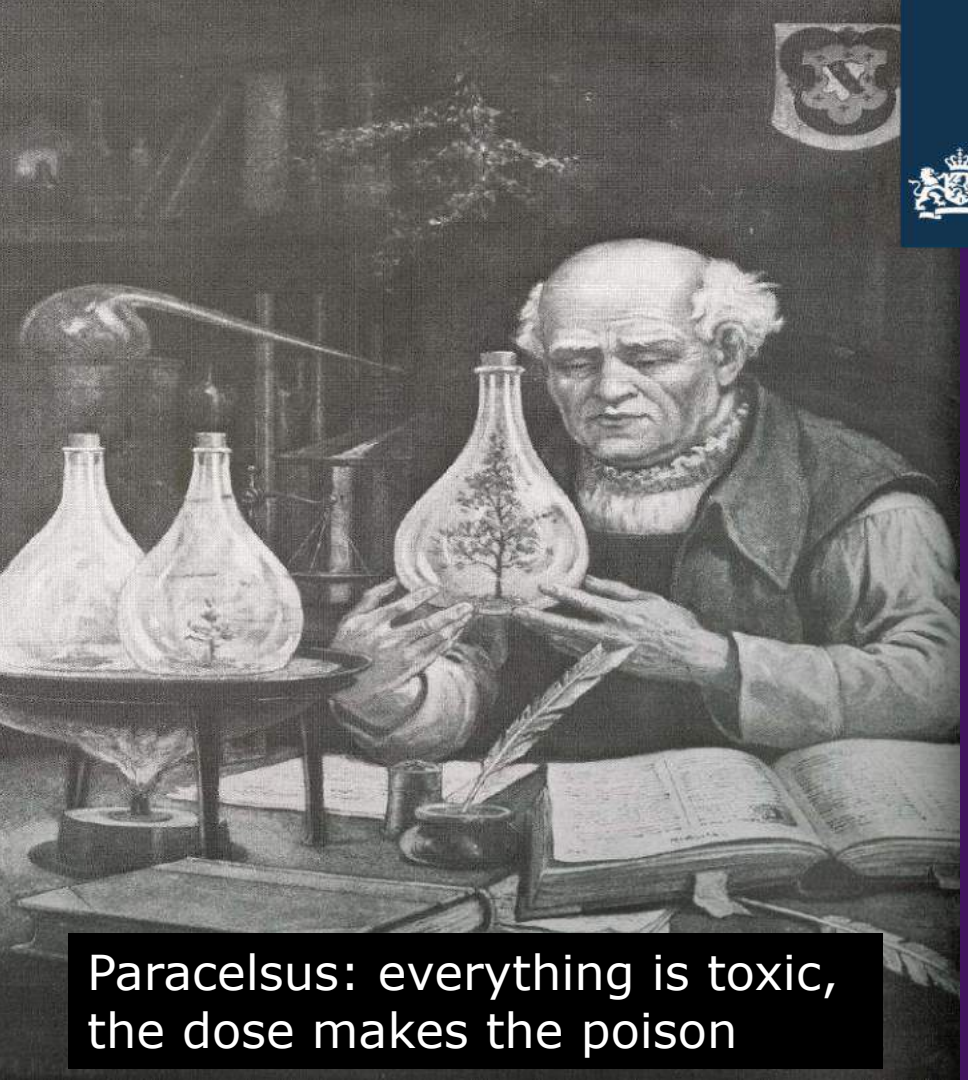


Paracelsus: everything is toxic, the dose makes the poison

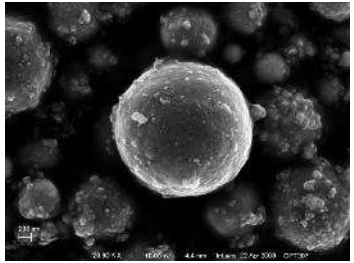
Utrecht University

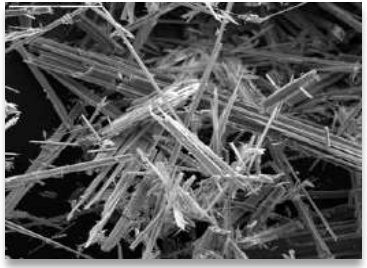
National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

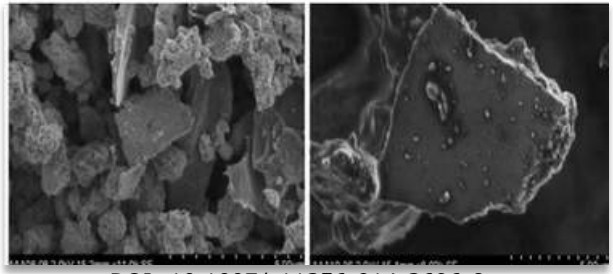
Health effects of air pollution from a toxicological perspective – effects of source specific emissions

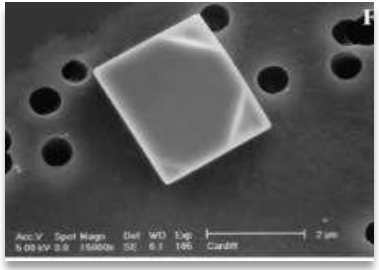
Prof.dr. Flemming R. Cassee

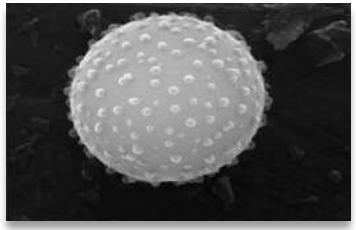
What can be detected in air? Particles and fibres

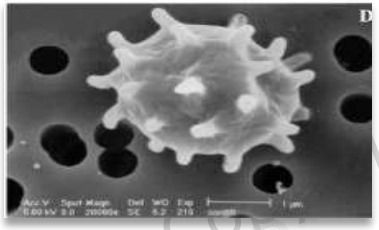


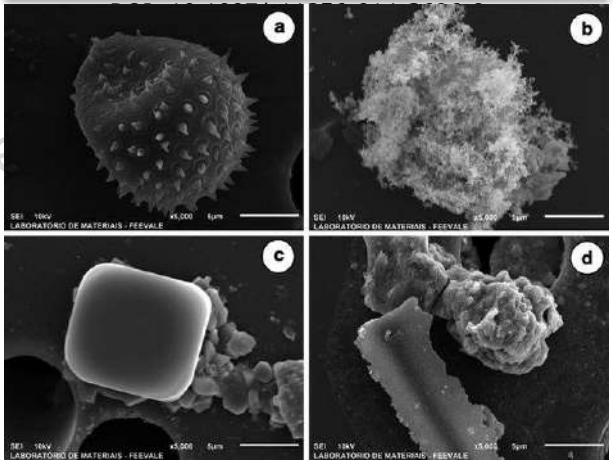






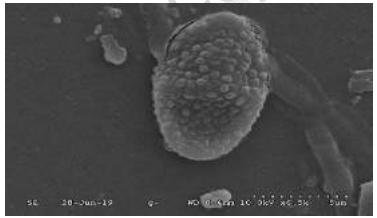


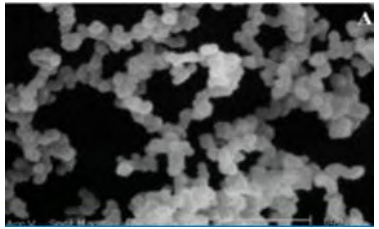




Particle of biological origin, (b) soot particle, (c) cubic-shaped particle, and (d) particle characteristic of soil resuspension

Gustavo Marques Costa via Research Gate





Health effects of particles in the air

Respiratory effects

- asthma
- inflammation
- impaired lung function

Health effects beyond the lung

Cardiovascular system

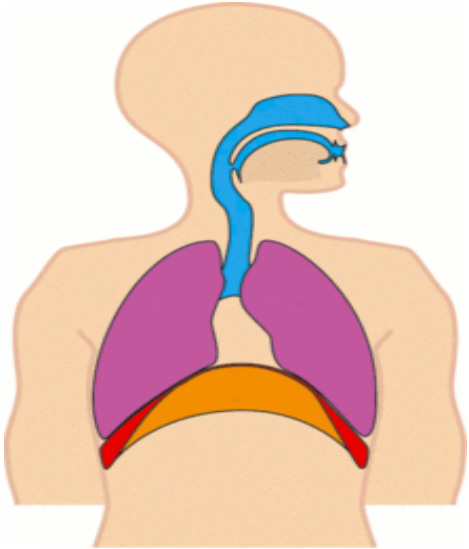
- impairment of vascular function
- Vasoconstriction
- Vascular inflammation

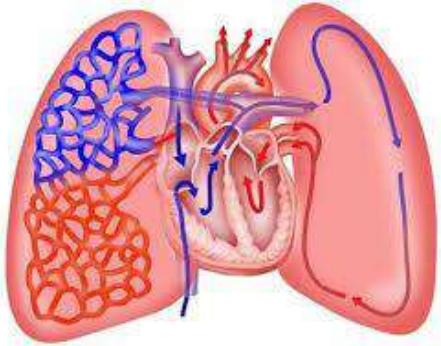
Brain

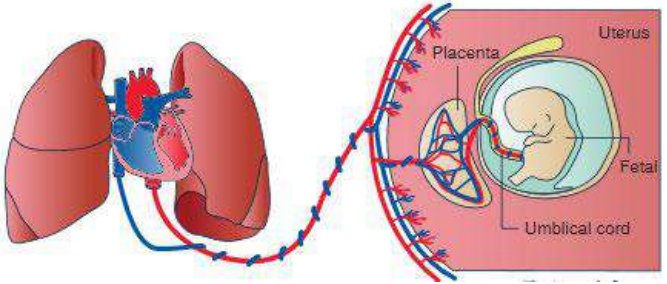
- Neuroinflammation
- Neurodegeneration

Placenta and fetus

- Inflammation







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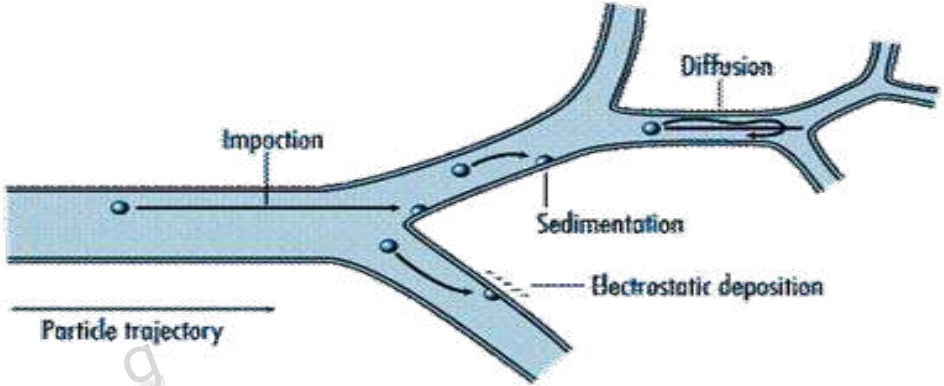
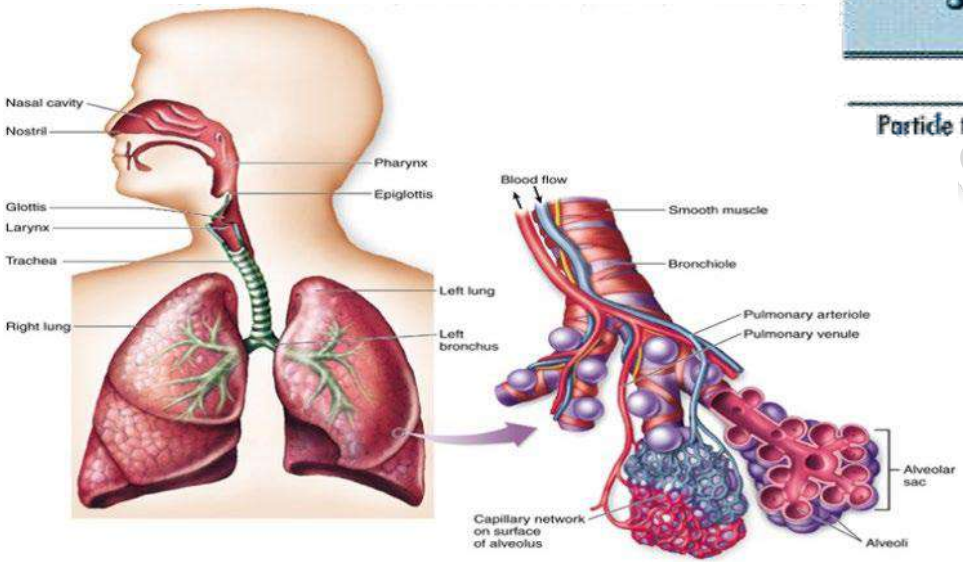
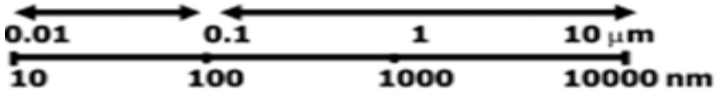
Mechanism of particle deposition in the lung

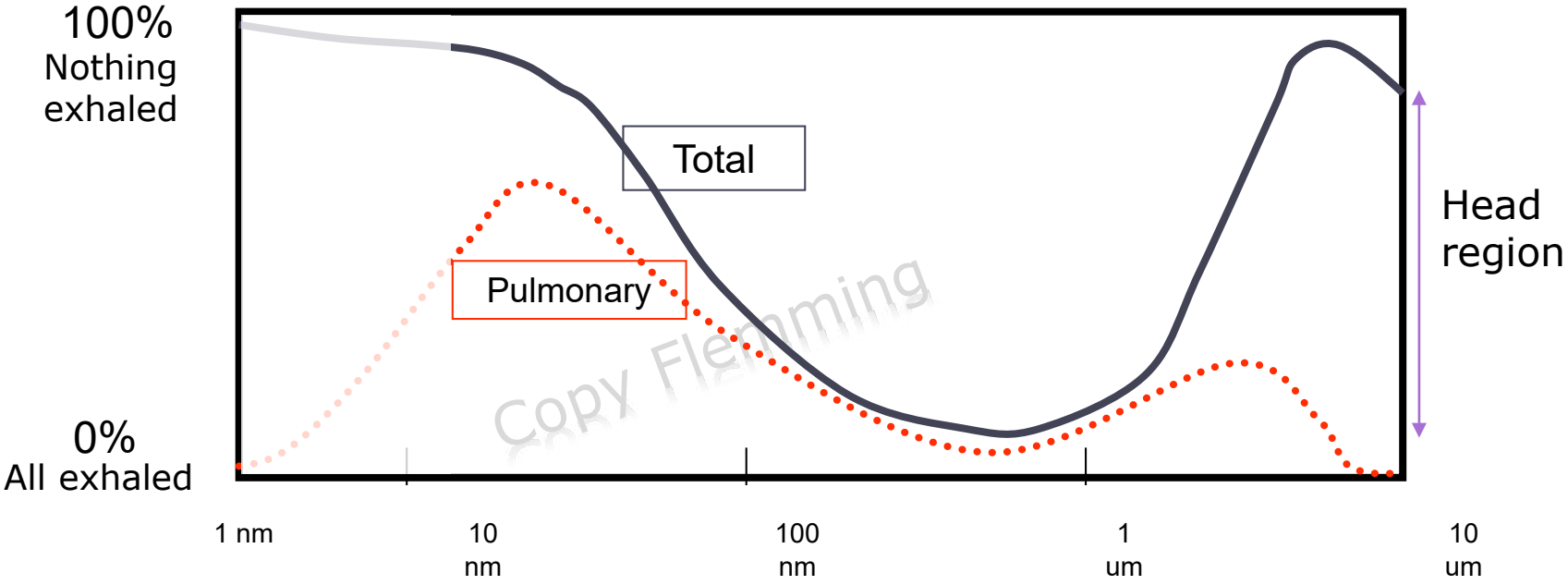






Deposition after inhalation

MPPD
MULTIPLE-PATH PARTICLE DOSIMETRY MODEL
VERSION 2.0
Co-developed RIVM
v 3.04



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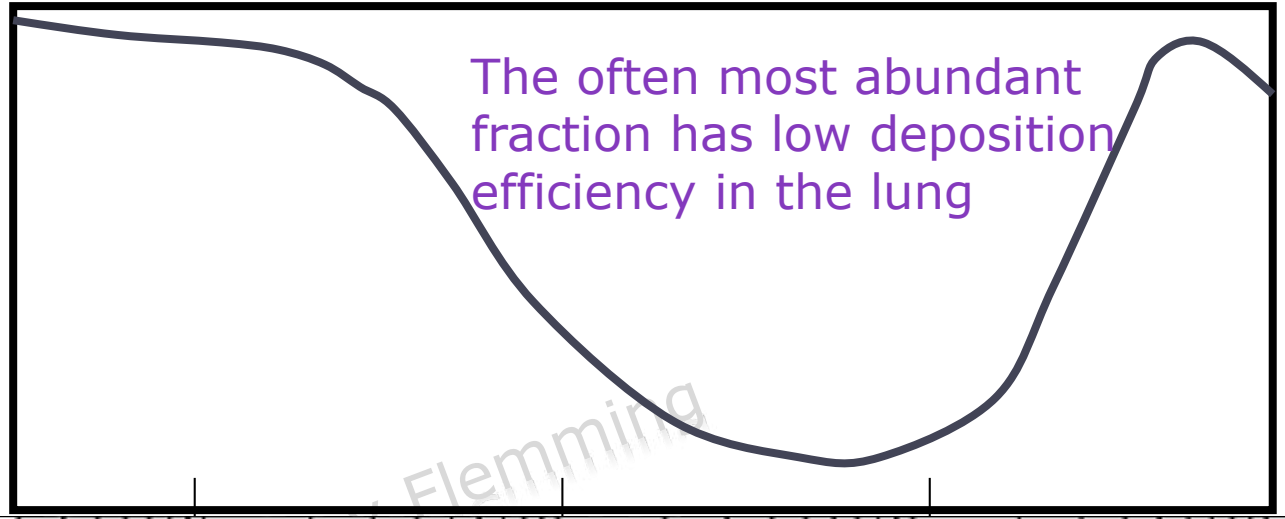
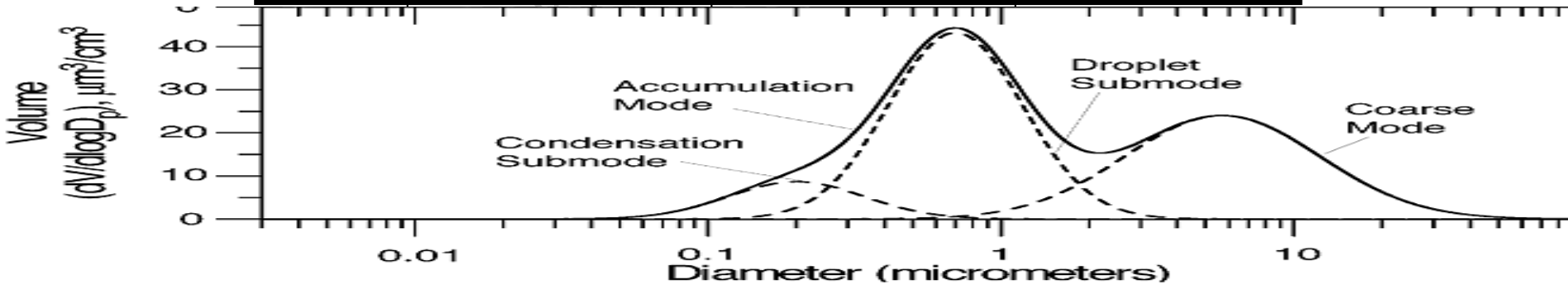
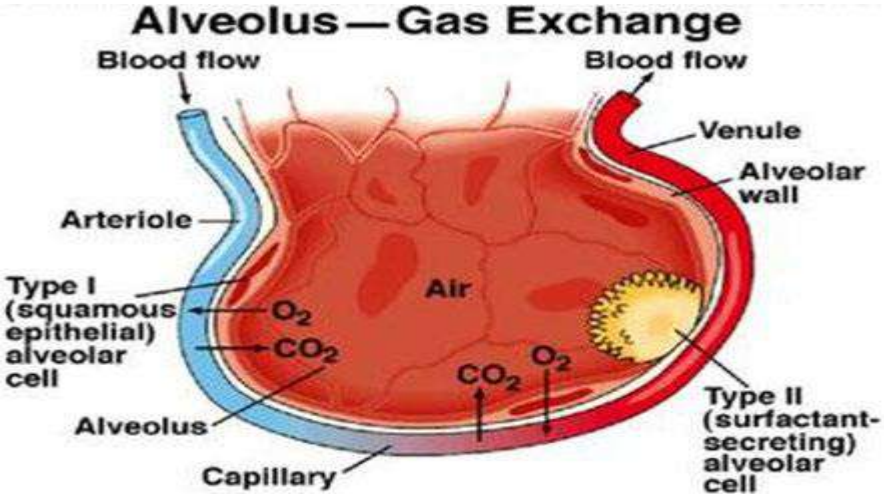
Size affects the internal dose

Deposition human versus distribution outdoor





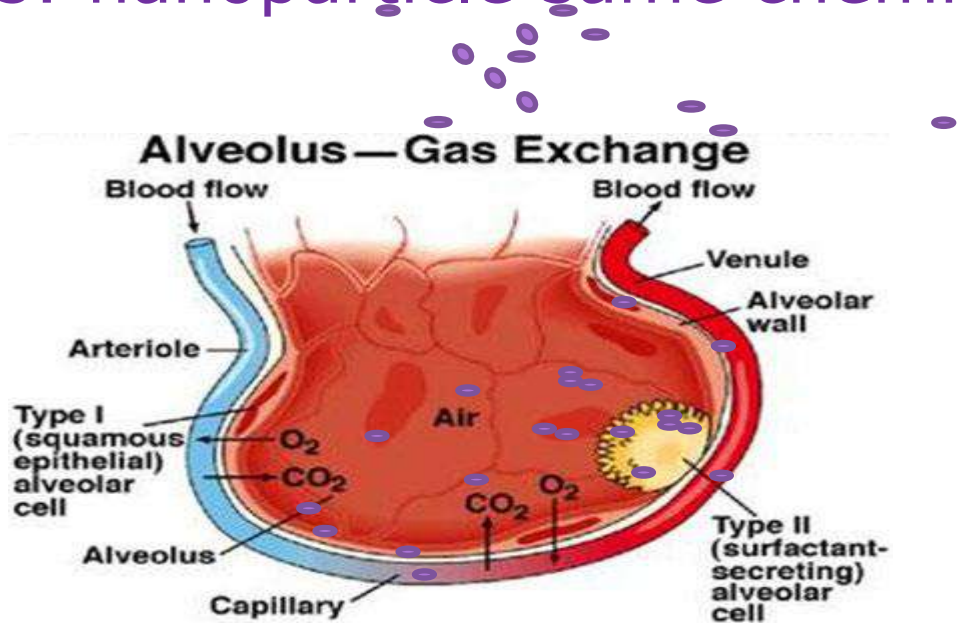
Size matters: micro particle



Clearance micro-size particles withing 6-14 hr

Modified after https://birdrespiratory.weebly.com/gas-exchange.html

Size matters: nanoparticle same chemical



NP uptake by epithelial cells + interstitial translocation + lack of macrophage recognition

What are the most toxic parts of PM?

- Health effects related to (groups of) chemical and physical properties

World Health Organization – REVIHAAP project

Black carbon

Secondary inorganic aerosols

Redox active components

Particle number

PM2.5

Coarse PM

Surface area

Transition metals

Primary organic aerosols

Secondary organic aerosols

Ultrafines

WHO concluded: Almost everything (?) can be harmful

Cassee FR, Héroux ME, Gerlofs-Nijland ME, Kelly FJ., Inhal Tox 2013

Sources of emissions and health effects

- Break pads
- Dust from farms
- Ultrafine particles from aircrafts

Collection of source-specific fine particulate matter (PM2.5)

Different source-specific PM2.5 Gerlofs-Nijland et al. 2019

- Brake wear (4 different brake pad types, realistic combined driving conditions)

- Wood combustion (modern technology/efficient combustion and old technology/efficient combustion)

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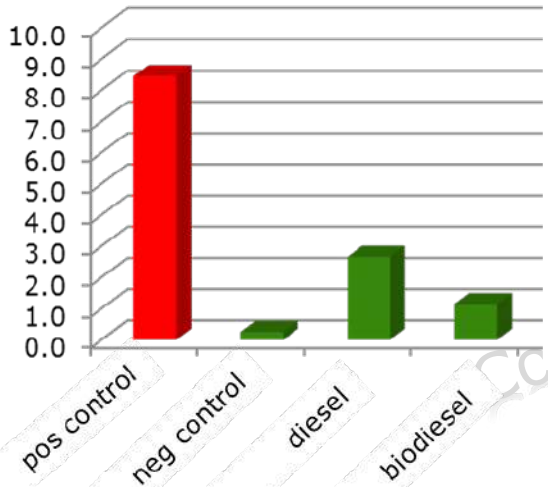
- Diesel combustion (stationary HD diesel engine, Euro III / Euro V combined)
  - TU Eindhoven; Reijnders et al, SAE Technical paper 2013-24-0108, 2013, doi:10.4271/2013-24-0108

- Poultry farm (±70,000 animals)

- Tyre/road wear (spiked tyres, asphalt concrete pavement)

Exposure mice – source specific PM2.5

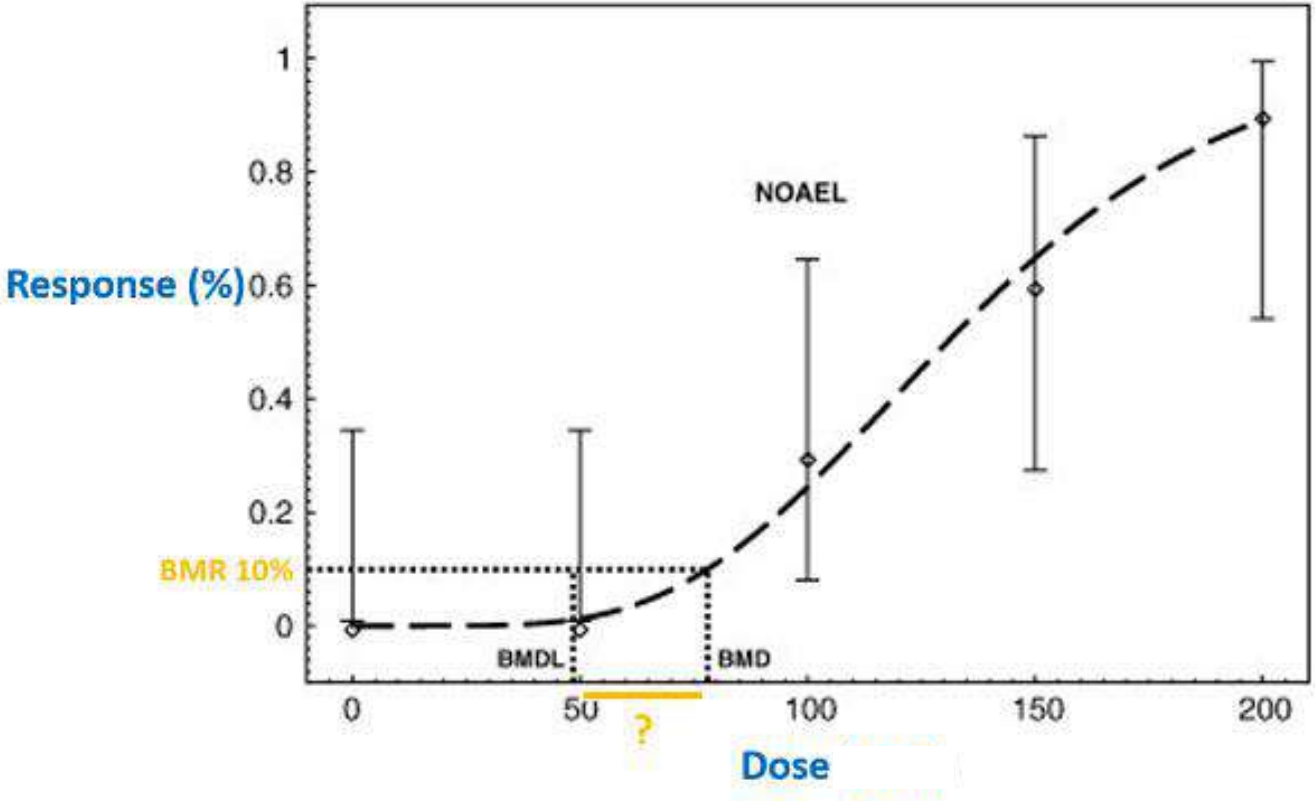
Oxidative potential in a test tube



Gerlofs-Nijland et al. 2019

Brake wear more potent than diesel particles based on PM mass

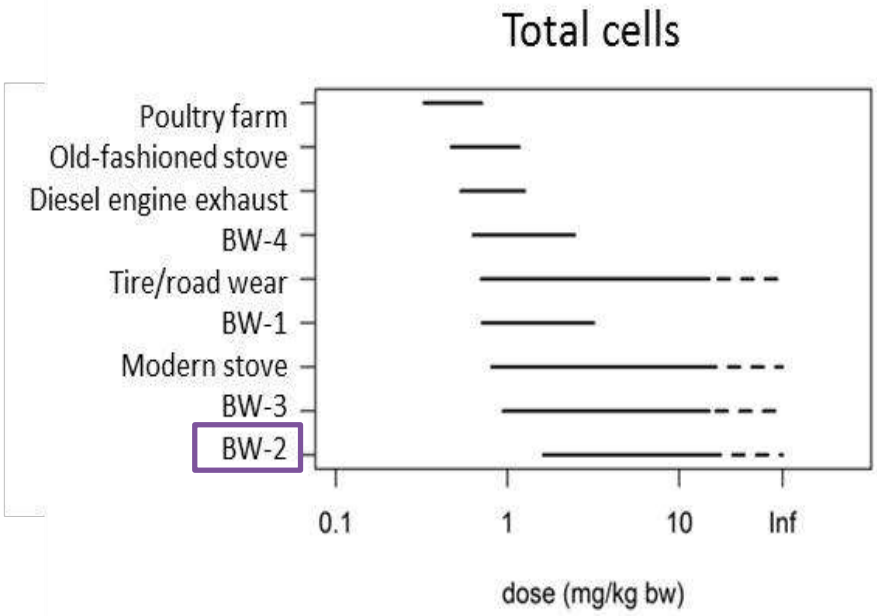
Ranking based on mice toxicity - inflammation markers

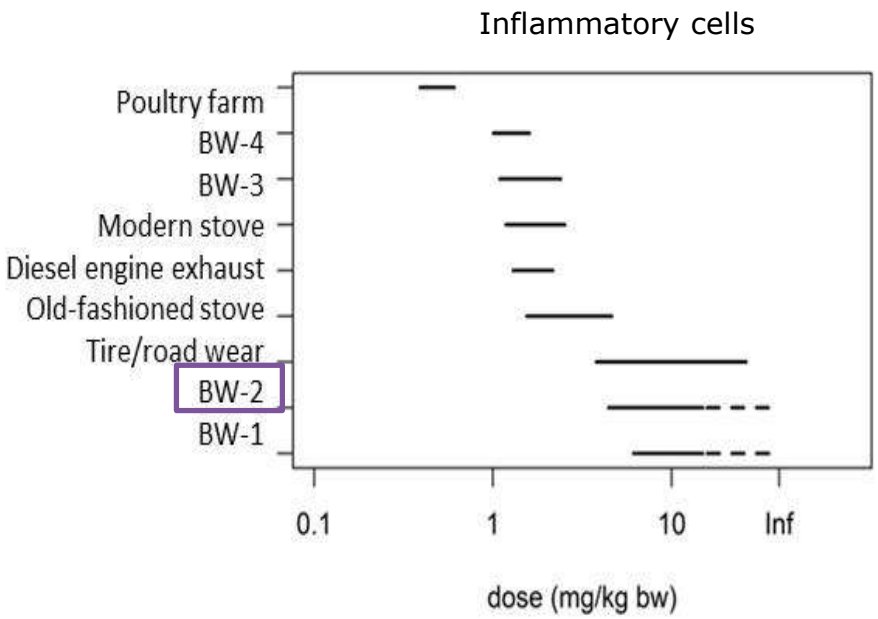


1. Define critical effect level,
2. Construct dose-response
3. Derive benchmark dose

Ranking based on mice toxicity - inflammation markers

The more to the left the higher the toxic potency





BW=Brake wear

Conclusions

- Considerable variability in the toxic potency of brake wear particles.

Car

woodsmoke

chicken

brakes

tires

- Understanding of sources that are most harmful to health can provide valuable information for risk management strategies and could help decision-makers to develop more targeted air pollution regulation.

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BioPM
micro organisms as part of particulate matter in air

Comparison dust chicken - goat – pig farms

study

Dominika A. Kalkowska[1], Gert Jan Boender[1], Lidwien A. M. Smit[2], Christos Baliatsas[3], Joris Yzermans[3], Dick J. J. Heederik[2], Thomas J. Hagenaars[1]*

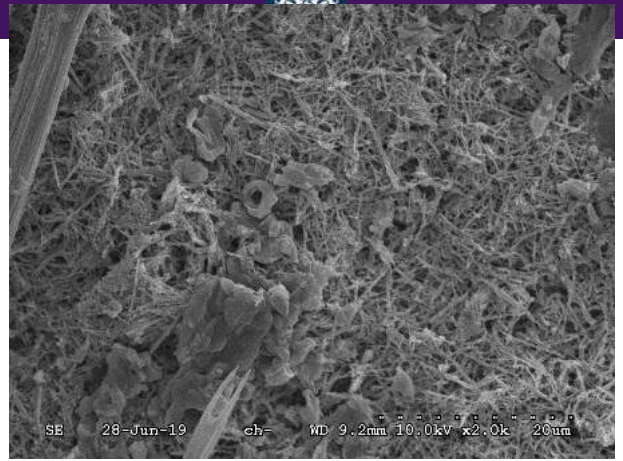
1 Wageningen Bioveterinary Research, Lelystad, The Netherlands, 2 Department of Environmental Epidemiology, Institute for Risk Assessment Sciences (IRAS), Utrecht University, Utrecht, The Netherlands 3 NIVEL, Netherlands Institute for Health Services Research, Utrecht, The Netherlands

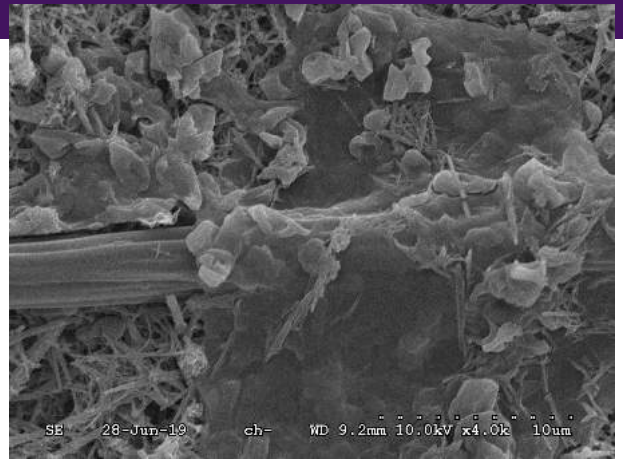
* thomas.hagenaars@wur.nl

Check for updates

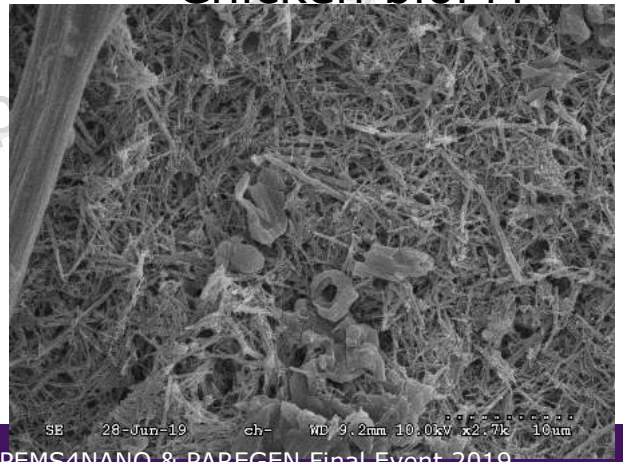
disease

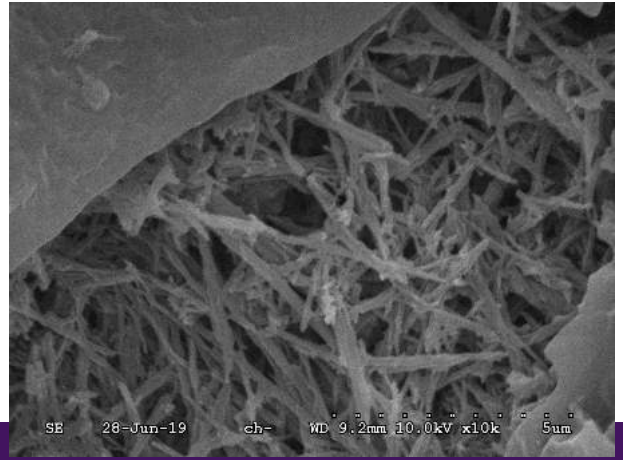
Amy A. Schultz [a], Paul Peppard [a], Ron E. Gangnon [a, b], Kristen M.C. Malecki [a]

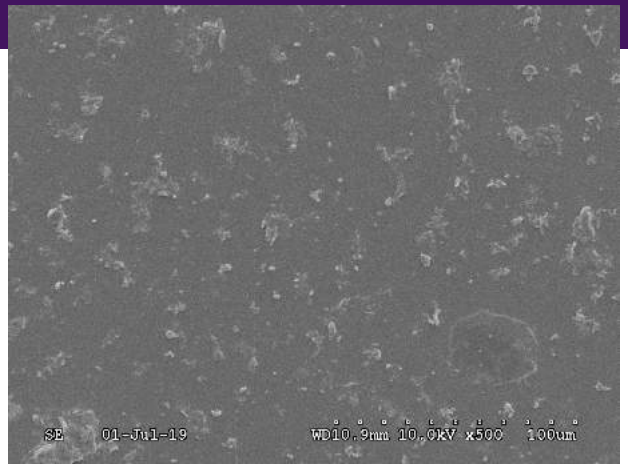


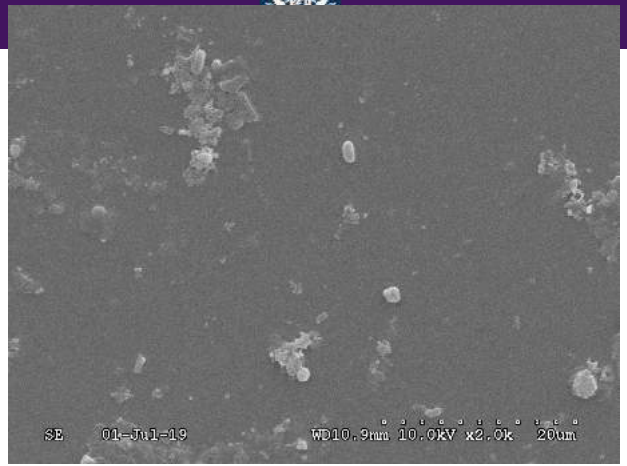


Chicken bioPM






SE 01-Jul-19 WD10.9mm 10.0kV x500 100um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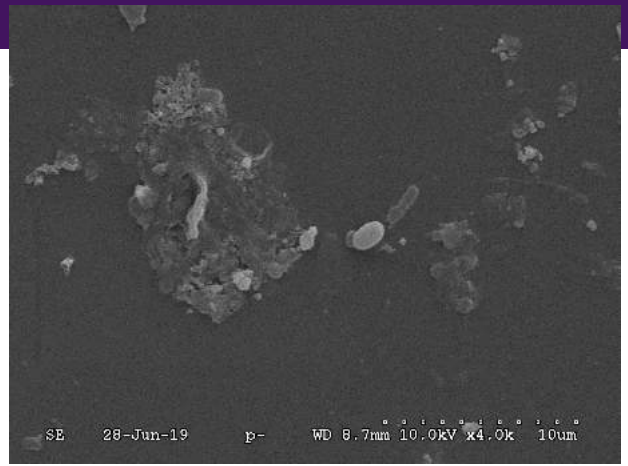
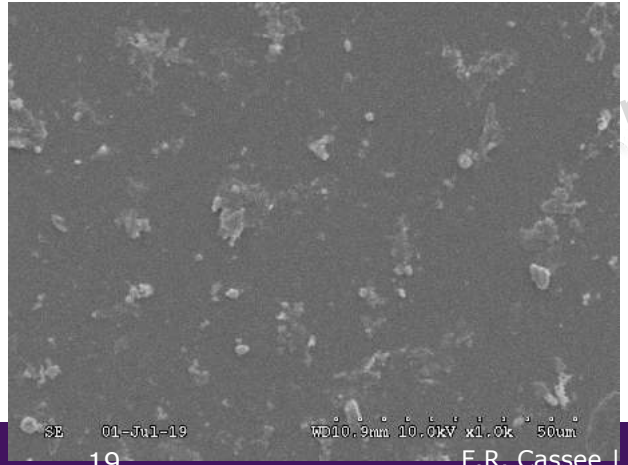
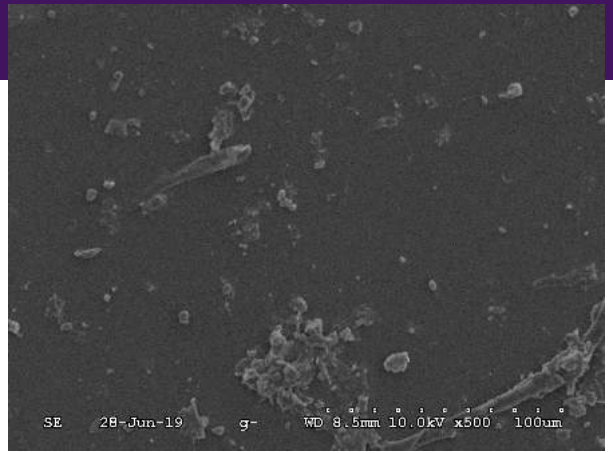

SE 28-Jun-19 p- WD 8.7mm 10.0kV x4.0k 10um

Pig bioPM


SE 01-Jul-19 WD10.9mm 10.0kV x1.0k 50um

SE 01-Jul-19 WD10.9mm 10.0kV x10k 5um

SE 01-Jul-19 WD10.9mm 10.0kV x10k 5um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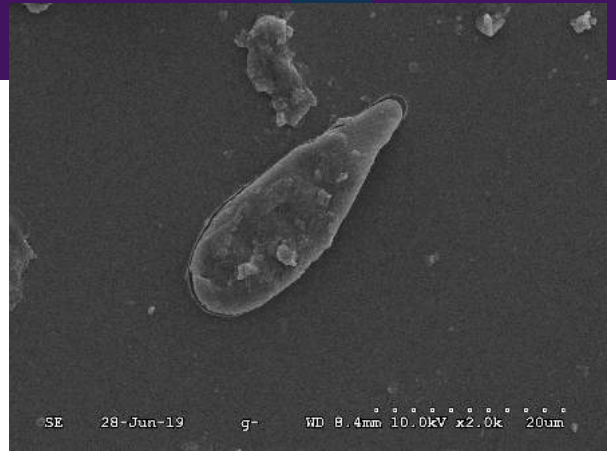
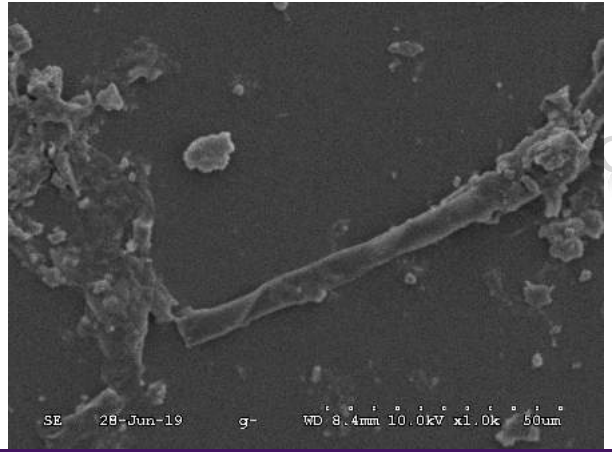
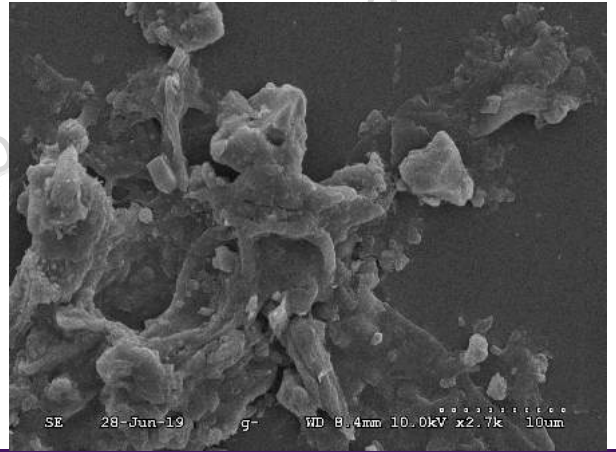
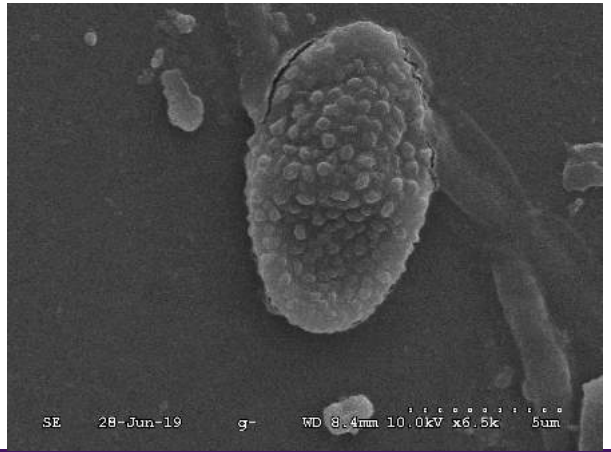

SE 28-Jun-19 g- WD 8.4mm 10.0kV x2.0k 20um

SE 28-Jun-19 g- WD 8.4mm 10.0kV x4.0k 10um

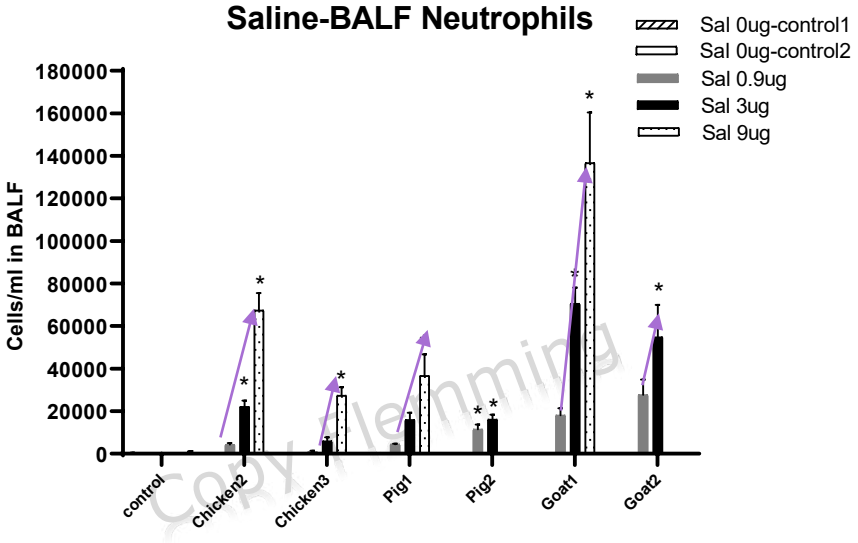
Goat bioPM


SE 28-Jun-19 g- WD 8.4mm 10.0kV x1.0k 50um


SE 28-Jun-19 g- WD 8.4mm 10.0kV x2.7k 10um


SE 28-Jun-19 g- WD 8.4mm 10.0kV x6.5k 5um

Inflammation in mice exposed to PM



Inflammation markers dose dependent increased

- more potent than diesel soot
- suppressed by antioxidant (not shown here)

Airport

- Increased levels of ultrafine around Amsterdam Schiphol airport

- What are the health implications for local residents?

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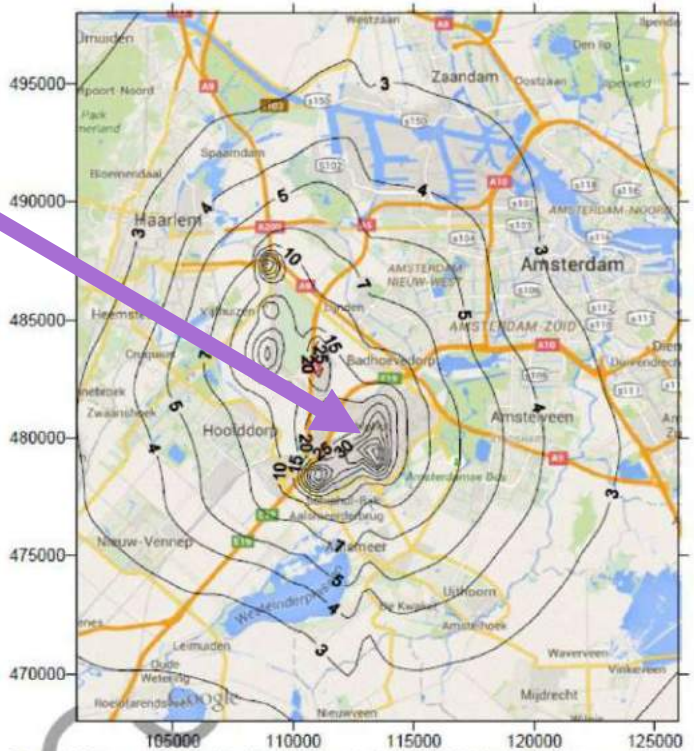
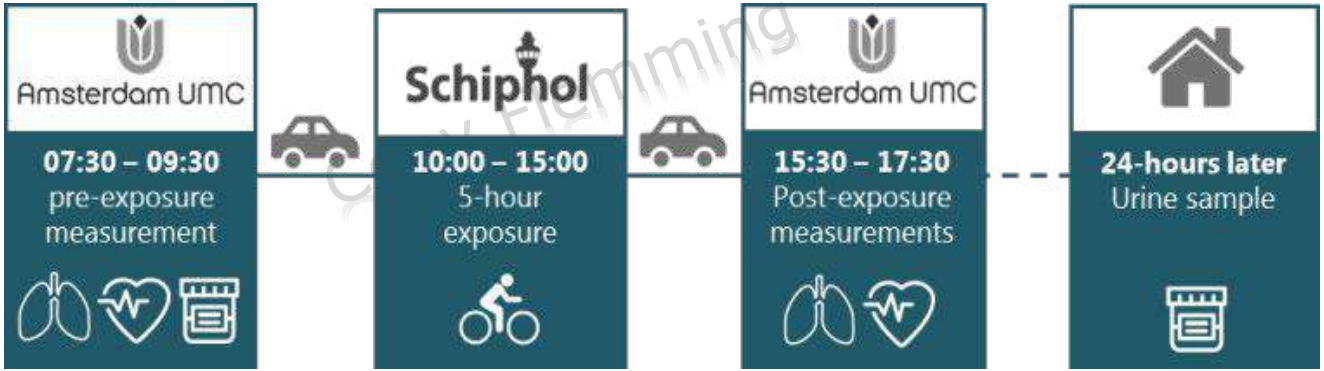


Annual mean UFP concentrations only from aviation

Study in volunteers: procedure

- 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 was conducted at Amsterdam UMC (Amsterdam, the Netherlands).



Variability in runway use, based on noise and wind

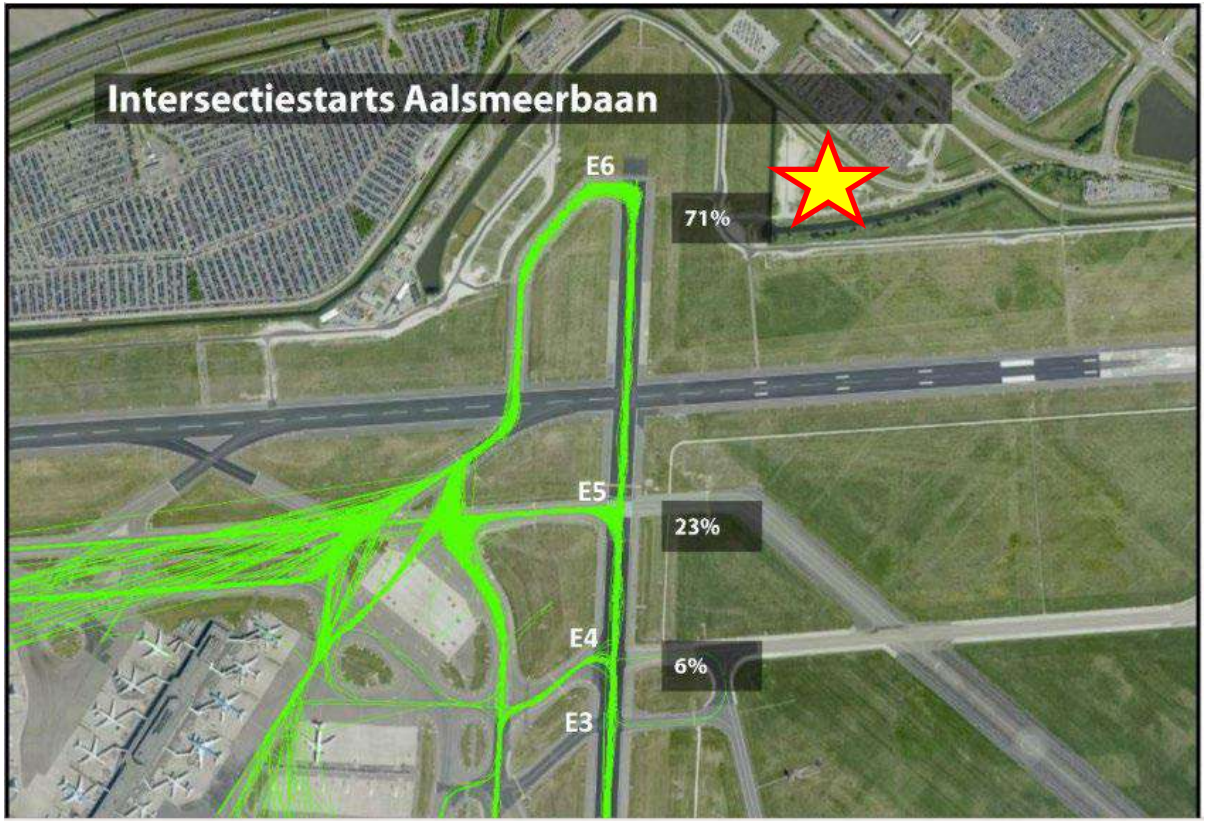
Set up

Table 4.2 Baseline characteristics

	Subjects (n=21)	Min - max
Age (years)	22.5	19.0 – 27.0
Gender (female)	17 (14)	
BMI (kg/m2)	22.6 (2.4)	19.3-26.1
FVC (% of predicted)	113 (11)	88 – 134
FEV1 (% of predicted)	106 (13)	85 – 132
FeNO (ppb)	15.0	8.0 – 58.0
Blood pressure		
Systolic (mmHg)	123 (12)	
Diastolic (mmHg)	77 (9)	
Heart rate (c/min) [a]	65 (8)	48.00 – 79.00
Saturation (%)	99.0	97.00 – 100.0

Data from measurements performed during the screening visit presented as mean (SD)

Take off runway



Exposure summary 32 days

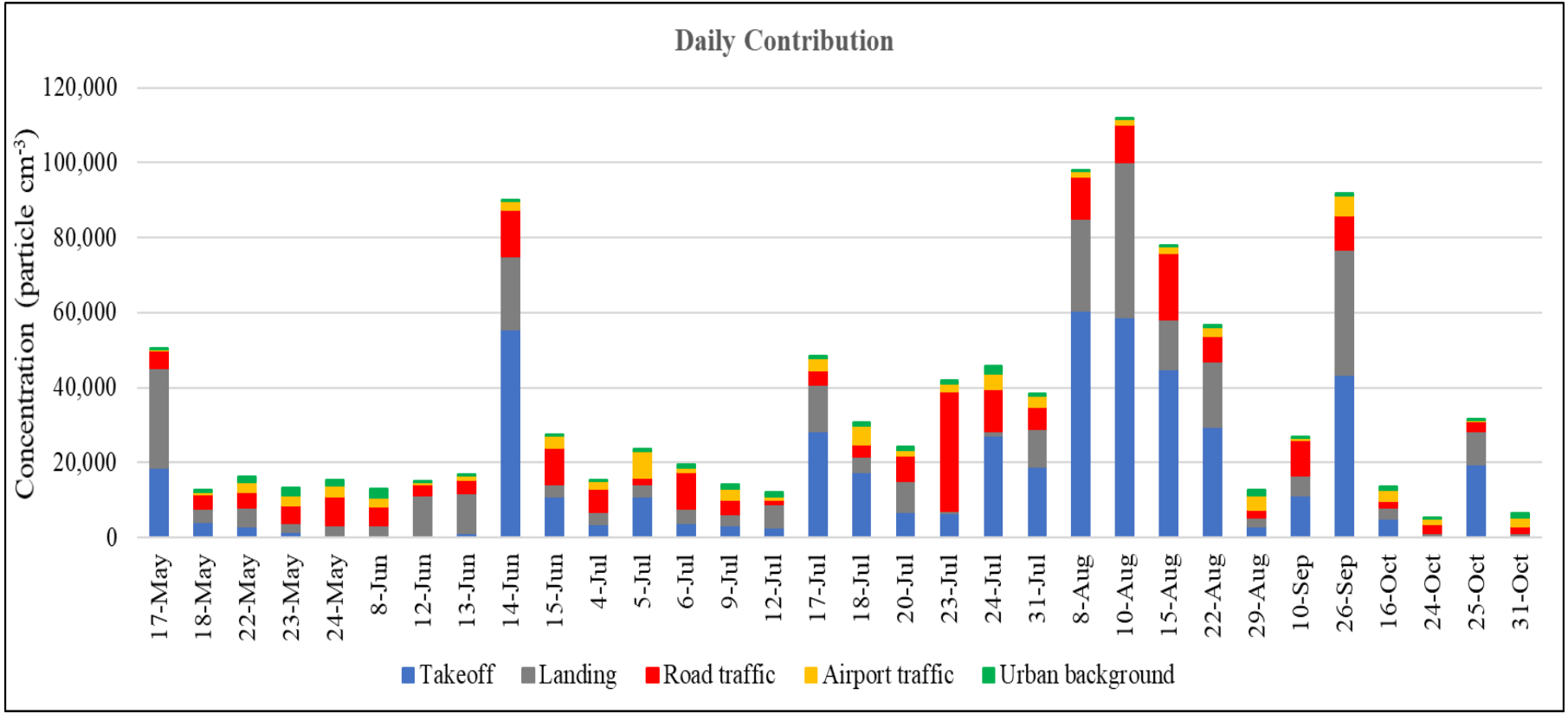
Summary of exposure variables. Values are averages for a 5-hr period as measured in the exposure cabin.

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

Sources ultrafine particles



Measure health indicators

- Spirometry
- FeNO
- ECG & blood pressure
- eNose (exhaled breath analysis)
- Metabolome (oxidative stress) in urine - tbd

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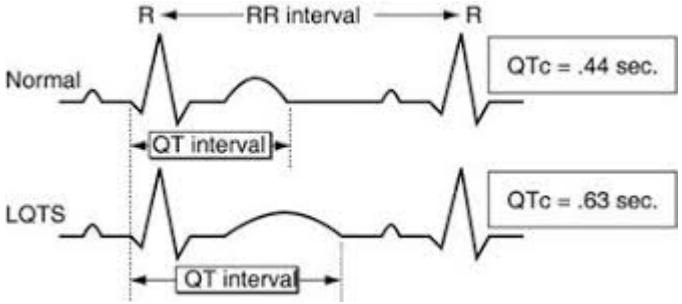
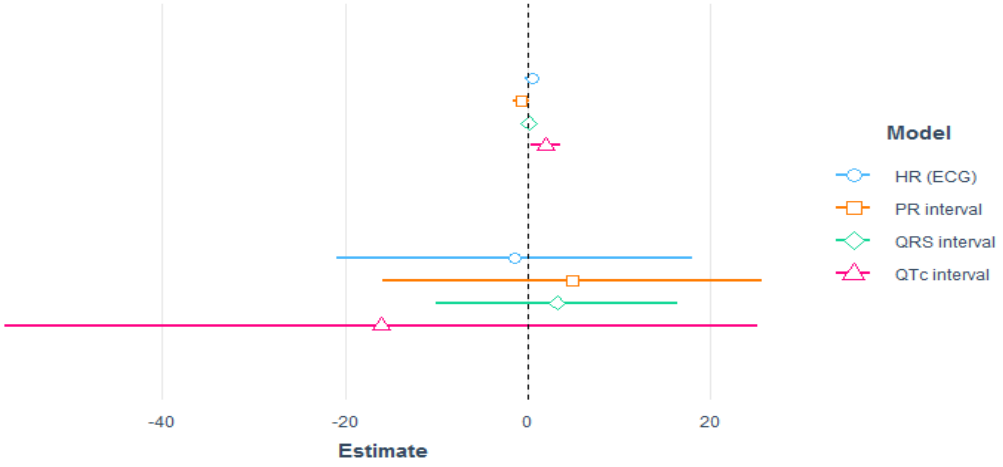


Relating exposure to health effects

- 81 observations form 21 exposure days
- Linear regression models
  - Single pollutant
  - Two polluntant
  - Multi pollutants



  - Effect estimate (per unit of exposure variable)
    - Statistically significant when de 95% confidence interval does not cross zero

Single-pollutant models

Per 10^4 #/cc

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	$PM_{2.5}$[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)

BOLD figures = statistically significant

FVC = marker lung function

ECG = heart function

BP = blood pressure

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

Two-pollutant models

Estimate for FEV1 hardly effected by adjustement for typical road traffic markers

Outcome	PNC[a] + BC[b] N=86				PNC[a] + NO_2[c] N=86				PNC[a] + PM2.5[c] N=86			
	Est.	95%CI			Est.	95%CI			Est.	95%CI		
FVC (mL)	**-6.31**	**-11.81**	–	**-0.81**	**-6.69**	**-12.60**	–	**-0.67**	-5.19	-10.54	–	0.47
FEV1 (mL)	-4.34	-9.70	–	1.93	-3.53	-9.55	–	2.89	-3.32	-8.56	–	3.16
FEV1/VC	0.00	0.00	–	0.00	0.00	0.00	–	0.00	0.00	0.00	–	0.00
PEF (L/s)	-0.01	-0.03	–	0.01	0.00	-0.03	–	0.02	-0.01	-0.03	–	0.02
FeNO (ppb)	0.02	-0.09	–	0.13	-0.01	-0.13	–	0.11	0.01	-0.10	–	0.13
$HR_{sitting}$ (bpm)	-0.07	-0.36	–	0.21	-0.06	-0.37	–	0.24	-0.08	-0.37	–	0.20
Saturation (%)	0.00	-0.04	–	0.05	0.00	-0.04	–	0.06	0.00	-0.04	–	0.05
BP_{sys} (mmHg)	-0.19	-0.41	–	0.03	**-0.25**	**-0.50**	–	**-0.02**	-0.15	-0.39	–	0.08
BP_{dia} (mmHg)	-0.18	-0.41	–	0.05	**-0.29**	**-0.54**	–	**-0.06**	-0.14	-0.38	–	0.10
ECG - HR (bpm)	0.27	-0.04	–	0.61	0.31	-0.01	–	0.68	0.28	-0.02	–	0.62
ECG - PR (ms)	-0.28	-0.71	–	0.03	-0.32	-0.84	–	0.00	-0.18	-0.60	–	0.14
ECG - QRS (ms)	0.12	-0.08	–	0.33	0.11	-0.11	–	0.34	0.11	-0.10	–	0.31
ECG - QTc (ms)	**0.80**	**0.16**	–	**1.54**	**0.93**	**0.25**	–	**1.71**	**0.82**	**0.18**	–	**1.54**

Outcome	PNC[a] + CO[d] N=86				PNC[a] + O_3[c] N=86			
	Est.	95%CI			Est.	95%CI		
FVC (mL)	**-5.95**	**-11.12**	–	**-0.07**	**-6.72**	**-12.52**	–	**-0.30**
FEV1 (mL)	-4.05	-9.38	–	2.36	-3.94	-9.89	–	3.07
FEV1/VC	0.00	0.00	–	0.00	0.00	0.00	–	0.00
PEF (L/s)	-0.01	-0.03	–	0.02	0.00	-0.03	–	0.02
FeNO (ppb)	0.02	-0.09	–	0.14	-0.03	-0.15	–	0.10
$HR_{sitting}$ (bpm)	-0.09	-0.37	–	0.19	0.08	-0.24	–	0.36
Saturation (%)	0.00	-0.04	–	0.05	-0.01	-0.06	–	0.04
BP_{sys} (mmHg)	-0.15	-0.38	–	0.07	-0.21	-0.48	–	0.04
BP_{dia} (mmHg)	-0.15	-0.38	–	0.08	**-0.33**	**-0.57**	–	**-0.09**
ECG - HR (bpm)	0.26	-0.04	–	0.60	**0.33**	**0.00**	–	**0.71**
ECG - PR (ms)	-0.18	-0.58	–	0.14	-0.25	-0.91	–	0.06
ECG - QRS (ms)	0.10	-0.10	–	0.30	0.09	-0.14	–	0.32
ECG - QTc (ms)	**0.78**	**0.15**	–	**1.51**	**1.08**	**0.40**	–	**1.89**

Results of the two-pollutant models were corrected for room temperature and relative humidity (MAPCEL), respiratory symptoms, age, gender and BMI. a= per 10,000 particles/cm^3 ; b = per 1 $\mu g/m^3$; c = per 10 $\mu g/m^3$; d= per 1000 $\mu g/m^3$. Numbers in bold are significant ($p<0.05$)

Main findings

- An increase in small particle numbers showed to
  - prolonged repolarization of the heart (QTc interval of the ECG recordings)
  - decrease the lung function (FVC).

- These associations not affected by adjustment for other pollutants (i.e. BC, NO_2, PM10, O_3) and strongest in the smallest size fraction assessed in this study (i.e. 10-20 nm).

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- No statistical significant associations were observed for other lung function parameters (FEV1, PEF), exhaled NO and oxygen saturation

Summary

- Not the external air concentration but the dose makes the poison
  - Dosimetry is crucial for extrapollation finding animals to human
  - Biodistribution data provide insight in other target organs than respiratory tract

- Not all PM is equally toxic
  - Even traffic has various more and less emissions
  - BioAerosol (containg micro organisms) - effects poorly understood
  - Size fractions **within** UFP can have different effects

    in part mayby due to differences in dosimetry

Cary Fleming

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