse airways by neutrophils, lymphocytes and eosinophils
- Heightened IL-6 in serum of asthmatic patients

Oxidative stress

- Production of ROS by bronchial epithelial cells
- Depletion of antioxidants in cell-free systems

Reduced lung and cardiovascular function

- Decreased forced vital capacity and prolonged QT intervals in healthy individuals

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Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Alterations to the urinary metabolome following semi-controlled short exposures to ultrafine particles at a major airport

Liza Selley [a,*,1], Ariana Lammers [b,1], Adrien Le Guennec [c], Milad Pirhadi [d], Constantinos Sioutas [d], Nicole Janssen [e], Anke H. Maitland - van der Zee [b], Ian Mudway [f,g], Flemming Cassee [e,h]

To identify changes to the human urinary metabolome that accompany exposure to UFP at Amsterdam Schiphol Airport

To establish which emissions sources are responsible for these changes

Impact of major pollutants on urinary metabolome

Total PNC associated with reductions in urinary taurine and dimethylamine concentration

- This effect was attributable to PM within the 6-20 nm fraction
- But not larger particles
- Or pollutant gases which had distinct and smaller effects than PNC

Metabolite	**Total PNC** (5-95p = 120,280 particles/ cm^3)	**PNC < 20nm** (5-95p = 51,160 particles/ cm^3)	**PNC > 50nm** (5-95p = 3,900 particles/ cm^3)
	Coef. (lower – upper CI)	**Coef. (lower – upper CI)**	**Coef. (lower – upper CI)**
Taurine	**-0.263 (-0.507 – -0.020)**	**-0.298 (-0.550 – -4.709)**	-0.044 (-0.396 – 0.307)
Dimethylamine	**-0.023 (-0.040 – -0.067)**	**-0.023 (-0.040 – -0.067)**	0.006 (-0.018 – 0.029)
Unassigned N-acetylated compound	0.000 (-0.002 – 0.002)	-0.001 (-0.002 – 0.001)	0.000 (-0.002 – 0.003)
3-Hydroxyisovalerate	-0.001 (-0.005 – 0.004)	0.000 (0.000 - 0.000)	-0.002 (-0.008 – 0.004)
3-Hydroxyisobutyrate	-0.002 (-0.005 – 0.001)	-0.002 (-0.005 – 0.002)	-0.002 (-0.006 – 0.002)
N-Acetylglutamine	0.000 (-0.015 – 0.015)	0.002 (-0.014 – 0.017)	0.001 (-0.022 – 0.023)

Taurine synthesis slows during oxidative stress

Source apportionment for PNCs

Source apportionment: Pirhadi et al

Pirhadi *et* al. used a positive matrix factorisation source apportionment model to calculate PNCs for different emission sources at the airport

- Time resolved PNC size distribution data, auxiliary pollutant concentrations, aircraft arrival/departure timings, highway traffic counts, meteorological data

Environmental Pollution 260 (2020) 114027

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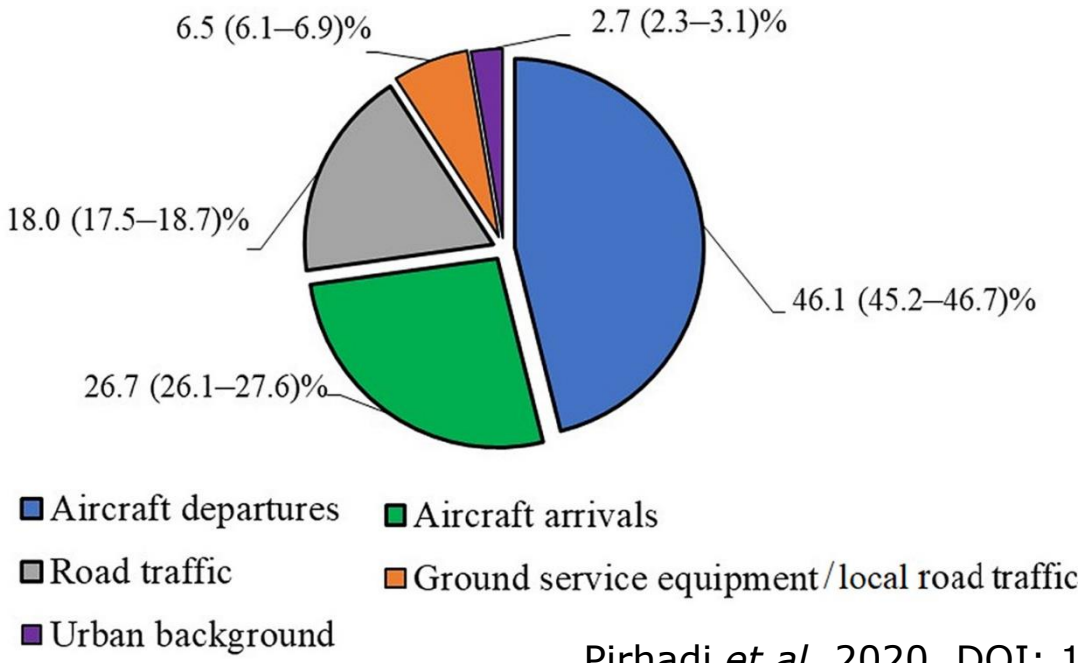
Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Relative contributions of a major international airport activities and other urban sources to the particle number concentrations (PNCs) at a nearby monitoring site☆

Milad Pirhadi [a], Amirhosein Mousavi [a], Mohammad H. Sowlat [a], Nicole A.H. Janssen [b], Flemming R. Cassee [b,c], Constantinos Sioutas [a,*]



Pirhadi *et al.* 2020, DOI: 114027

Source-dependent alterations to the metabolome

- Reductions in urinary taurine and dimethylamine concentration associated with aviation emissions
- As did pyroglutamate – a marker of glutathione synthesis

Metabolite	**Total aviation PNC** (5-95p= 73485 particles/ cm^3) **Coef. (lower – upper CI)**
Taurine	**-0.263 (-0.503 - -0.023)**
Dimethylamine	**-0.021 (-0.037 - -0.005)**
Pyroglutamate	**-0.005 (-0.010 - < 0.000)**
3-aminoisobutyrate	0.002 (-0.006 -0.010)
Methylguanidine	-0.001 (-0.001- < 0.000)
Isocitrate	0.001 (-0.001 - 0.003)

- UFPs emitted by ground service vehicles also influenced glutathione synthesis pathways
- Non-airport traffic UFPs caused a different response, including altered energy metabolism

Metabolomic change is dependent on flight behaviours

- Focusing on **landing UFPs** doubles the association with reductions in urinary taurine concentration

	Landing PNC (5-95p = 31200 particles/ cm^3)		
	Single pollutant model	**Accounting for airport traffic PNC** (5-95p= 5077 particles/ cm^3)	**Accounting for non-airport traffic PNC** (5-95p= 15290 particles/ cm^3)
	Coef. (lower – upper CI)	**Coef. (lower – upper CI)**	**Coef. (lower – upper CI)**
Taurine	**-0.413 (-0.689 - -0.136)**	**-0.414 (-0.692 - -0.136)**	**-0.414 (-0.692 - -0.136)**
Dimethylamine	**-0.031 (-0.049 - -0.013)**	**-0.031 (-0.049 - -0.012)**	**-0.031 (-0.050 - -0.013)**
Pyroglutamate	-0.004 (-0.010 - 0.002)	**-0.002 (-0.004 - < 0.000)**	**-0.002 (-0.004 - 0.000)**
Isocitrate	0.001 (-0.001- 0.003)	0.001 (-0.001 - 0.004)	0.002 (-0.001 - 0.004)
2-hydroxyisobutyrate	-0.001 (-0.004 - 0.002)	-0.001 (-0.004 - 0.002)	-0.001 (-0.004 - 0.002)

- The associations with energy metabolism and fuel additive exposure are not present

Metabolomic change is dependent on flight behaviours

- UFPs produced during **take-off** do not associate significantly with reduced urinary taurine
  - Perhaps due to compositional differences

	Take-off PNC (5-95p= 56130 particles/ cm^3)		
	Single pollutant model	Accounting for airport traffic PNC (5-95p= 5077 particles/ cm^3)	Accounting for non-airport traffic PNC (5-95p= 15290 particles/ cm^3)
Metabolite	Coef. (lower – upper CI)	Coef. (lower – upper CI)	Coef. (lower – upper CI)
Taurine	-0.224 (-0.495 - 0.047)	-0.223 (-0.494 - 0.047)	-0.232 (-0.513 - 0.050)
Dimethylamine	**-0.019 (-0.037 - -0.001)**	**-0.019 (-0.037 - -0.001)**	**-0.020 (-0.038 - -0.001)**
Pyroglutamate	**-0.006 (-0.012 - -0.001)**	**-0.006 (-0.012 - -0.001)**	**-0.008 (-0.014 - -0.002)**
Isocitrate	0.001 (-0.001 - 0.003)	0.001 (-0.001 - 0.003)	**0.002 (> 0.000- 0.004)**
2-hydroxyisobutyrate	-0.002 (-0.005 - > 0.000)	-0.002 (-0.005 - < 0.000)	**-0.003 (-0.006 - < 0.000)**

- Accounting for co-exposure to UFPs from non-airport traffic unmasked associations with TCA cycle activity and a potential marker of fuel additive exposure

In summary…

Our study identified changes to the human urinary metabolome that associate with different UFP emission sources at Amsterdam Schiphol Airport.

Aviation UFP emissions caused the greatest impact, with some changes being dependent on flight behaviours

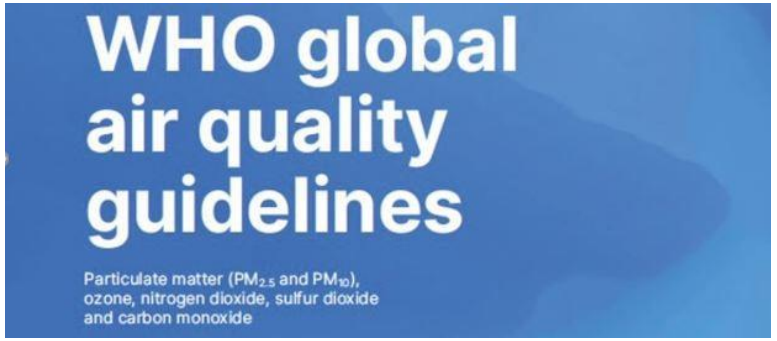
Generally, the responses are adaptive- heightened antioxidant activity and control of NO synthesis

Summary airport study acute exposures

Health marker	Location	Associations UFP aircrafts	Associations UFP road traffic
Among school children (panel study			
Daily symptoms	Home	Yes, especially for wheezing and phlegm giving up	Yes, especially for wheezing and shortness of breath at rest
Medication use	Home	Yes	Yes
Daily long function	Home	No	Yes, in de morning
Longfunction, under supervision	School	No, not consistent	No, not consistent
NO exhaled air	School	No, inconsistent for children with and without asthma	No, inconsistent for children with and without asthma
Research among healthy adults (volunteer study)			
Long function	Near the airport	Yes, voor FVC	No
NO exhaled air; oxygen saturation		No	No
Heart function		Yes, voor QTc	No, not consistent
Blood pressure		No	Yes
Urine Oxidative stress		Yes	Yes, less evenident
Toxicological research lung cells		Degree of harmfulness	
Cell damage and production of signaling substances for acute inflammatory reactions	Near Schiphol and at the source	Yes, though no apparent differences in reactivity between UFP collected at different wind directions (airport vs. non-airport) and directly from a turbine engine	

Conclusions ultrafine and health risks

- Differences in toxicity among sources
- Short-term exposure to high levels of UFP associated with decreased lung function and prolonged repolarization of the heart, oxidative stress as well as arterial stiffness directly after exposure in adults
- Risk is related to both the toxic potency and the level of exposure/dose
- Plausible that ultrafine particles can affect heart, brain and even cross the placenta after inhalation



World Health Organization

Offers new good practice statements on the management of e.g. black carbon/elemental carbon and ultrafine particles).

Work in progress at RIVM: Effects of long-term exposure to ultrafine particles from aviation around Schiphol airport

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