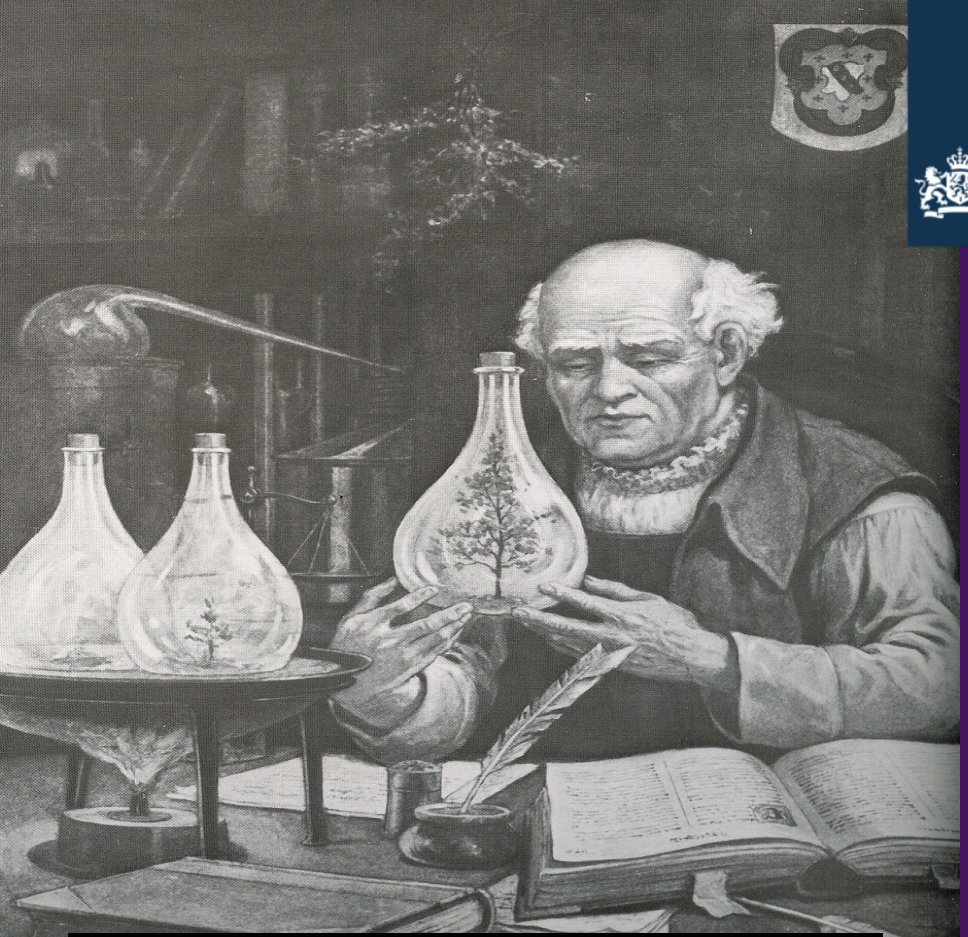


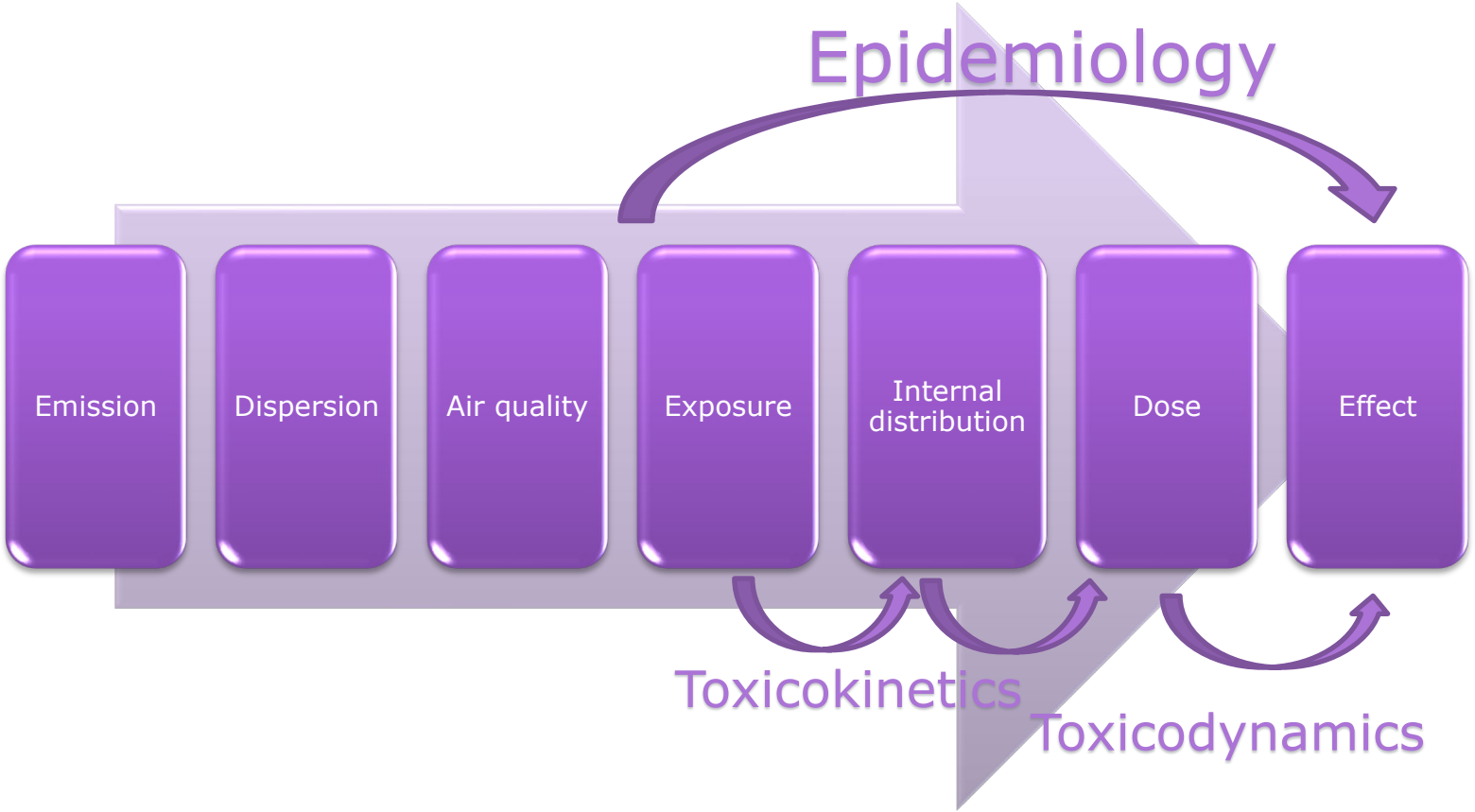
Paracelsus: everything is toxic, the dose makes the poison

Utrecht University

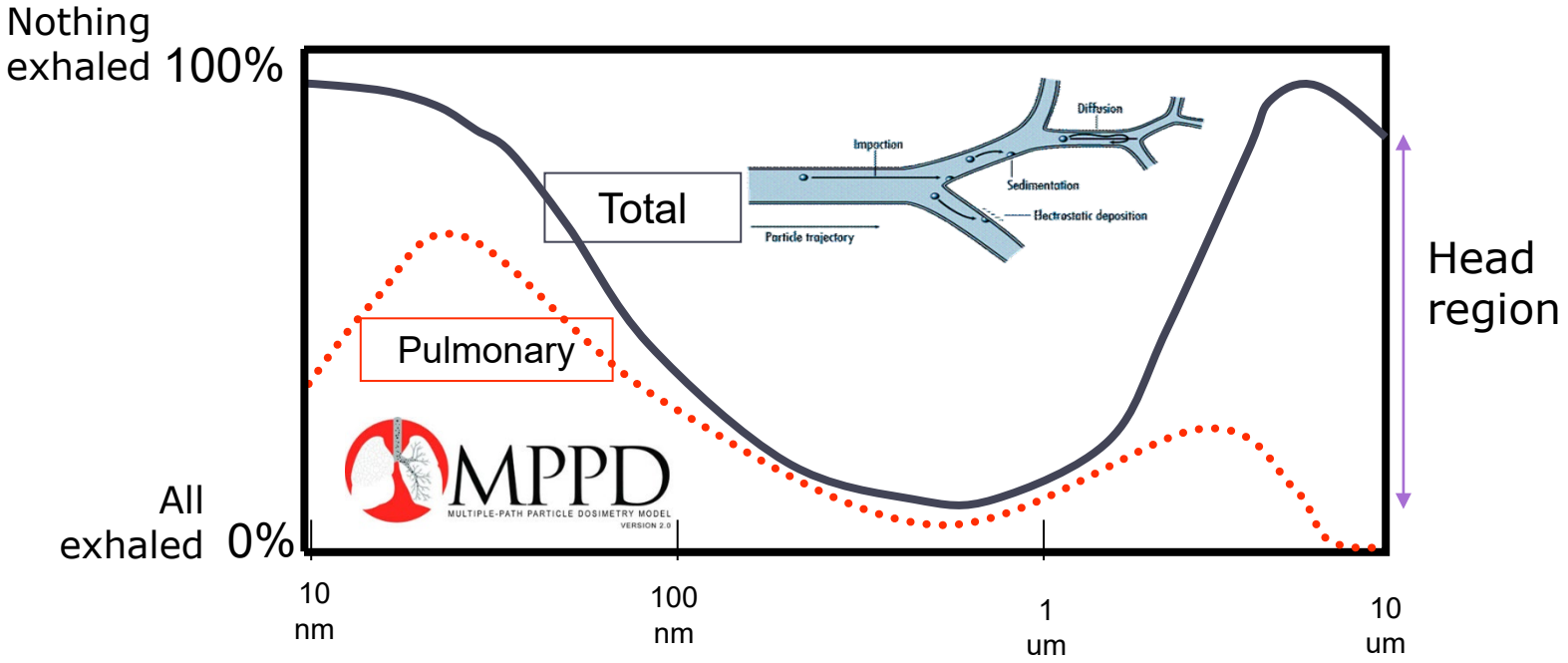
National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Advances in contributions of toxicology to the understanding of particle component toxicity

Prof.dr. Flemming R. Cassee


Epidemiology
Emission
Dispersion
Air quality
Exposure
Internal distribution
Dose
Effect
Toxicokinetics
Toxicodynamics

Deposition after inhalation



Size affects the internal dose

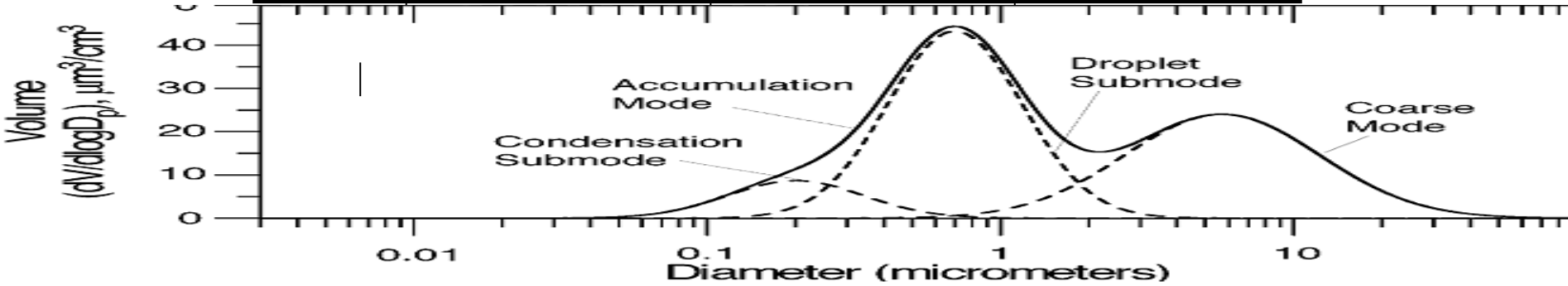
Deposition human versus distribution outdoor

Nothing exhaled

100%

All exhaled

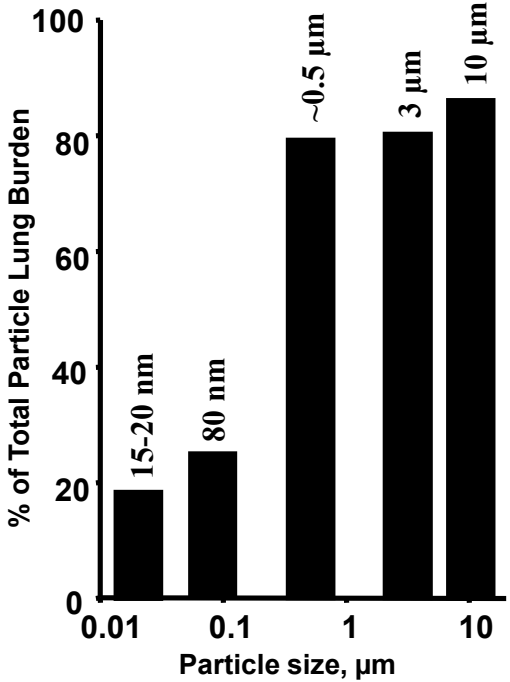
The often most abundant fraction has low deposition efficiency in the lung



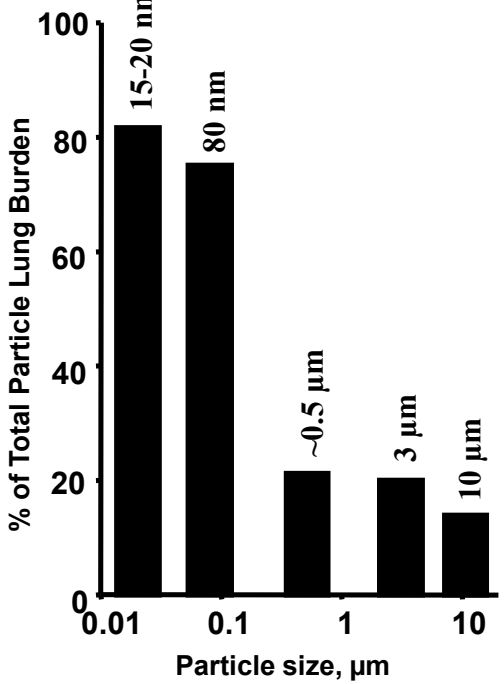
Retention of insoluble iridium particles in rat lungs

24 hrs post-exposure, extensive lavage

Alveolar Macrophages



Retained in lungs after washing



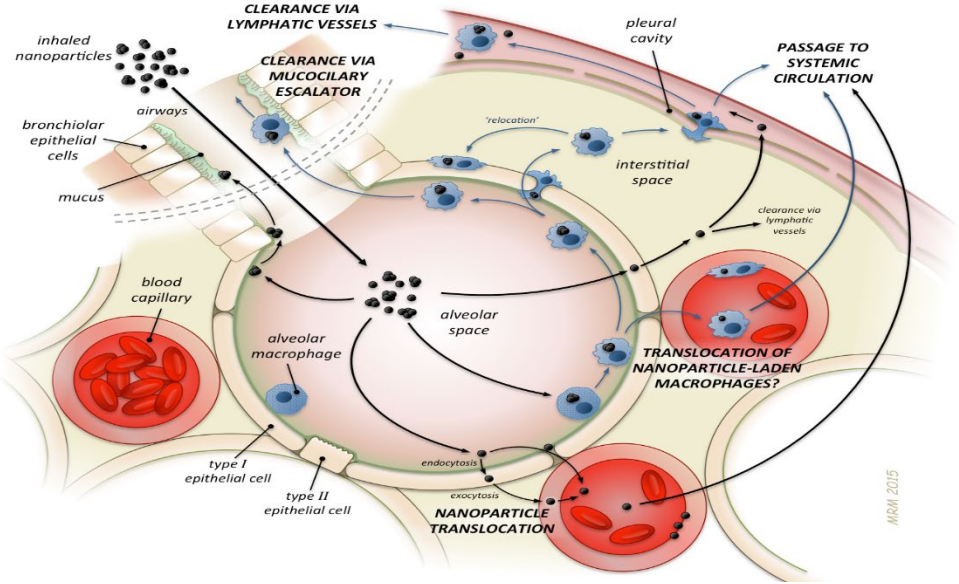
Kreyling et al, 2002: Oberdorster et al 2004

Size matters in terms of

- Deposition
- Clearance
- Retention
- Biodistribution

- Smallest particles can reach other organs explaining sytemic effects

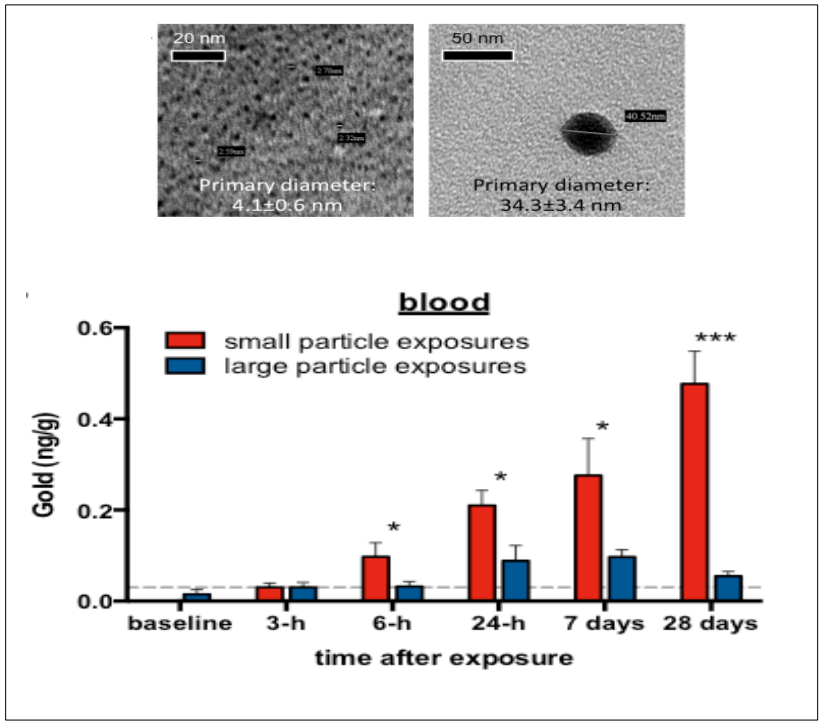
- They come from different sources



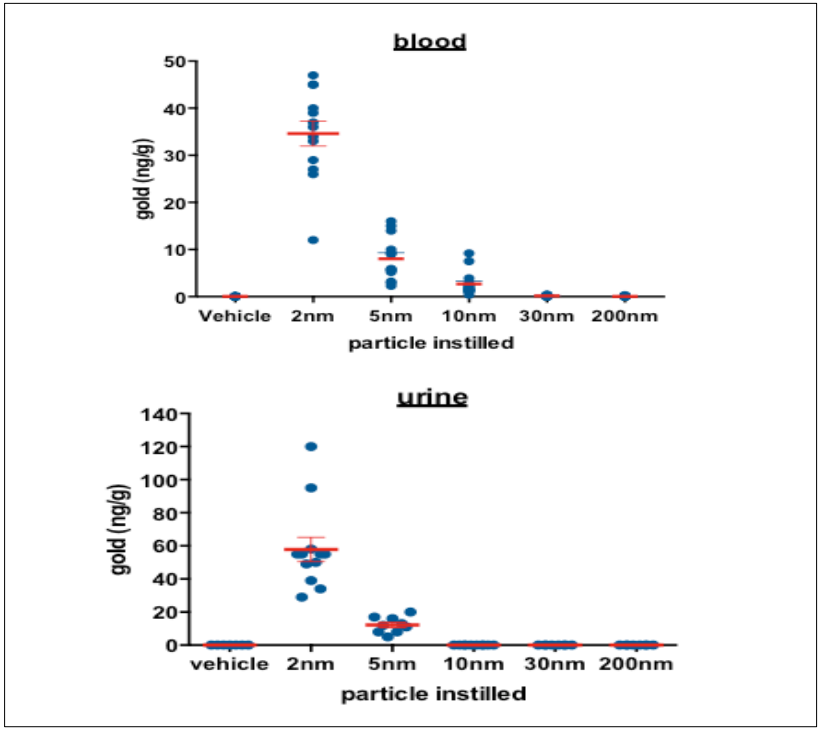
Stone, Cassee et al, EHP, 2017

Particle size dependent translocation!

Clinical exposures

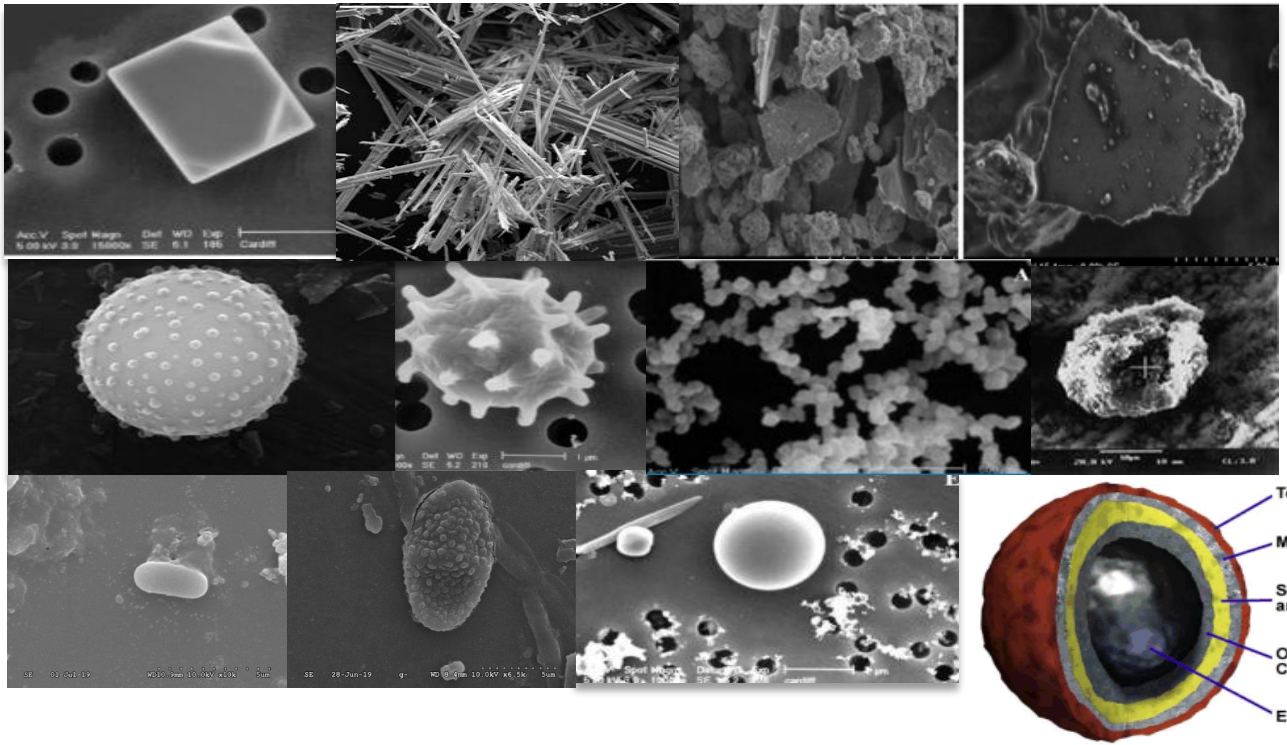


Exposure mice



Miller *et al*. (2017). *ACS Nano*

Sources and fractions in PM



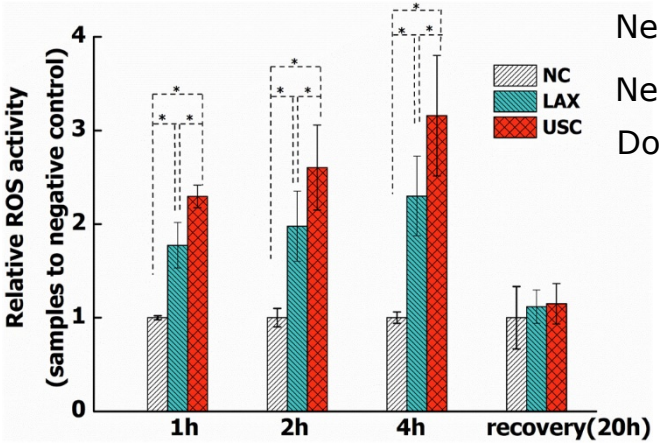
Past decade focus in road traffic tailpipe exhaust

But what about
- Biological fraction
- Wear particle
- Aviation

PM from road traffic versus aviation

- Is all PM equally toxic?

Average relative ROS activity in bronchials cells



He et al., Sci Total Environ. 2018 Nov 1;640-641:997-1003

Negative control

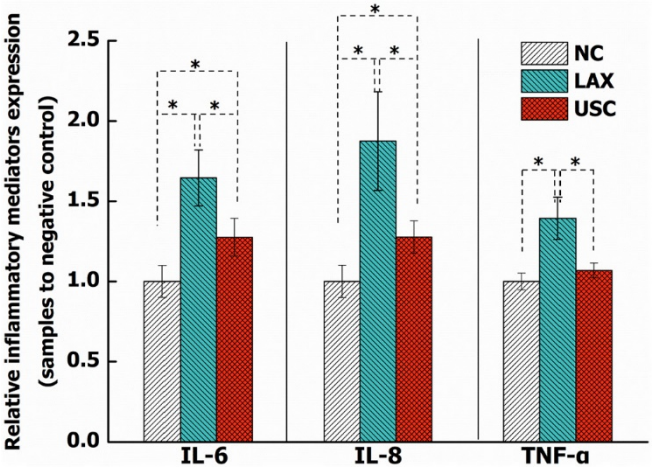
Near airport

Downtown LA

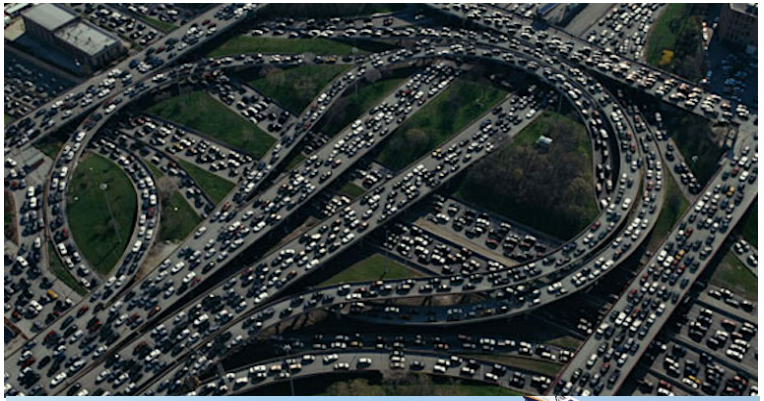
PM from road traffic versus aviation

- Is all PM equally toxic?

Average inflammatory mediators in 16HBE cells



He et al., Sci Total Environ. 2018 Nov 1;640-641:997-1003

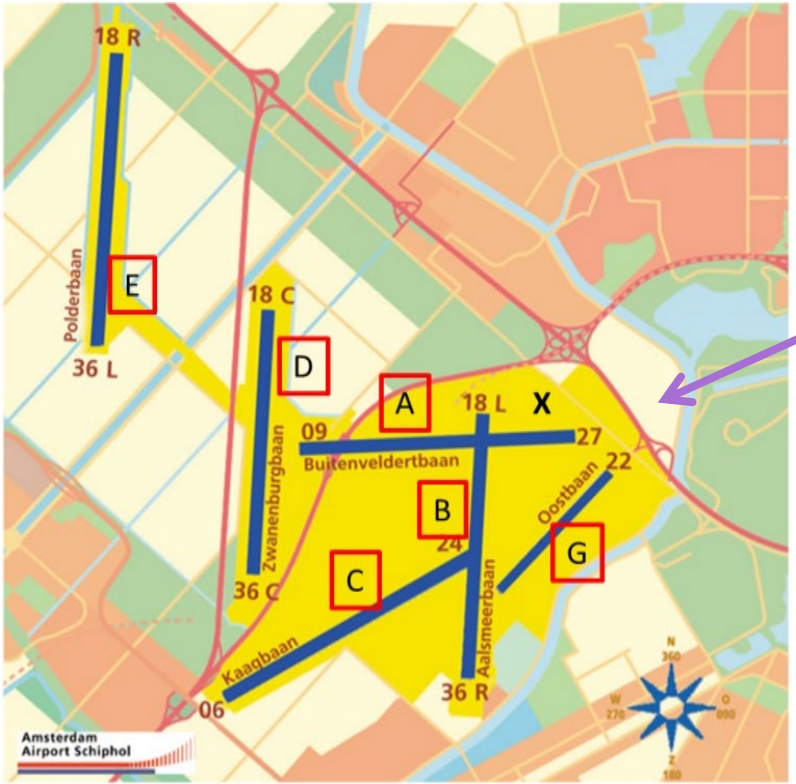


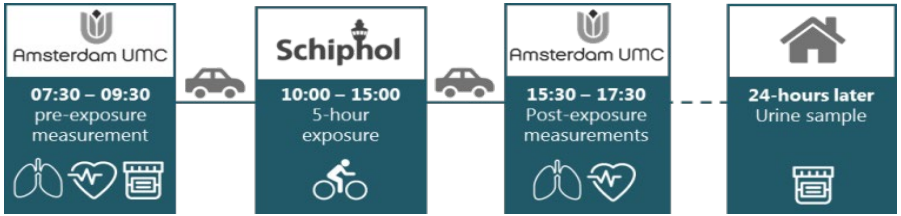
Negative control

Near airport

Downtown LA

Amsterdam Schiphol airport human study





5-hour exposure to air next to the airport, 2 freeways and a runway intersection near Amsterdam

Lammer et al., Environ. Int, 2020

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)

Spirometry
FeNO
ECG & blood pressure

Exposure summary 32 days

Summary of exposure variables. PNC= particle number counts. Values are averages for a 5-hr period as measured in the exposure cabin.

Exposure day	Mass (µg/m³)	PNC (#/cm³)	BC (µg/m³)	NO_2 (µg/m³)	CO (µg/m³)
Average	23.1	53,469	0.6	28.2	638
SD	8.3	43,776	0.4	12.2	83
Highest	47.5	173,187	1.9	60.2	830
Lowest	10.6	10,520	0.1	12.4	494

Mass concentrations are based on Filter measurements. PNC = particle numb

DL= Below the detection limit of the instrument

	PNC	PM	BC	NO_2	CO
PNC					
PM	-0.11				
BC	0.14	0.38			
NO_2	0.37	0.13	**0.79**		
CO	0.08	0.33	0.59	0.57	

Sources

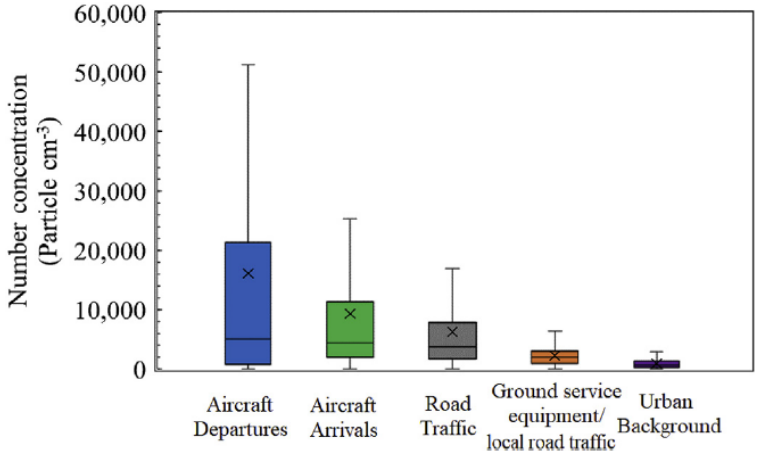


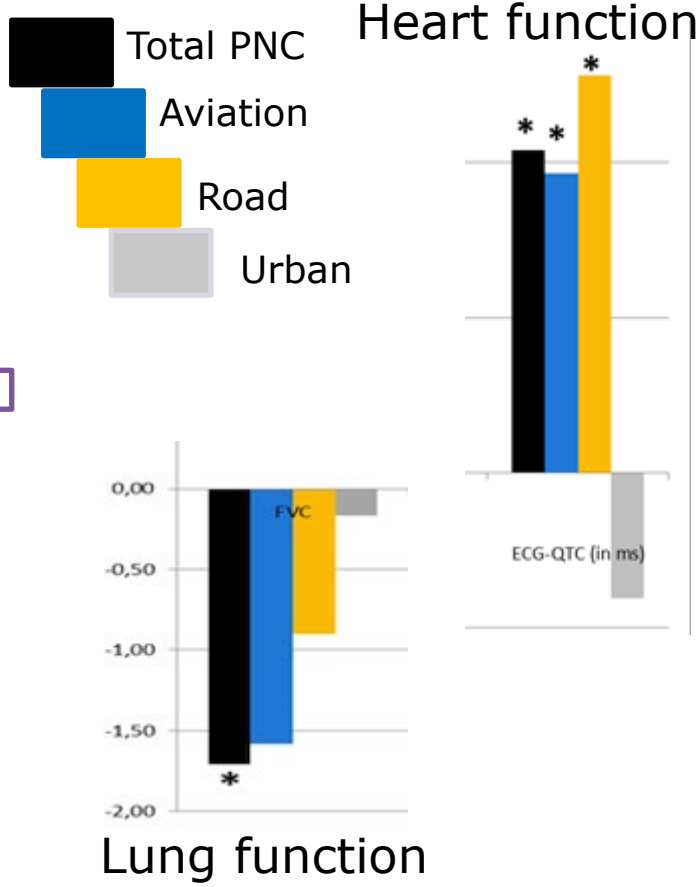
Fig. 4. Absolute contribution (particle cm^{-3}) of each of the PMF-resolved factors to the total particle number concentrations (PNCs).

Pirhadi et al., Environ Pollut. 2020 May;260:114027.

Two-pollutant models

Outcome	PNC[a] ≤20 nm N = 86			PNC[b] >50 nm N = 86		
	Est.	**95%CI**		**Est.**	**95%CI**	
FVC (mL)	**-13.70**	**-26.64**	**– -0.52**	10.22	-13.09	– 34.21
HR (bpm)	-0.29	-0.97	– 0.33	0.49	-0.80	– 1.68
BP_{sys} (mmHg)	-0.37	-0.91	– 0.15	0.80	-0.18	– 1.87
BP_{dia} (mmHg)	-0.45	-0.98	– 0.09	**1.03**	**0.03**	**– 2.07**
ECG – HR (bpm)	0.57	-0.14	– 1.33	-0.30	-1.67	– 1.05
ECG – PR (ms)	-0.63	-1.58	– 0.10	0.14	-1.59	– 1.59
ECG – QRS (ms)	0.21	-0.28	– 0.69	0.25	-0.64	– 1.13
ECG – QTc (ms)	**1.89**	**0.41**	**– 3.55**	-0.94	-3.70	– 2.19

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/cm³. b = per 10,00 particles/cm³. Numbers in bold are significant (p<0.05)



Toxicity of different source-specific PM2.5

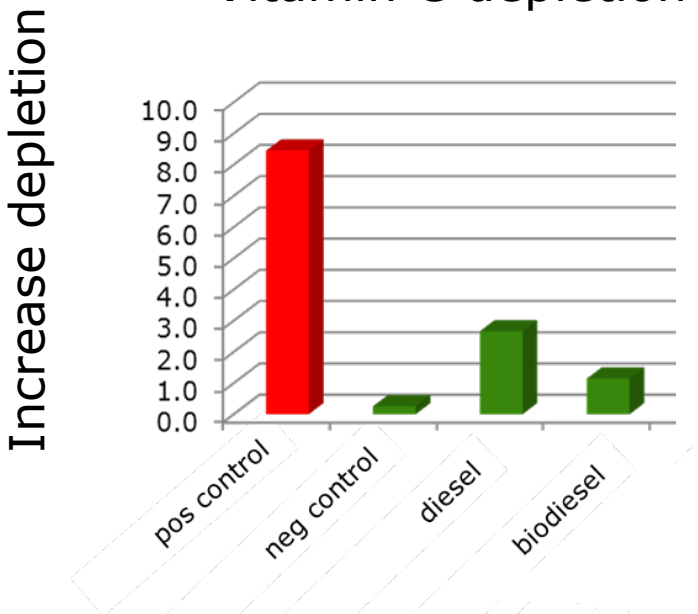
- Brake wear (4 different brake pad types)
- Wood combustion (modern technology/efficient combustion and old technology/efficient combustion)

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

Gerlofs-Nijland et al. 2019

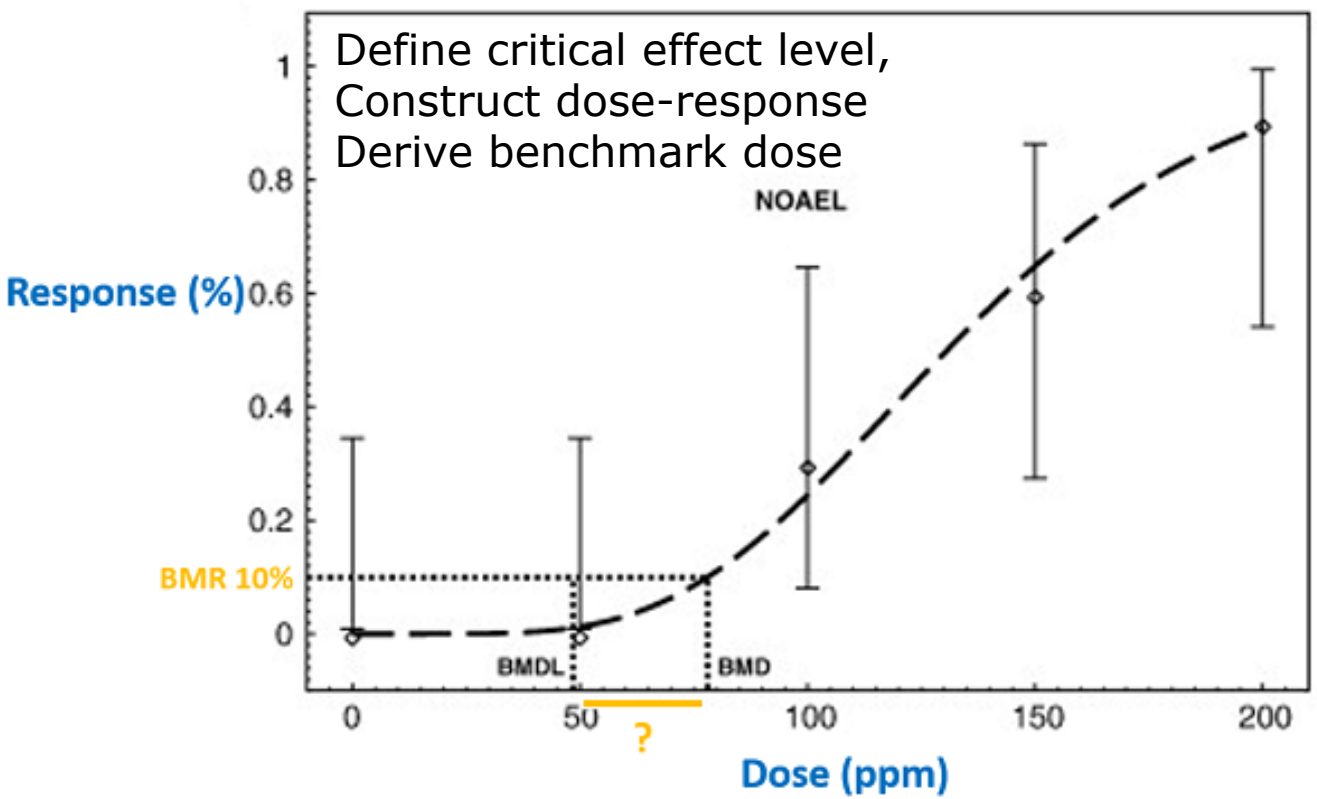
Oxidative potential– source specific PM2.5

Vitamin C depletion in test tube



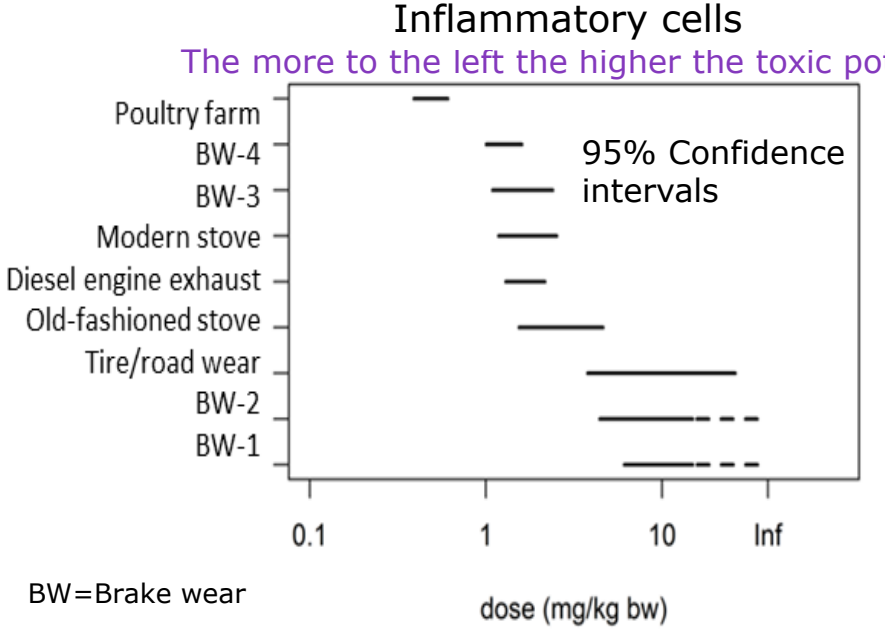
Brake wear more potent than diesel particles based on PM mass – role of Cu

Ranking based on mice toxicity - inflammation markers



Inflammatory cells

Conclusions



BW=Brake wear

- Farm PM most potent to induce acute inflammation
- Considerable variability in the toxic potency of brake wear particles.

Gerlofs-Nijland et al. 2019

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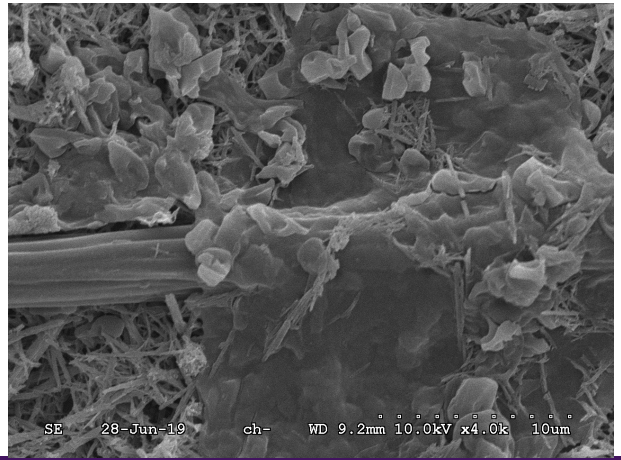
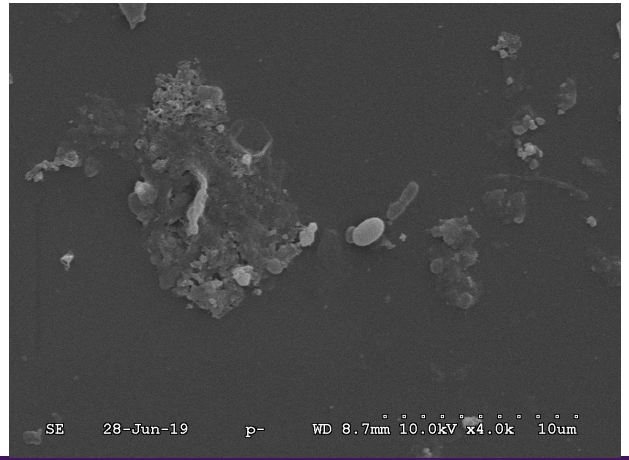
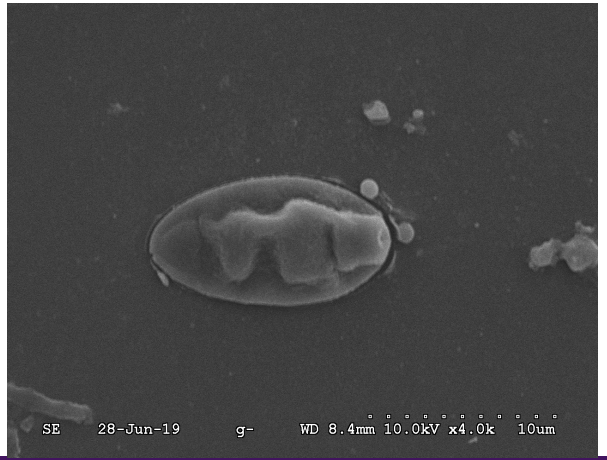
BioPM
Micro organisms as part of particulate matter

Comparison PM from chicken –pig - goat farms





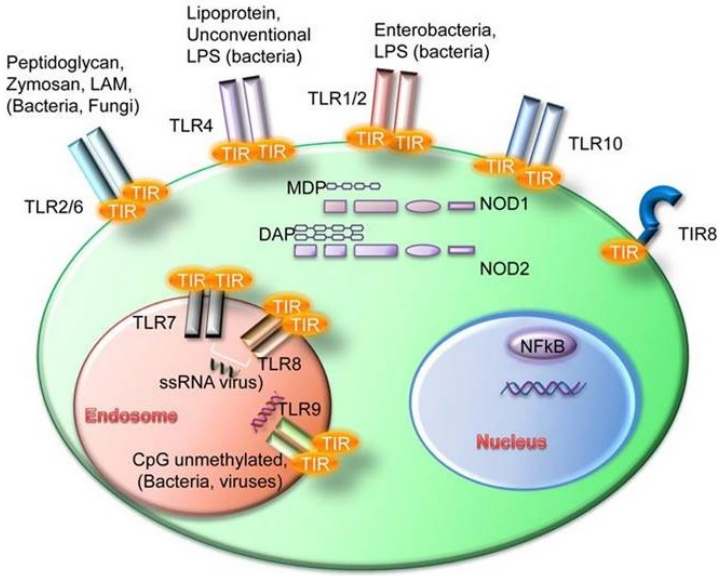


BioPM activated innate immune receptors and cells

BioPM

Toll like **receptors** play a crucial role in the proper function of the innate immune system

PRRs



Each **receptor** related to activation by micro organism group

cytokines → **Inflammatory response**

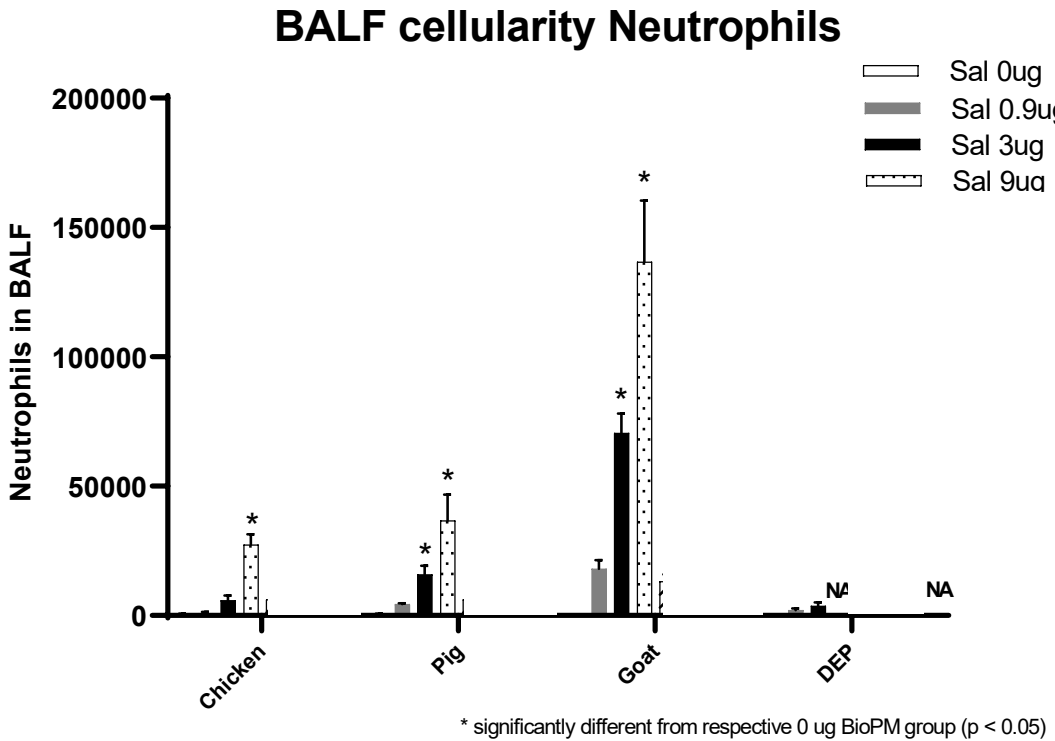
Muzio *et al.*, 2012. MJHID, Vol 4, No 1

Summary of Toll like receptor activation:

BioPM Source / farm	TLRs Potentially different effects due to different activation						
	TLR2	**TLR3**	**TLR4**	**TLR5**	**TLR7**	**TLR8**	**TLR9**
Chicken	+	-	+	-	-	-	-
Pig	+	-	+	+	-	-	-
Goat	+	-	+	-	-	-	-
PM urban	-	-	-	-	-	-	-
Ligands	**Lipo-protein**	**Double stranded RNAs**	**LPS/endo toxin**	**Flagellin**	**Single stranded RNAs**	**Single stranded RNAs**	**CpG Micro-bial DNA**

" – " minor or no

Inflammation in mice exposed to PM



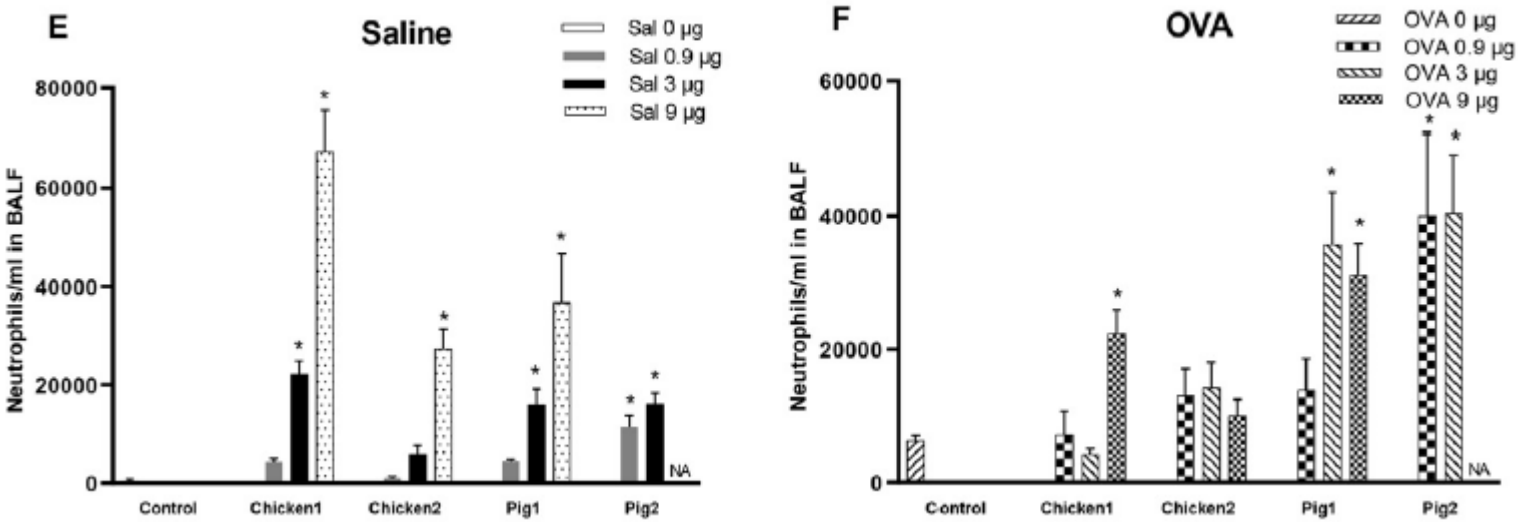
Healthy

Allergic

Stronger responses bioPM vs diesel

Inflammation in mice exposed to PM

Chicken versus pig PM



Inflammation dose and source dependent and stronger in allergy model

Liu et al., World Allergy Organ J. 2020 Apr 3;13(4):100114

Conclusions

- Not all PM is equally potent on a per gram mass basis
  - See also Cassee et al., Inhal Toxicol. 2013 Dec;25(14):802-12.
- Differences in toxicity among sources depend on outcome as well as organs
- Combustion in engines: differences between road and air traffic, most likely due to size difference
- Biological fraction in PM understudied, but seems rather potent compared to diesel PM for airway diseases
- Risk is related to both the toxic potency and the level of exposure/dose
- Source apportionment approaches are the way forward to help policies

Acknowledgements

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