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Combustion Aerosol Conference
Cambridge 2019

Particulate air pollution and health

Terry Tetley

National Heart and Lung Institute
Imperial College London

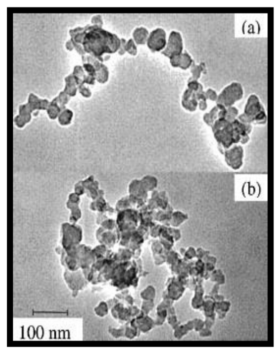
Ambient air pollution

London smog 1952:

Increased hospital admissions with

>4,000 of premature deaths.

Clean air act 1956 “solved” the problem



TODAY - PM10, PM2.5, gases etc, due to urban traffic, industry, combustion…

DEP: <100nm diameter; high particle number concentration/m^3 and /unit mass

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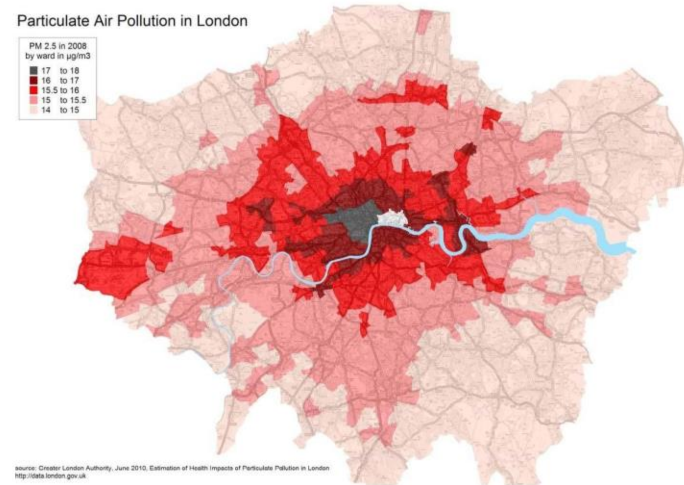
Air pollution in London today – effect on cardiopulmonary health involves fine and ultrafine (nanosized) particles



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- **PM2.5 caused 4.2 million deaths/year globally in 2015, compared to 3.5 million in 1990;**

- **5^{th} highest ranking mortality risk factor**

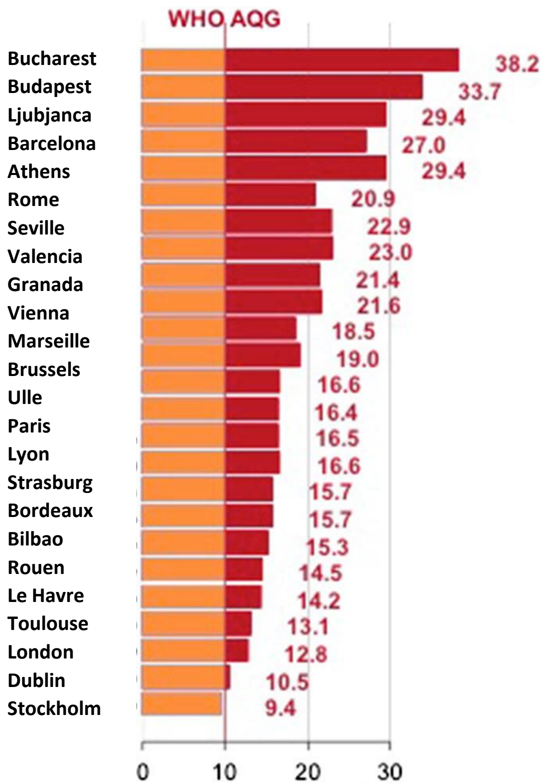
Deaths associated with fine ambient particulate matter ($PM_{2.5}$):

- Cardiovascular (~48%; ischaemic heart disease and stroke),
- Respiratory conditions (~35%; asthma, chronic obstructive pulmonary disease, cystic fibrosis).
- Lung cancer (~9%)

Particulate air pollution was classified as a carcinogenic agent by the International Agency for Research on Cancer (IARC) in 2013

WHO; Global Burden of Disease; European Environment Agency.
AJ Cohen et al. Lancet 2017; 389:1907-1918

Ambient PM2.5 levels in cities across Europe



Ave PM2.5 (mg/m3)

Improving knowledge and communication for decision making on air pollution and health in Europe.
Aphekom. (2011).
Summary report of the Aphekom project 2008–2011.

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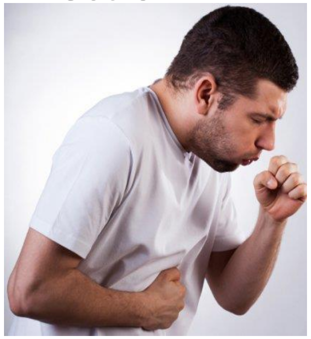
Respiratory effects of air pollution

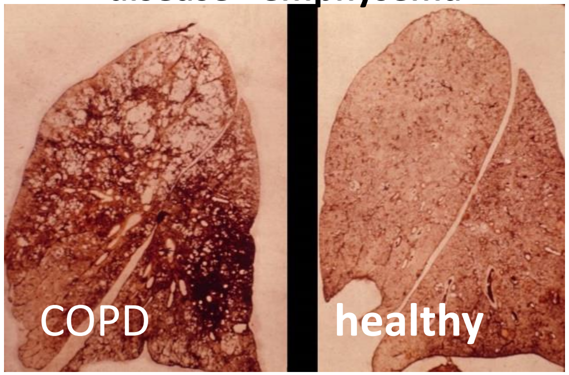
Healthy lungs | Outdoor air pollution exposure | Tobacco smoke

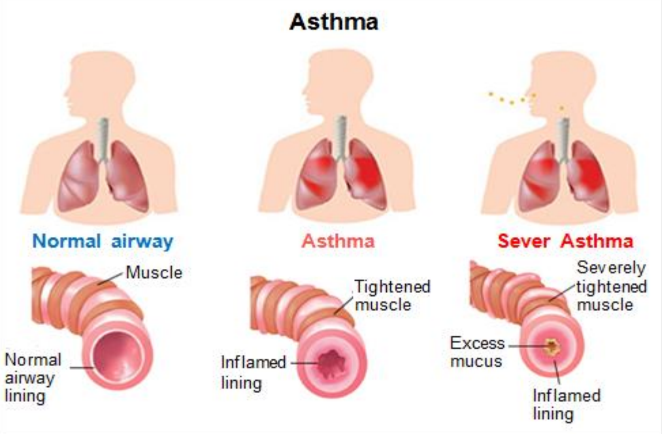
Source: Pathology slides - Courtesy Prof. Saldiva, São Paulo, Brazil

Cough
Infection



Chronic obstructive pulmonary disease - emphysema

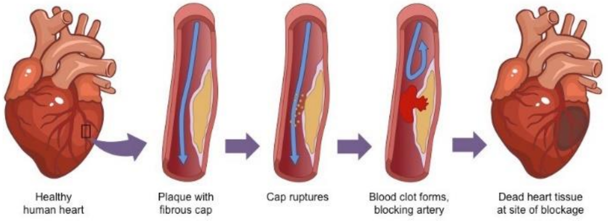




Cancer

Heart rate variability

Atherosclerosis



SYSTEMIC EFFECTS

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Respiratory effect:

- Increased respiratory mortality
- Increased incidence and exacerbation of chronic pulmonary diseases:
  asthma, chronic obstructive pulmonary disease, cystic fibrosis
- Increased pulmonary infections – compromised, young and elderly
- Increased symptoms: cough, phlegm, wheezing, breathlessness
- Increased lung cancer
- Reduced lung function/growth in childhood which affects adult health

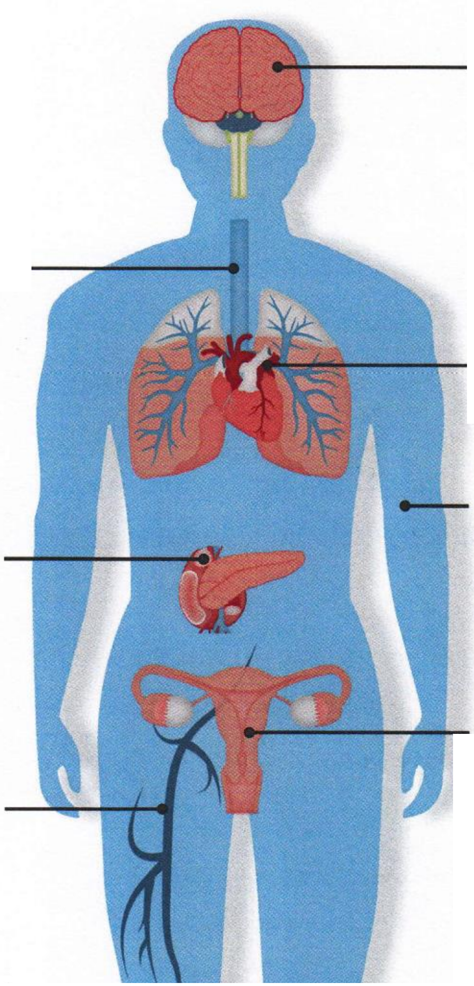
Health effects of air pollution

Respiratory disease – COPD, asthma, infection, lung cancer

Reduced lung growth
Reduced lung function

Strokes
Neurological development
Mental health
Neurodegenerative disorders

Cardiovascular disease – myocardial infarction, cardiac arythmia, cardiac failure



Type 2 diabetes
Type 1 diabetes
Liver toxicity
Renal disease
Altered bone metabolism

Accelerated aging
Autoimmune rheumatic disease

High blood pressure
Endothelial dysfunction
Increased blood clotting
Systemic inflammation
Thrombosis
Atherosclerosis

Premature birth
Low birth weight
Reduced/delayed foetal growth
Lower sperm quality, infertility
Preeclampsia

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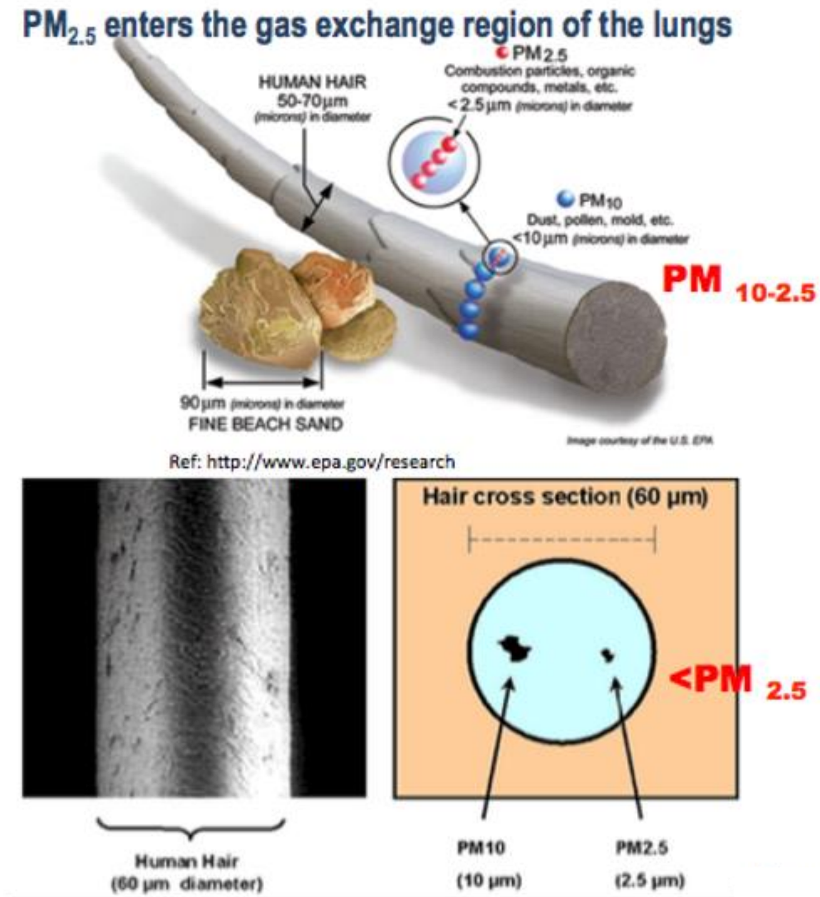
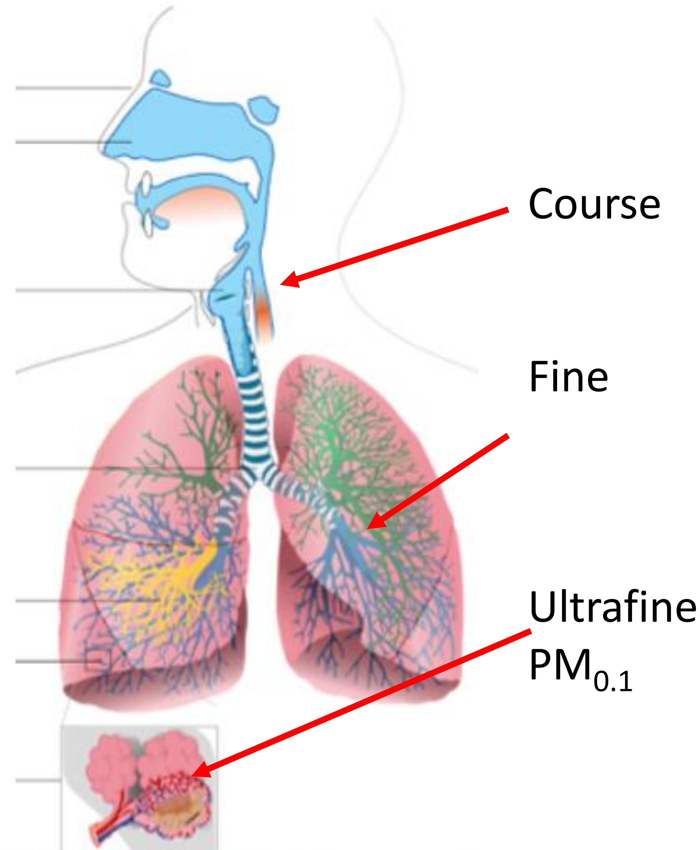
Respirable PM_{10} and $PM_{2.5}$





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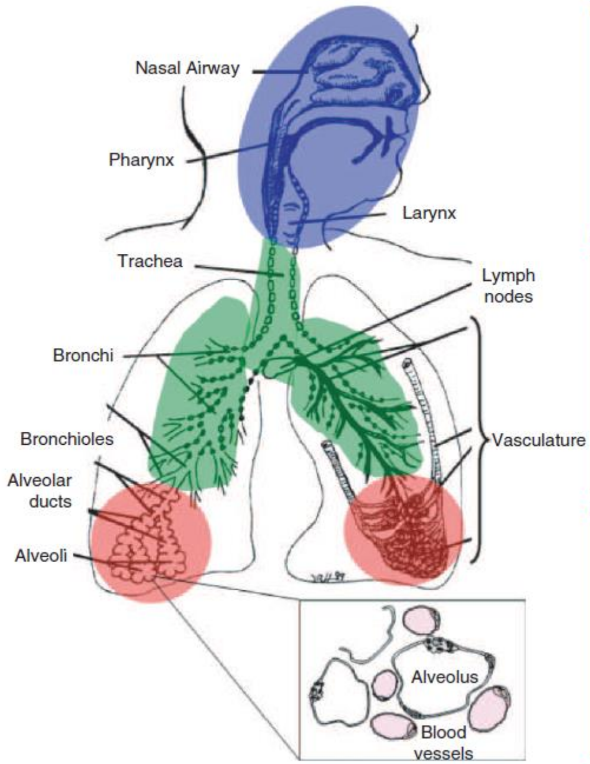
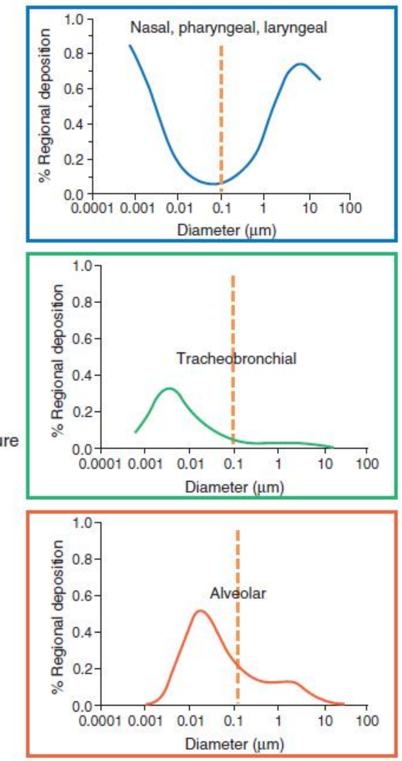
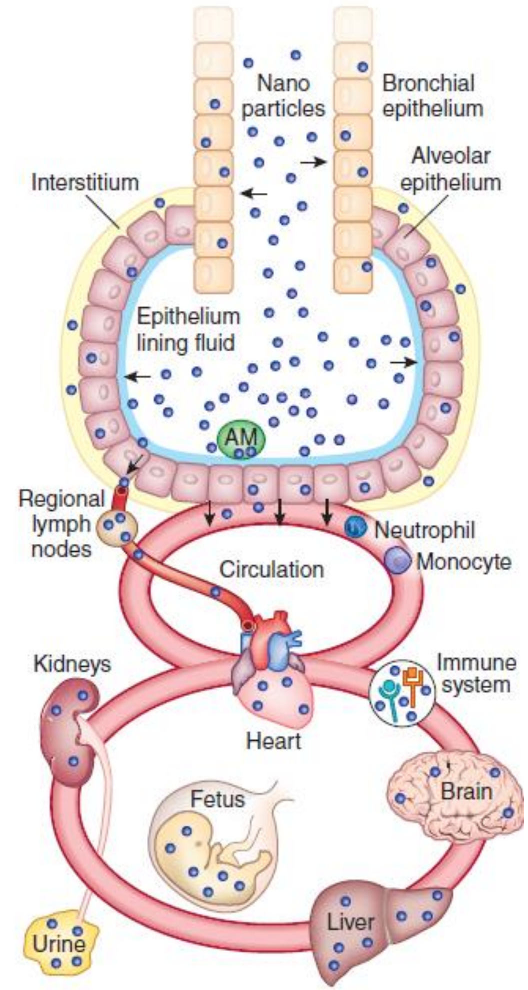
Deposition and impact of inhaled $PM_{2.5}$ and $PM_{0.1}$







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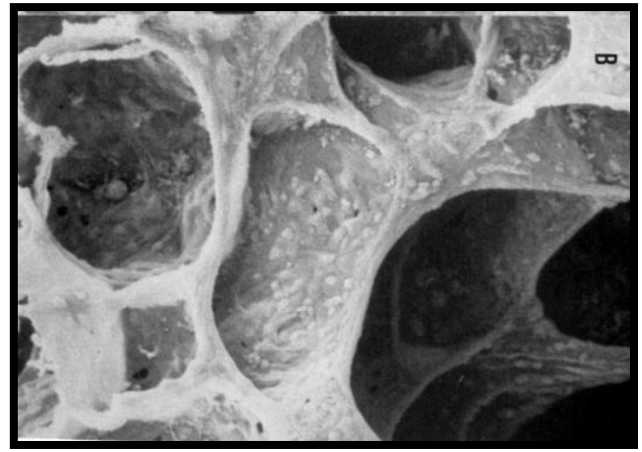
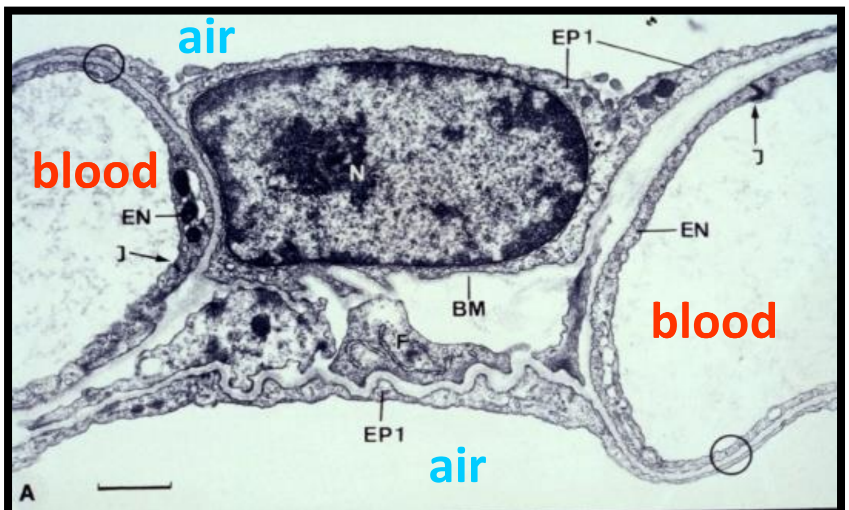
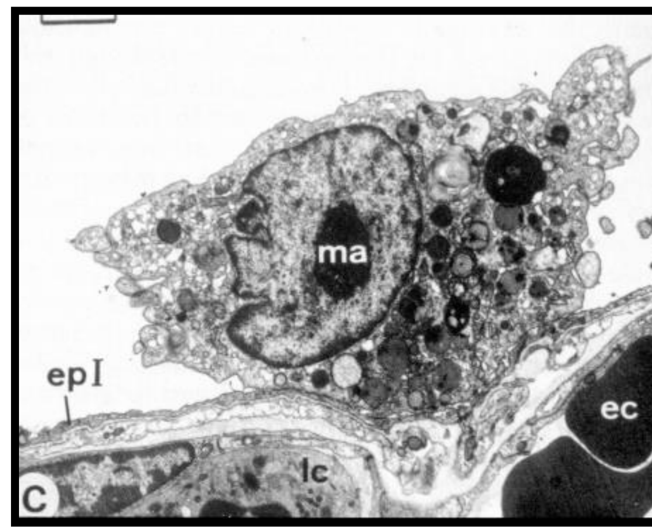
Structure of the lung







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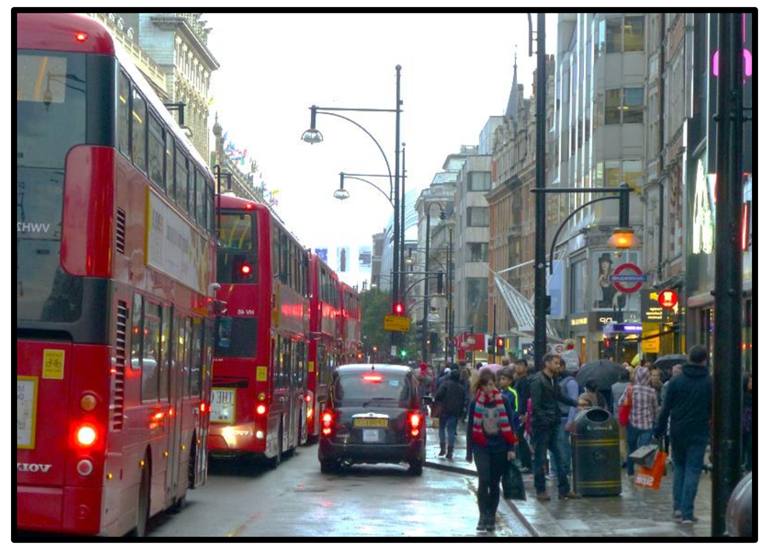
OXFORD STREET II

Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung (COPD) or heart disease (IHD) and age-matched healthy controls: a randomised, crossover study.

Sinharay et al. Lancet 2018;391(10118):339-349



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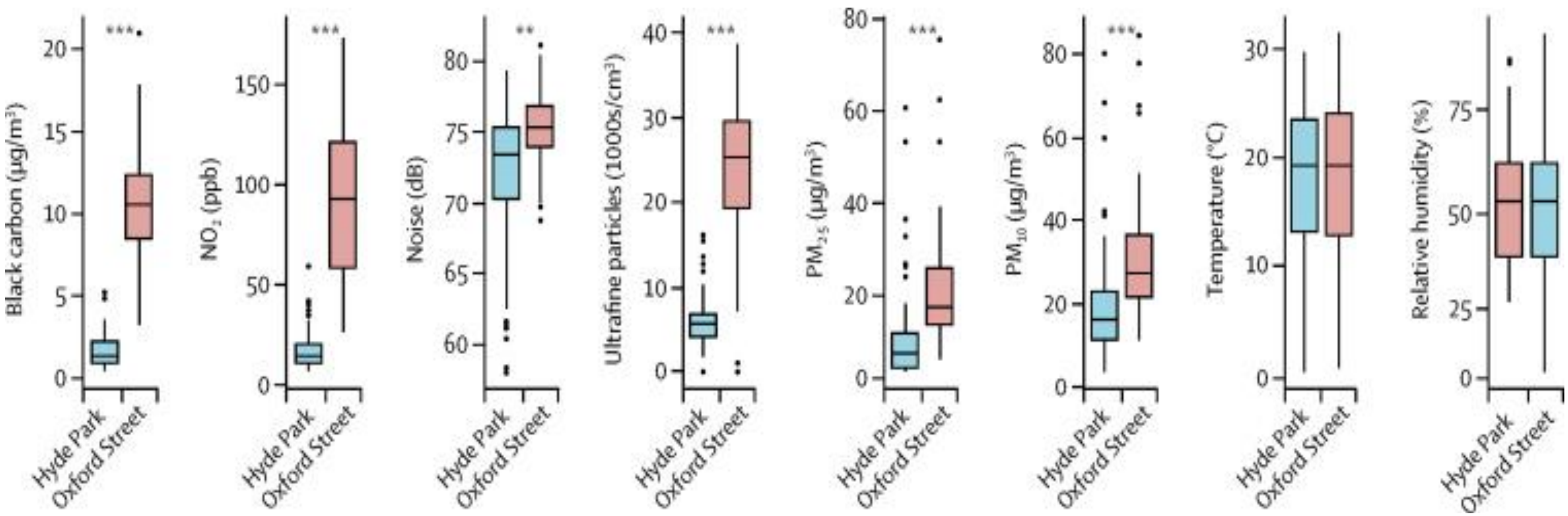
OXFORD STREET II STUDY
Distribution of black carbon, nitrogen dioxide (NO_2), noise, ultrafine particles, $PM_{2.5}$ and PM_{10}concentrations, temperature, and relative humidity on the visit days to Oxford Street or to Hyde Park – *Sinharay et al. Lancet 2018, **391**:339*

BC NO$_2$ Noise PM$_{0.1}$ PM$_{2.5}$ PM$_{10}$ Temp Humidity



Box plots with 95% CIs. PM=particulate matter.
***p<0·01. ***p<0·001.*

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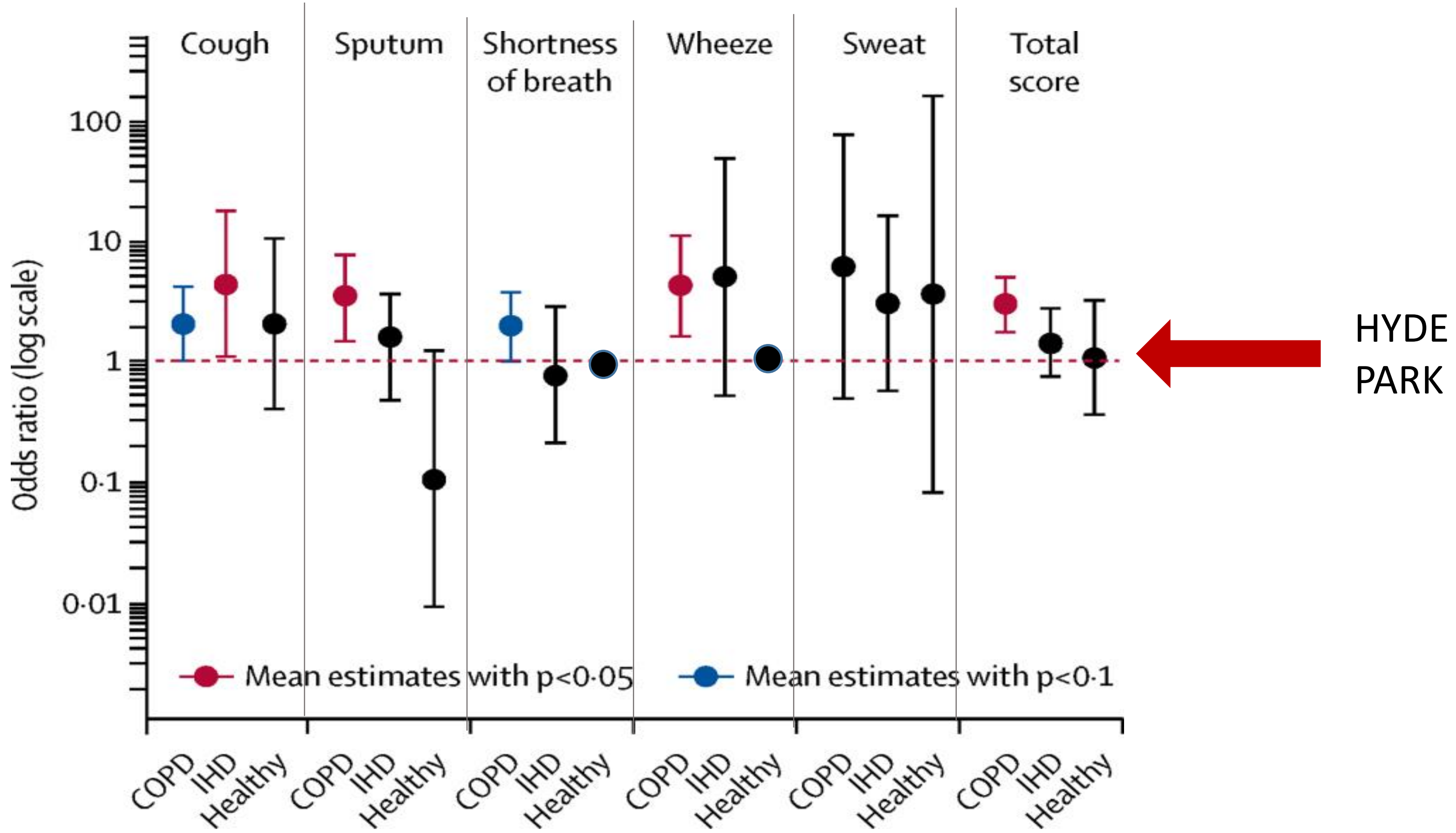
OXFORD STREET II STUDY

Odds ratio of getting worse symptoms of cough, sputum, shortness of breath, wheeze, sweat, and total scores for all these symptoms at Oxford Street versus Hyde Park for healthy volunteers and participants with COPD or IHD – *Sinharay et al. Lancet 2018, **391:** 339*



COPD=chronic obstructive pulmonary disease.
IHD=ischaemic heart disease.

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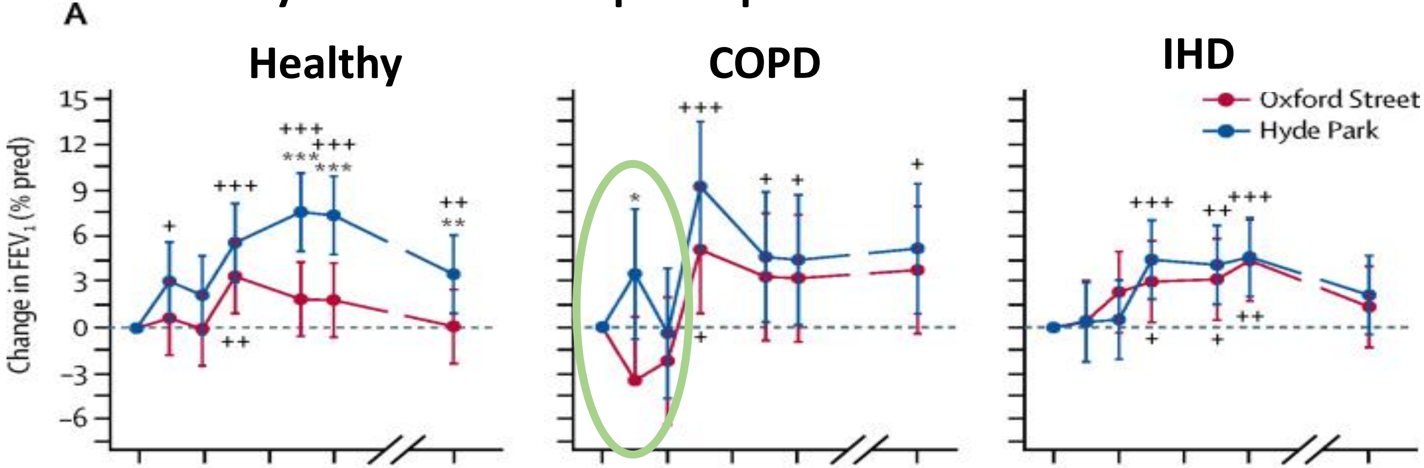
OXFORD STREET II

Change in FEV_1 % of predicted value (A), and FVC % of predicted value (B) from the time 0 and at intervals after the start of the 2 hour walk in Oxford Street or Hyde Park. For healthy volunteers and participants with COPD or IHD



FEV_1=forced expiratory volume in the first second. FVC=forced vital capacity.
**p<0·05, **p<0·01, ***p<0·001, comparing Oxford Street with Hyde Park.*
+p<0·05, ++p<0·01, +++p<0·001, compared with time point 0.

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- Symptoms, including cough and wheeze increased in Oxford Street

- Reduced lung function in COPD subjects was related to levels of NO_2, ultrafine $PM_{0.1}$ and fine $PM_{2.5}$ particles.

- Cardiovascular changes, including increased arterial stiffness in Oxford Street, were seen in healthy and COPD subjects and related to NO_2 and ultrafine particles.

- Cardiovascular medication prevented the effects of air pollution on (increased) arterial stiffness in subjects with heart disease

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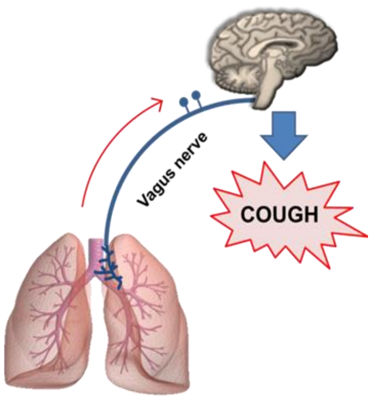
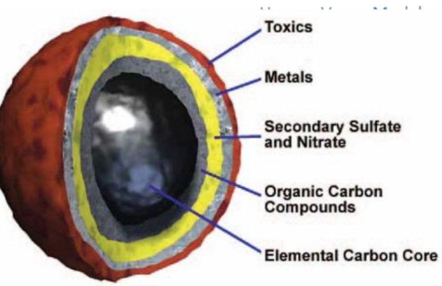
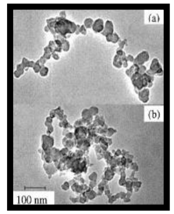
Diesel exhaust particles (DEP) activate guinea pig and human airway sensory nerves- involvement in cough?

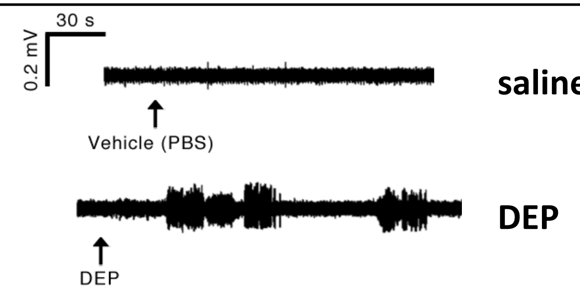


SPECIALIST PRE-CLINICAL MODELS

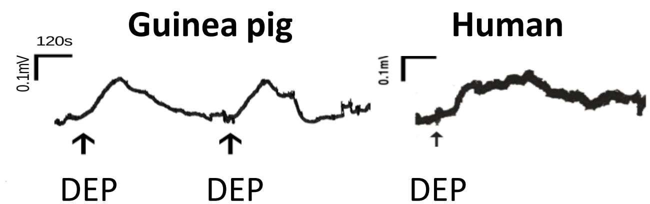




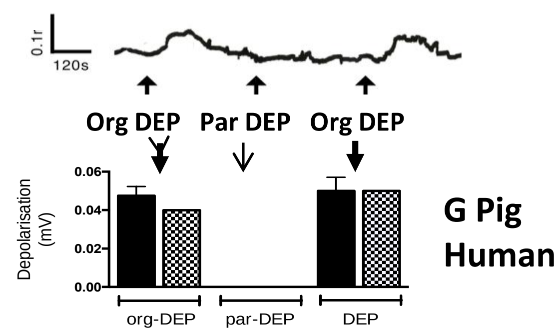
Introduction of DEP into the airways caused airway nerve activation in a guinea pig model



DEP caused activation of isolated guinea pig and human vagus nerve



The organic soluble component, not the carbon core, caused guinea pig and human afferent vagal nerve activation



Mechanistic link between diesel exhaust particles and respiratory reflexes. Robinson et al. J Allergy Clin Immunol. 2018; 141(3): 1074–1084

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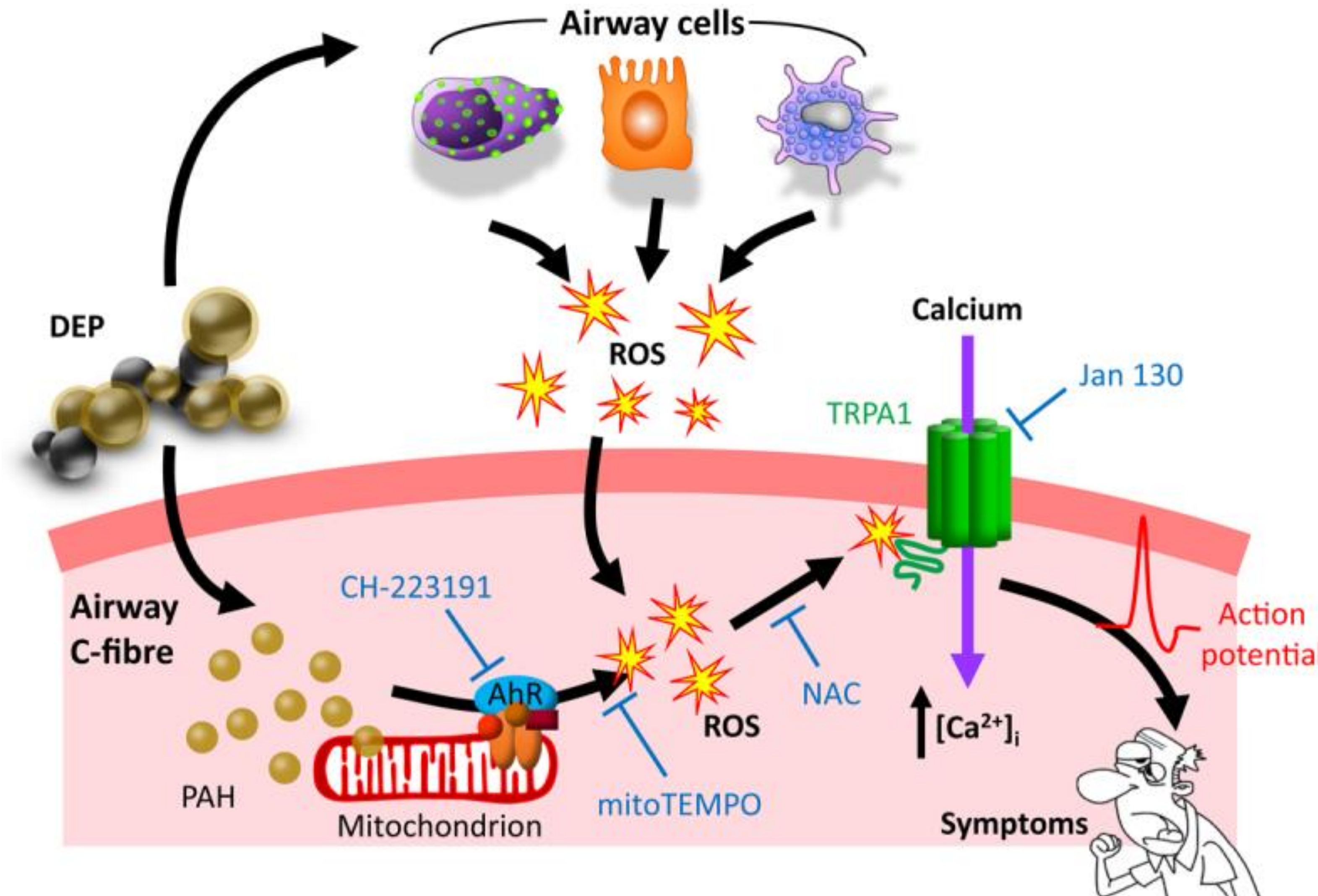
Mechanistic link between diesel exhaust particles and respiratory reflexes.

Robinson et al. J Allergy Clin Immunol. 2018; 141(3): 1074–1084



DEP: Diesel exhaust particles; TRPA1: transient receptor potential Ankyrin-1;
PAH's: Polycyclic aromatic hydrocarbons; ROS: Reactive oxygen species.

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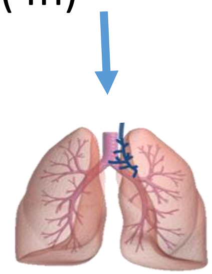
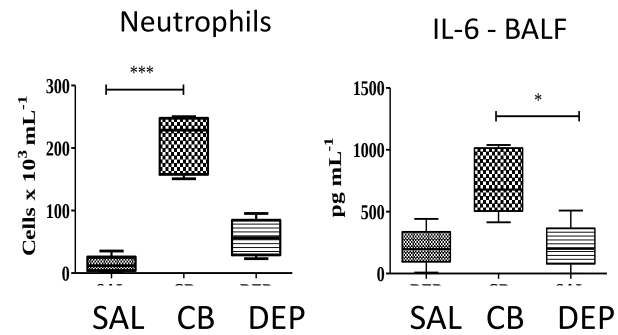
Effect of intratracheal instillation of DEP and carbon black (CB) on lung inflammation and pulmonary vascular platelet activation (thrombosis) in mice (4h).

Introduce 25 µg DEP or carbon black into lung (4h)

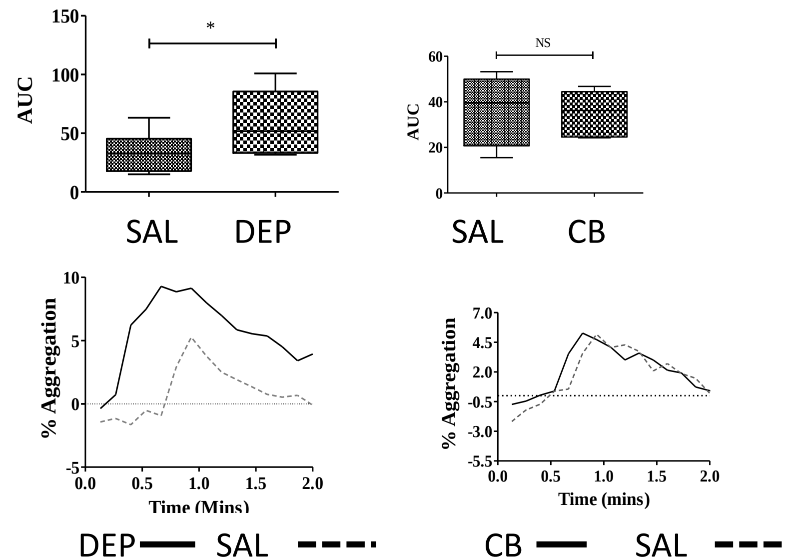


Track and localise labelled platelets

Intratracheal instillation of **CB**, but not DEP, causes marked **pulmonary inflammation in mice**



Intratracheal instillation of **DEP,** not CB, causes significantly **greater vascular pulmonary platelet aggregation in mice** in vivo that is slow to resolve



Influence of inflammation and nitric oxide upon platelet aggregation following deposition of diesel exhaust particles in the airways.
Smyth et al. Br J Pharmacol. 2017 Jul;174(13):2130-2139

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How does addition of Envirox/nanoceria to diesel fuel affect the DEP-induced inflammatory response within the respiratory unit?

- Fan Chung and Terry Tetley ICL
- Jim Zhang Duke University

NATURAL ENVIRONMENT RESEARCH COUNCIL
This research is funded by Grant # NE/H012893

This research is funded by U.S. EPA - Science To Achieve Results (STAR) Program Grant # 83469302

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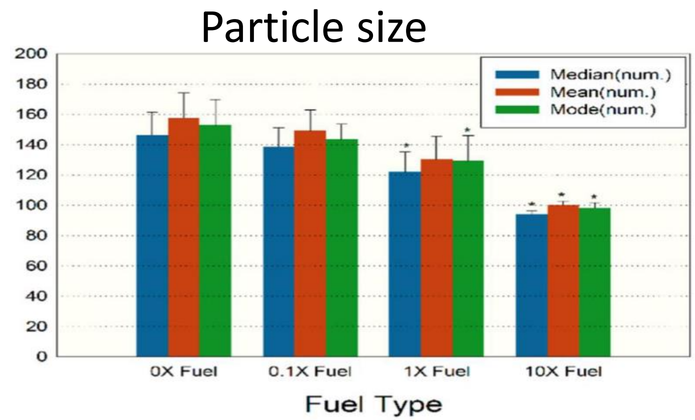
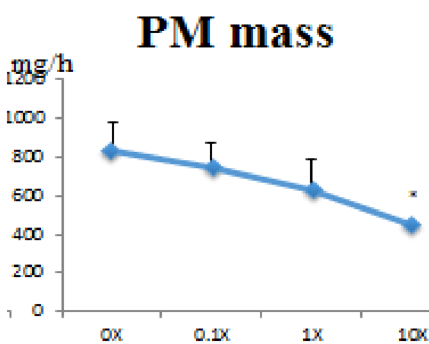
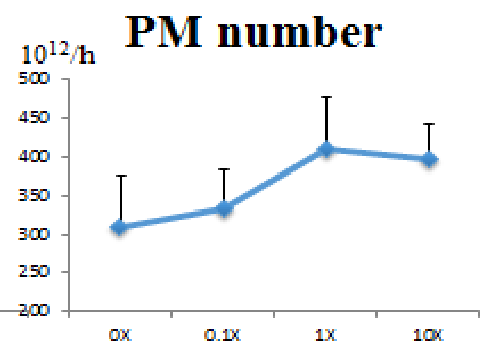
Generated DEP: single-cylinder, four-cycle diesel engine following addition of Envirox (catalyst cuts fuel use/costs) to the fuel at 0.1x, 1.0x, 10x recommended levels [1x = 0.5ml/9µg Envirox/L fuel]







Zhang…Mainelis et al. Environ Sci Technol 2013, 47:13077

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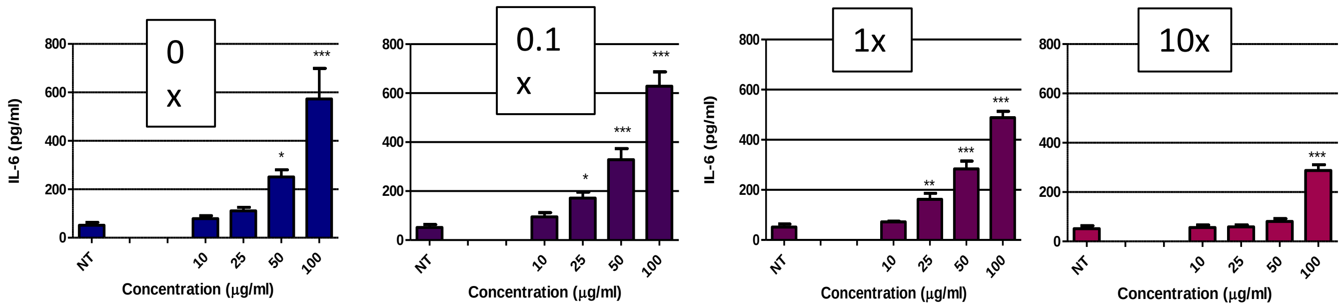
Percentage contribution of carbon, cerium, nitrogen and other components to DEP +/- Envirox

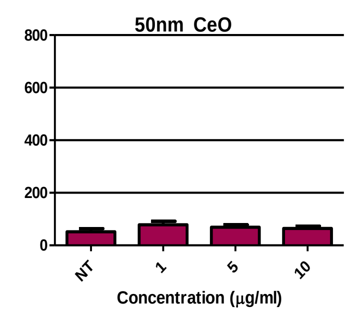
Fuel	Carbon	Hydrogen	Cerium	Nitrogen	Other
0X	91.84	2.23	0.3	0.23	5.4
0.1X	91.81	2.12	0.48	0.25	5.34
1X	89.63	2.12	0.73	0.35	7.17
10X	79.4	2.43	6.52	0.61	11.04

IL-6 mediator release from human lung respiratory epithelial cells following 24 hour exposure to DEP/Envirox



- DEP induces elevated release of an important pro-inflammatory mediator, IL-6
- DEP generated after addition of Envirox/ceria subdues the DEP-induced increase in IL6 release

Prenatal and early life diesel exhaust exposure disrupts (brain) cortical lamina organization: Evidence for a reelin-regulated pathogenic pathway induced by interleukin-6



Related to AUTISM SPECTRUM DISORDERS (ASD)

Chang YC et al. Brain Behav Immun. 2019 May;78:105-115

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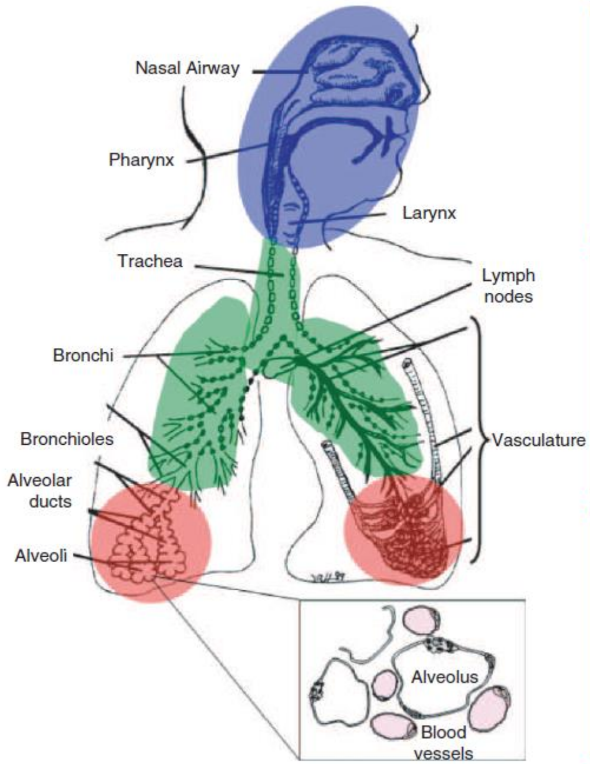
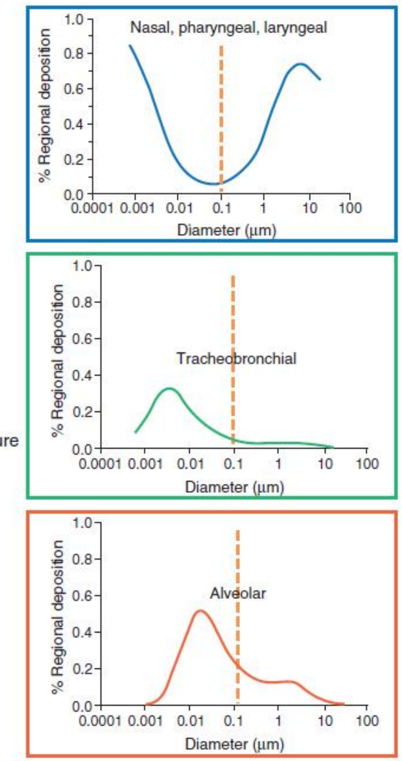
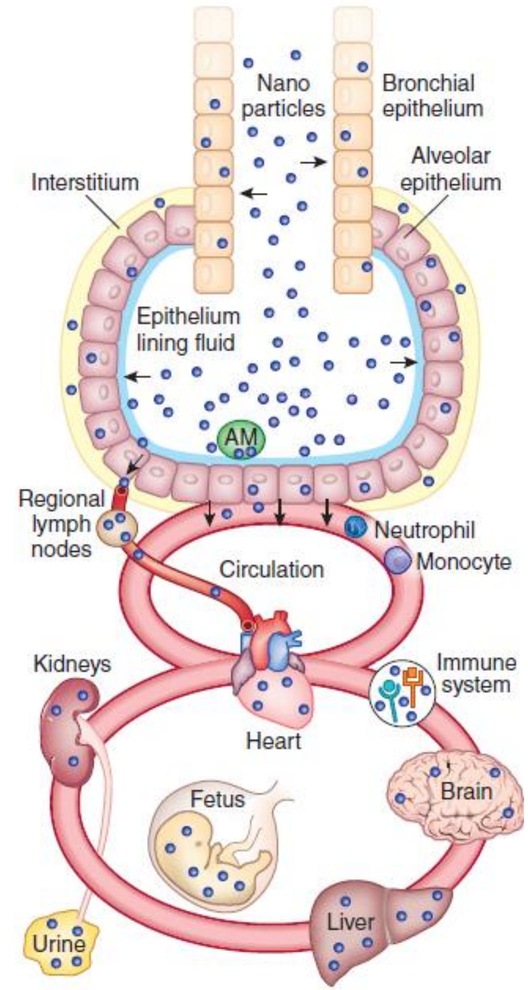
Deposition and impact of inhaled $PM_{2.5}$ and $PM_{0.01}$







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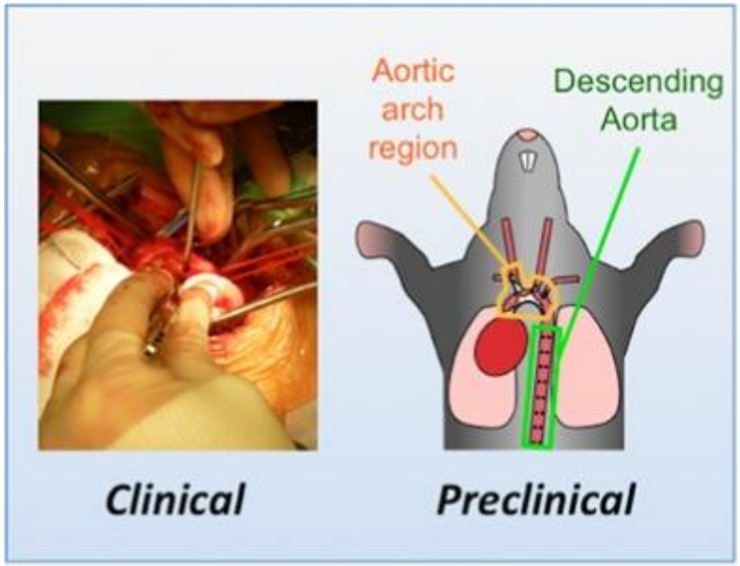
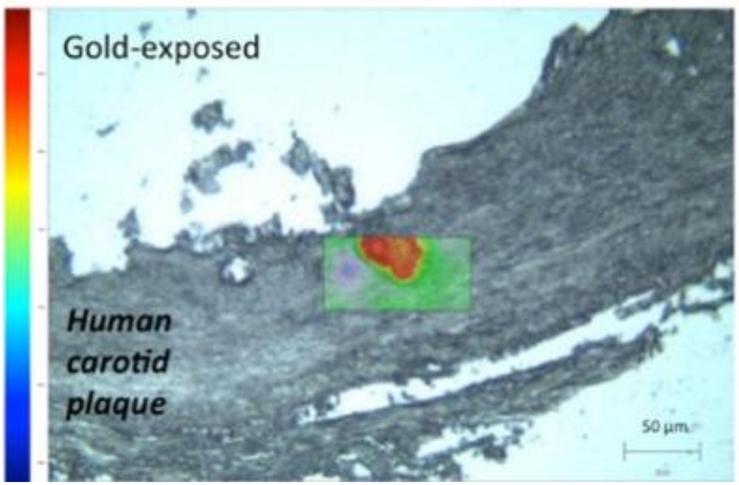
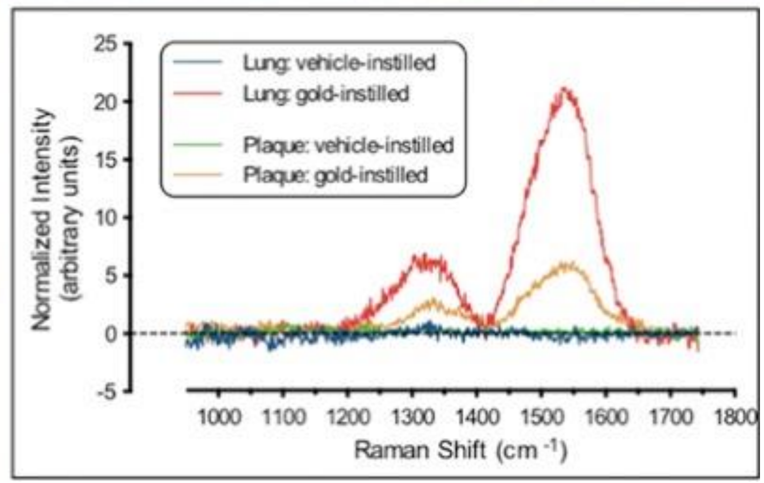


Inhaled Nanoparticles Accumulate at Sites of Vascular Disease.

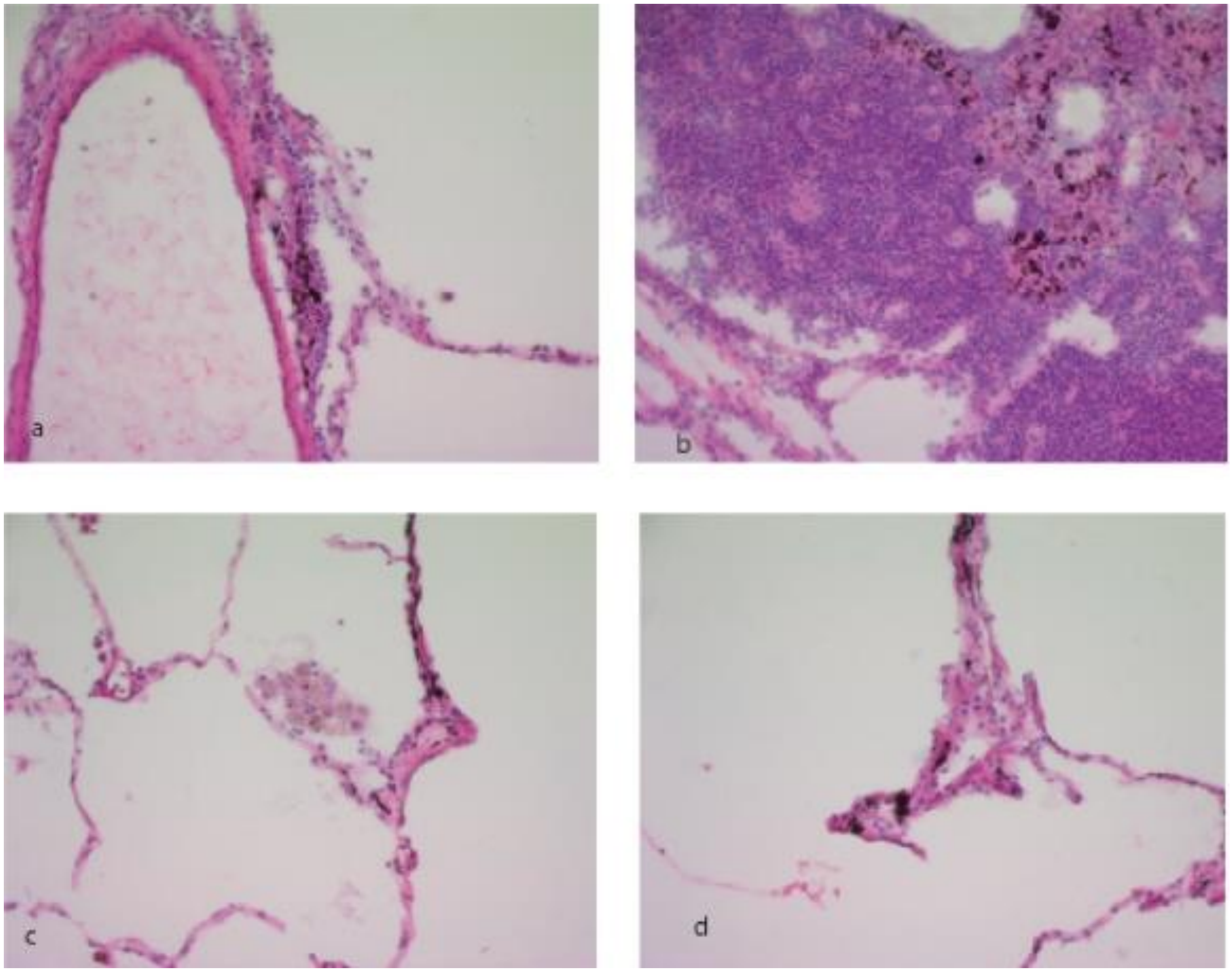
Miller et al. ACS Nano. 2017 May 23; 11(5): 4542–4552





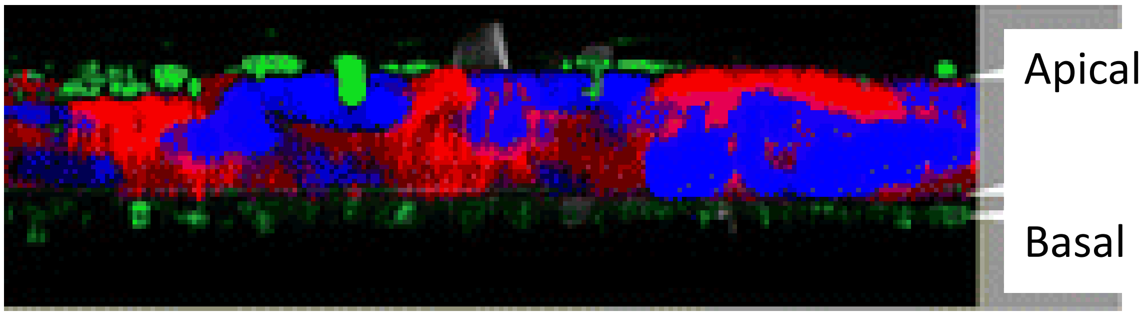
- 0.02% of inhaled nanogold (~20nm diameter) excreted in urine by healthy individuals after 2h exposure during exercise.
- Nanogold in human and mouse atherosclerotic plaques after 4h exposure.

Particles reach the interstitial tissues of the lung and can remain there



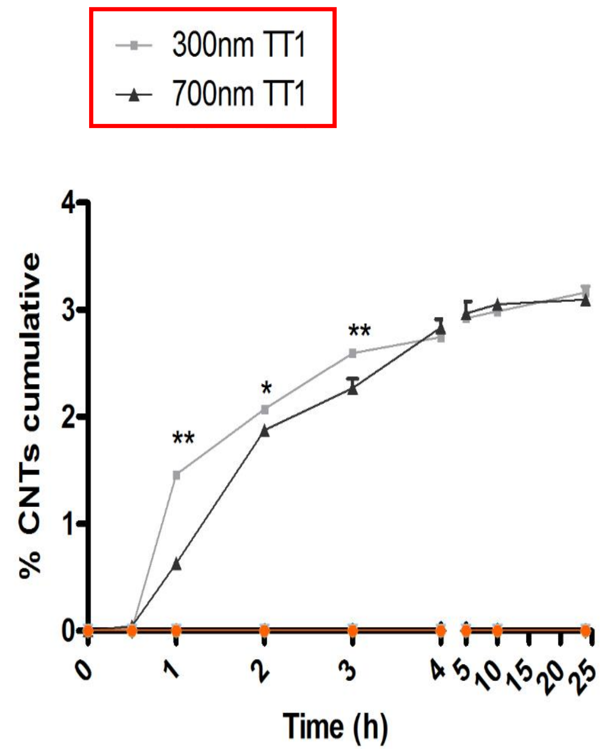
Uptake and translocation of MWCNTs by human alveolar epithelium

Alveolar epithelial type 1 cells exposed to MWCNTs



70-80% of 300nm CNTs (green) intracellular

2-3% translocate to the basolateral compartment



Rueuraroengsak, Porter, Tetley
unpublished

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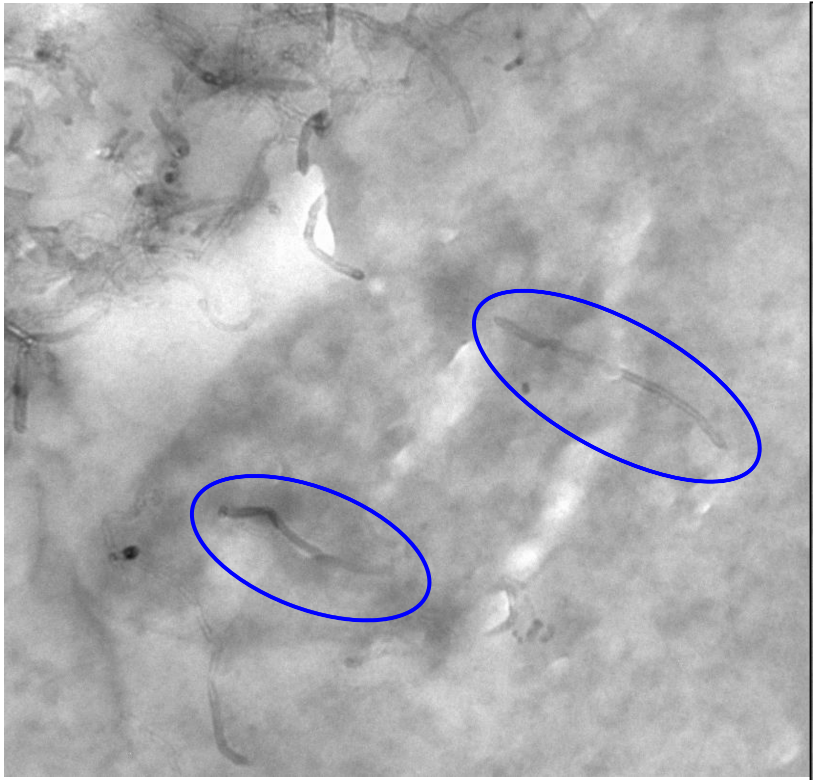
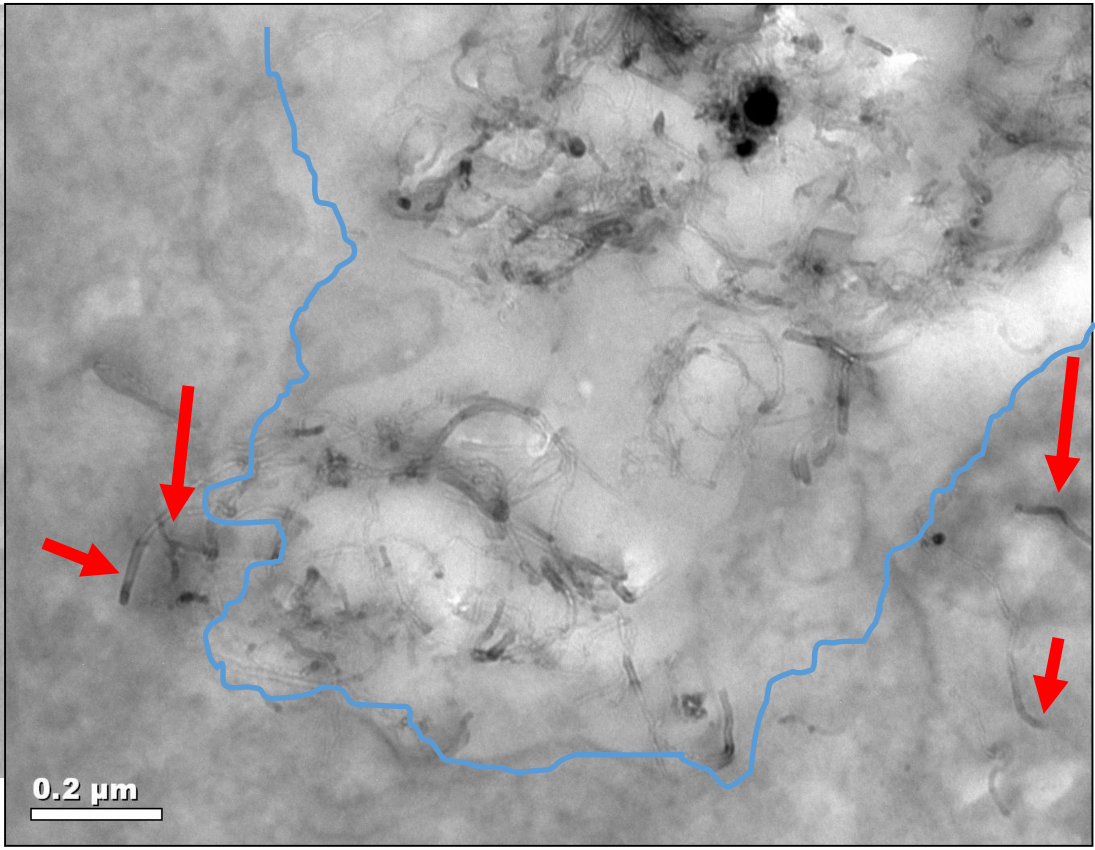
Uptake of MWCNTs by human respiratory alveolar epithelial cells

700nm 4VP CNTs, T=24h





Ruenraroengsak, Porter, Tetley
unpublished

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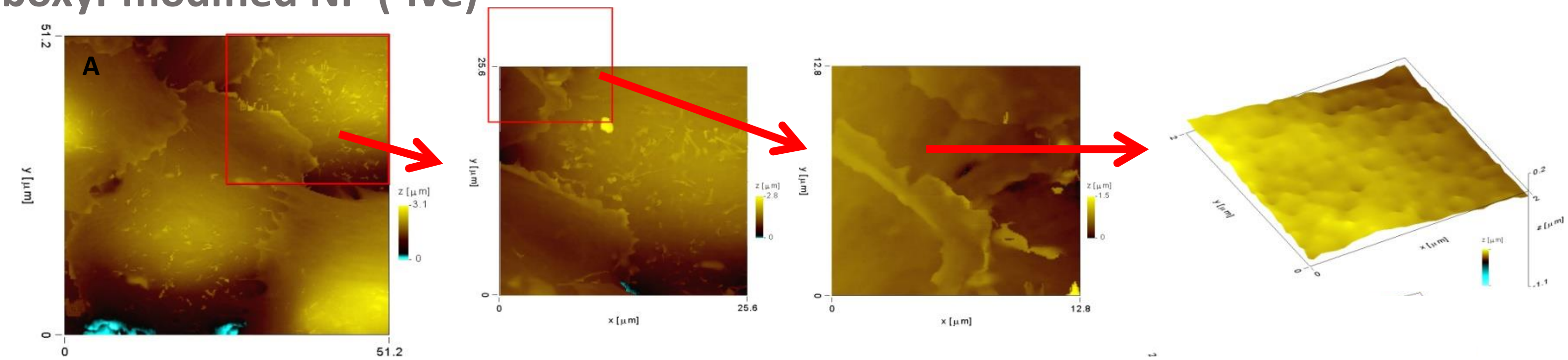
Hopping probe ion conductance microscopy of human respiratory alveolar epithelial cells exposed to carboxyl-modified and amine-modified particles for 4 hours.

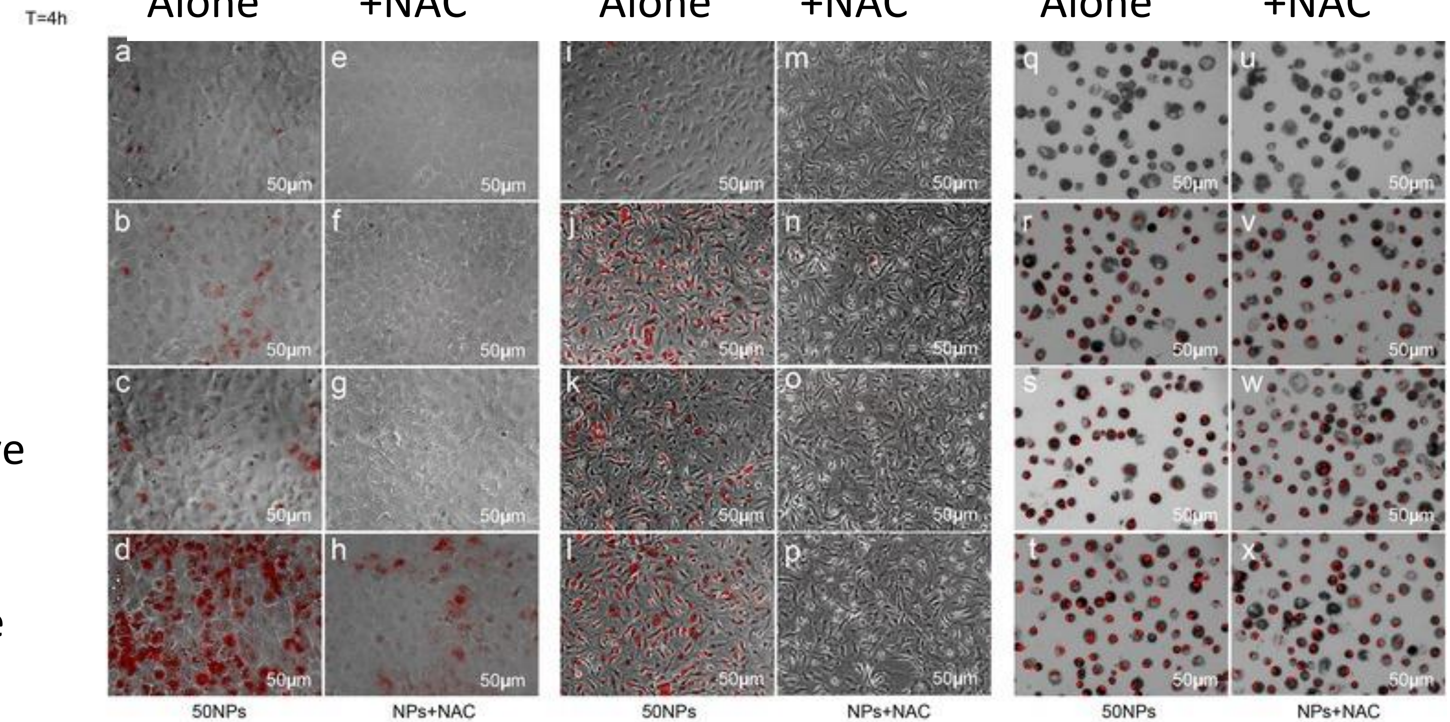
Carboxyl-modified NP (-ive)



Ruenraroengsak et al. Respiratory epithelial cell cytotoxicity and membrane damage (holes) caused by amine-modified nanoparticles, Nanotoxicology 2012, 6:94-108

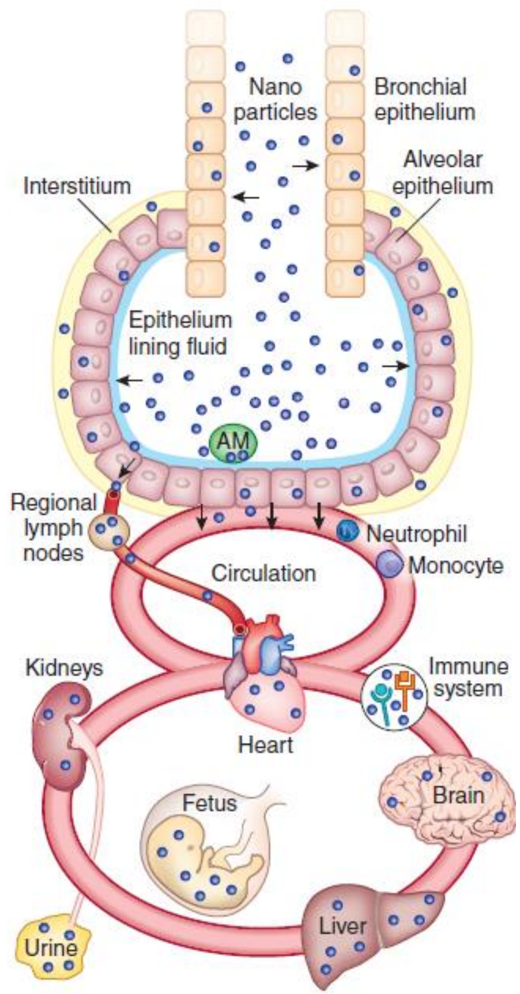
Nanoparticle-induced reactive oxygen species (ROS), importance of surface charge and protection by antioxidant treatment.

	Epithelium type 1 Alone	Epithelium type 1 +NAC	Epithelium type 2 Alone	Epithelium type 2 +NAC	Alveolar macrophages Alone	Alveolar macrophages +NAC
Control						
Neutral						
Negative						
Positive						



Rueuraroengsak & Tetley
PFT 2015

Systemic impact of inhaled $PM_{2.5}$ and $PM_{0.1}$



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Association between $PM_{2.5}$ and constituents of $PM_{2.5}$ and preterm delivery in California 2000-2006.

Basu et al. Paed. Perinatal Epidemiology, 2017; 31:424-434

231,637 births; 23,265 preterm births

50% PTB were 25-34 years old

PM2.5 data from 7 monitor sites, collected every 3rd or 6th day

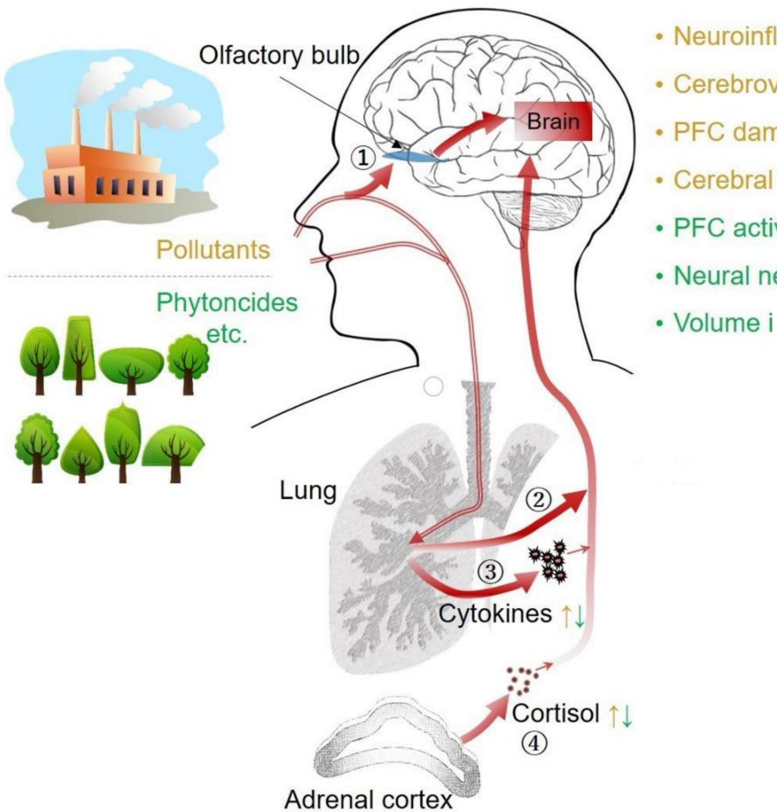
Related to:
Traffic and biomass combustion

Long term exposure

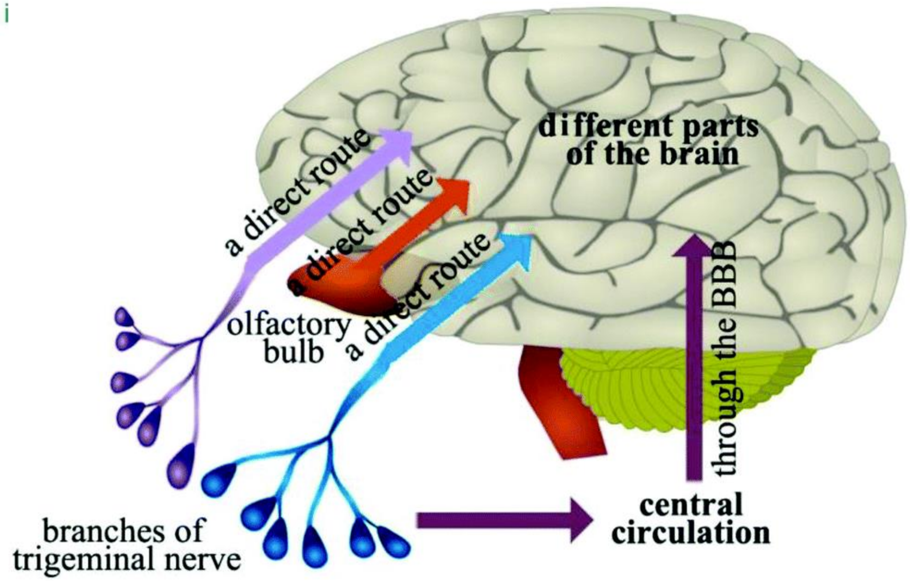
Hispanic and Asian background

Constituent	overall % change
Total PM2.5	+16.4 (13.5-19.5
NH_4^+	+21.2 (17.1-25.4)
NO_3^-	+18.1 (14.9-21.4)
Br	+16.7 (13.2-20.3)
Elem. Carbon	+10.9 (6.3-15.6)
Zn	+14.4 (10.3-18.6)
Cl	-8.2 (-10.3 - -6.0)
Na	-13.2 (-15.2 - -11.3)
Na^+	-11.9 (-14.1 - -9.6)
V	-19.2 (-25.3 - -12.6)

Particulate pollution can reach/affect the brain



Pre frontal cortex



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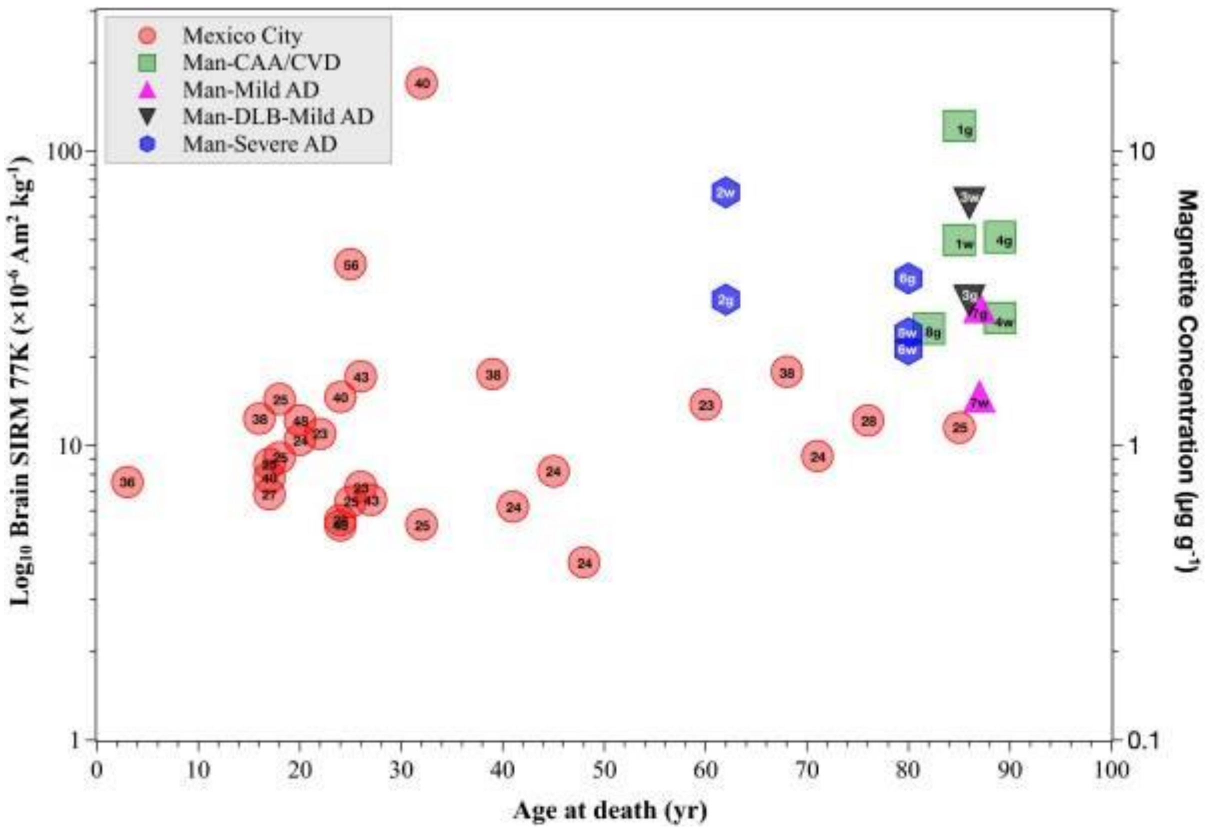
Magnetite pollution particles in the human brain

Maher BA et al Proc Natl Acad Sci U S A. 2016 Sep 27;113(39):10797-801



Magnetite concentration (micrograms per gram) for frontal cortex samples versus age at death, Mexico City and Manchester cases. The annual mean airborne PM2.5 concentration (micrograms per cubic meter) is given for the residence area of the Mexican cases (inside each data symbol); SIRM values for gray (g) and white (w) matter are given for the Manchester cases, together with their clinical diagnosis upon death (CAA, cerebral amyloid angiopathy; CVD, cerebrovascular disease; DLB, dementia with Lewy bodies)

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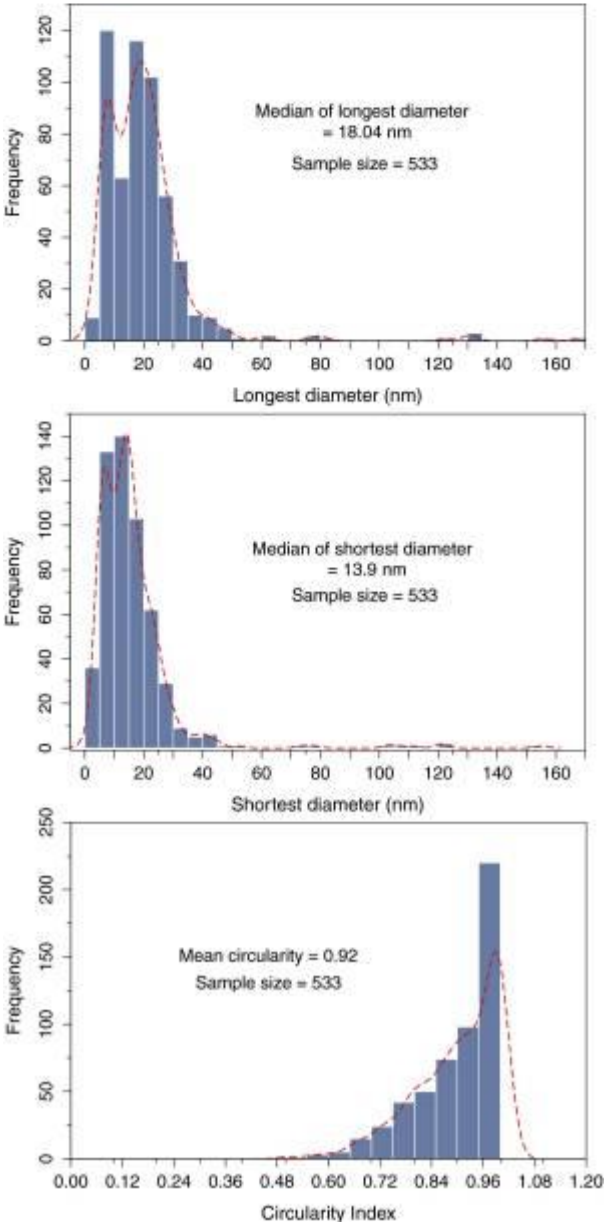
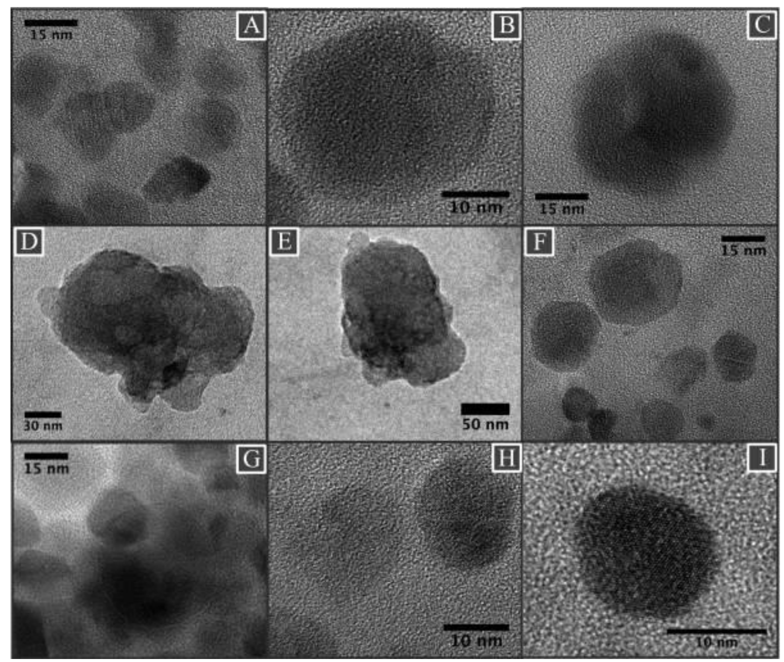


Characteristics of magnetite isolated from brain tissues was that generated at high temperatures as in exhaust emissions



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Effect of particulate air pollution on mental health

- Exposure in utero and during childhood is associated with delayed mental development, poorer cognitive abilities, and lower academic achievement

- Exposure in the elderly is associated with faster cognitive decline

- Short term acute exposure to PM_{10} and $PM_{2.5}$ is associated with increased suicide

- Increased PM 2.5 aggravates neuropsychiatric symptoms and related to impaired cognition/understanding

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Alzeimer’s disease and alpha synuclein pathology in the olfactory bulbs of infants, teens and adults up to 40 years in Metropolitan Mexico City. APOE4 carriers at higher risk of suicide accelerate their olfactory bulb pathology.

Calderón-Garcidueñas L et al. Environ Res. 2018 Oct;166:348-362

- Brain tissue from 11 months to 40 years of age; 179 subjects
- Olfactory bulb tissues analysed for proteins and markers of Alzeimer’s and Parkinson’s disease which were elevated in those exposed to chronic, high levels of PM, which were markedly different even in the second decade
- Those with APOE4 gene (susceptibility) exhibited far greater changes than those with APOE3 gene
- Those with APOE4 gene 5 times more likely to commit suicide

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SUMMARY

- There are significant systemic health effects of ambient air pollution particles
- Size, chemistry and shape matters
- Susceptibility eg age, defence mechanisms, genetics, existing disease all play a part
- Mechanisms involved remain unclear

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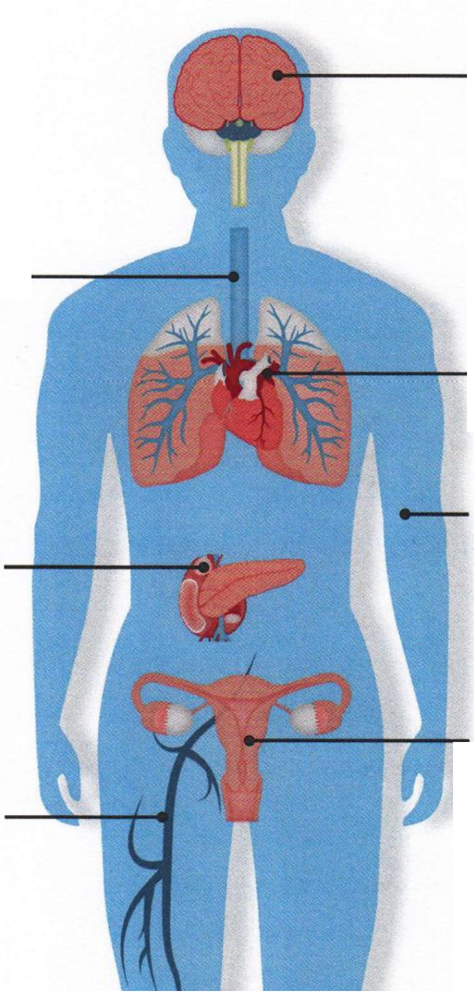
Health effects of air pollution

Strokes
Neurological development
Mental health
Neurodegenerative disorders

Respiratory disease – COPD, asthma, infection, lung cancer

Reduced lung growth
Reduced lung function

Cardiovascular disease – myocardial infarction, cardiac arythmia, cardiac failure



Type 2 diabetes
Type 1 diabetes
Liver toxicity
Renal disease
Altered bone metabolism

Accelerated aging
Autoimmune rheumatic disease

High blood pressure
Endothelial dysfunction
Increased blood clotting
Systemic inflammation
Thrombosis
Atherosclerosis

Premature birth
Low birth weight
Reduced/delayed foetal growth
Lower sperm quality, infertility
Preeclampsia

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THANK YOU

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Triggering Mechanisms and Inflammatory Effects of Combustion Exhaust **Particles** with Implication for Carcinogenesis.
Øvrevik J, Refsnes M, Låg M, Brinchmann BC, Schwarze PE, Holme JA.
Basic Clin Pharmacol Toxicol. 2017 Sep;121 Suppl 3:55-62

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Habre R, Zhou H, Eckel SP, Enebish T, Fruin S, Bastain T, Rappaport E, Gilliland F.
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Basu R, Pearson D, Ebisu K, Malig B.
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Xue T, Zhu T. Environ Int. 2018 Dec;121(Pt 1):955-962

Association between **fertility** rate reduction and pre-gestational exposure to ambient fine **particles**in the United States, 2003-2011.
Xue T, Zhu T. Environ Int. 2018 Dec;121(Pt 1):955-962

Ambient fine particulate **pollution** associated with **diabetes mellitus** among the elderly aged 50 years and older in China.
Yang Y, Guo Y, Qian ZM, Ruan Z, Zheng Y, Woodward A, Ai S, Howard SW, Vaughn MG, Ma W, Wu F, Lin H. Environ Pollut. 2018;243(Pt B):815-823

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Alzheimer's **disease** and alpha-synuclein pathology in the olfactory bulbs of infants, children, teens and adults ≤ 40 years in Metropolitan Mexico City. APOE4 carriers at higher risk of suicide accelerate their olfactory bulb pathology.
Calderón-Garcidueñas L, González-Maciel A, Reynoso-Robles R, Kulesza RJ, Mukherjee PS, Torres-Jardón R, Rönkkö T, Doty RL.
Environ Res. 2018 Oct;166:348-362

Exposure to ambient fine **particles** and neuropsychiatric symptoms in cognitive disorder: A repeated measure analysis from the CREDOS (Clinical Research Center for Dementia of South Korea) study.
Lee H, Kang JM, Myung W, Choi J, Lee C, Na DL, Kim SY, Lee JH, Han SH, Choi SH, Kim SY, Cho SJ, Yeon BK, Kim DK, Lewis M, Lee EM, Kim CT, Kim H.
Sci Total Environ. 2019 Jun 10;668:411-418

Clifford, A.; Lang, L.; Chen, R.; Anstey, K.J.; Seaton, A. Exposure to air pollution and cognitive functioning across the life course—A systematic literature review. *Environ. Res.* **2016**, *147*, 383–398

> For instance, as concluded by a recent systematic review [17], exposure during childhood is associated with delayed mental development, poorer cognitive abilities, and lower academic achievement, while exposure in the elderly is associated with faster cognitive decline.

Brain: *Stroke*, *Dementia*, *Parkinson's Disease*

Eye: *Conjunctivitis, Dry Eye Disease, Blepharitis, Cataracts*

Heart: *Ischemic Heart Disease*, *Hypertension*, *Congestive Heart Failure*, *Arrhythmias*

Lung: *Chronic Obstructive Pulmonary Disease Asthma*, *Lung Cancer*, *Chronic Laryngitis*, *Acute and Chronic Bronchitis*

Liver: *Hepatic Steatosis*, *Hepatocellular carcinoma*

Blood: *Leukemia*, *Intravascular Coagulation*, *Anemia*, *Sickle Cell Pain Crises*

Fat: *Metabolic Syndrome*, *Obesity*

Pancreas: *Type I and II Diabetes*

Gastrointestinal: *Gastric Cancer*, *Colorectal Cancer*, *Inflammatory Bowel Disease*, *Crohn's Disease*, *Appendicitis*

Urogenital: *Bladder Cancer*, *Kidney Cancer*, *Prostate Hyperplasia*

Joints: *Rheumatic Diseases*

Bone: *Osteoporosis*, *Fractures*

Nose: *Allergic Rhinitis*

Skin: *Atopic Skin Disease*, *Skin Aging*, *Urticaria*, *Dermographism*, *Seborrhea*, *Acne*

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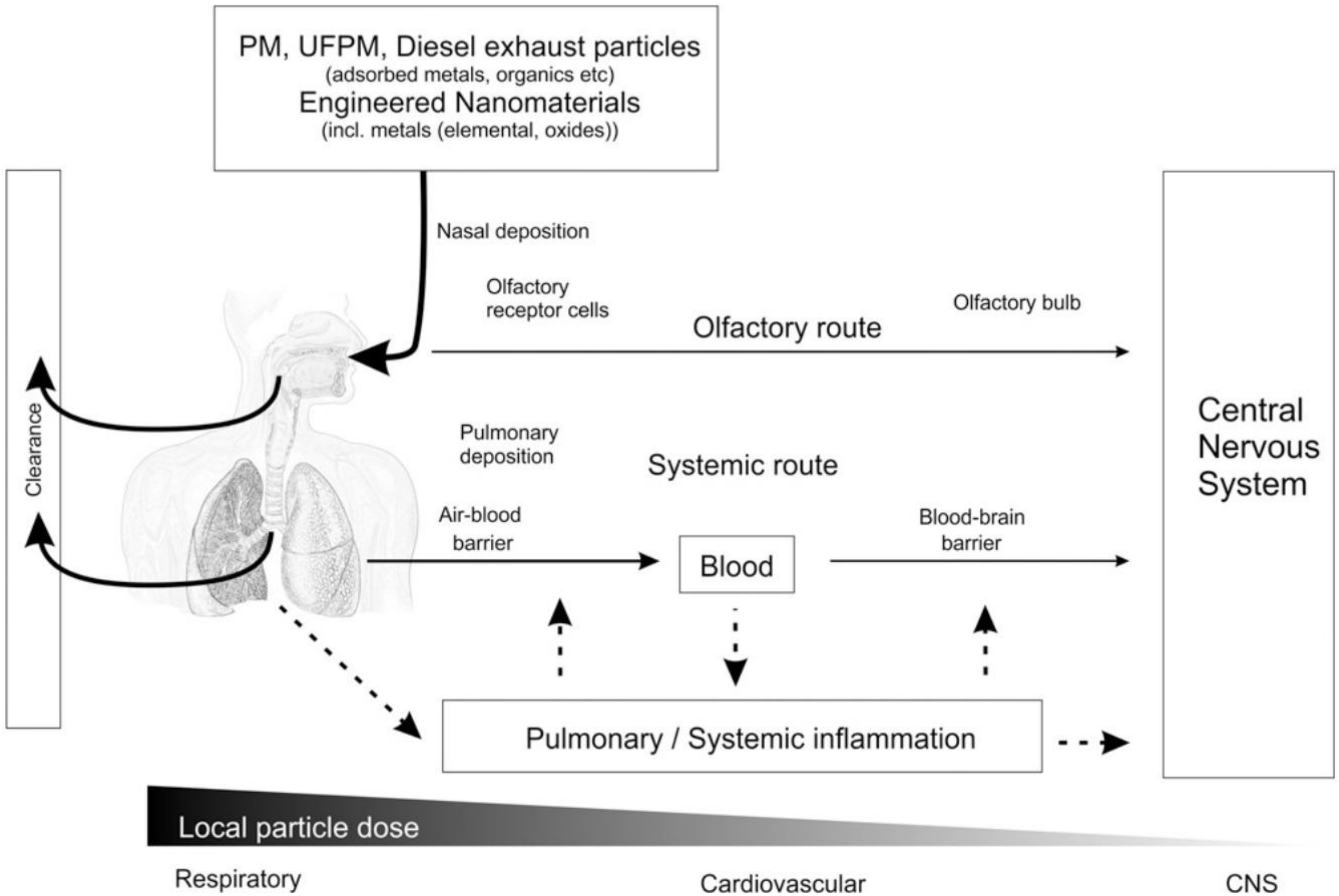

PM, UFPM, Diesel exhaust particles
(adsorbed metals, organics etc)
Engineered Nanomaterials
(incl. metals (elemental, oxides))
Nasal deposition
Olfactory receptor cells
Olfactory route
Olfactory bulb
Clearance
Pulmonary deposition
Systemic route
Air-blood barrier
Blood
Blood-brain barrier
Central Nervous System
Pulmonary / Systemic inflammation
Local particle dose
Respiratory
Cardiovascular
CNS