KATHOLIEKE UNIVERSITEIT LEUVEN

Health effects of (particulate) air pollution

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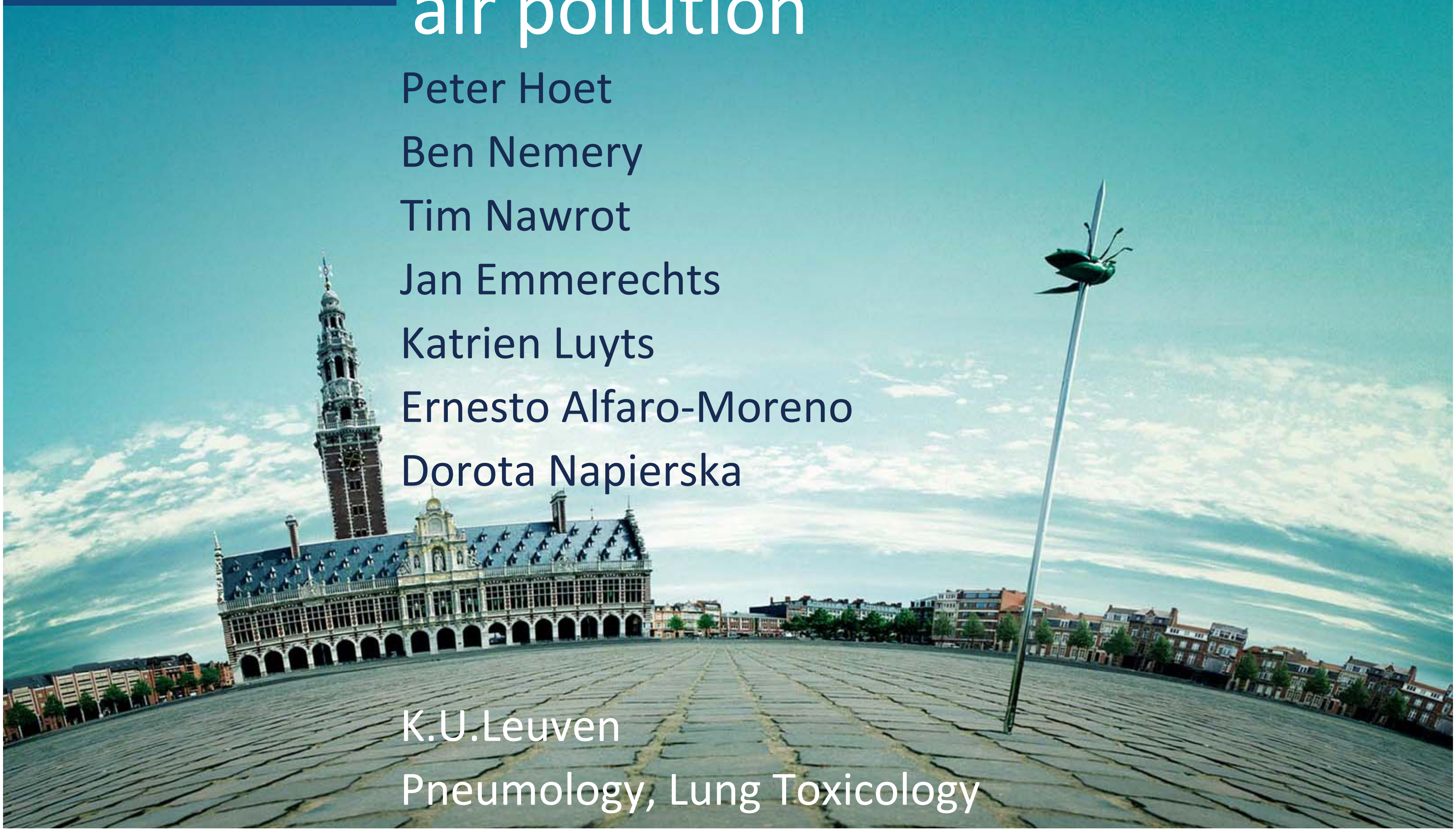
Pneumology, Lung Toxicology



Air pollution and Health

- Introduction
  - General observations
- General mechanisms involved
- Overview of a few key studies
  - Near Road…
  - Cardiovascular
  - Lung Cancer
- Final remarks

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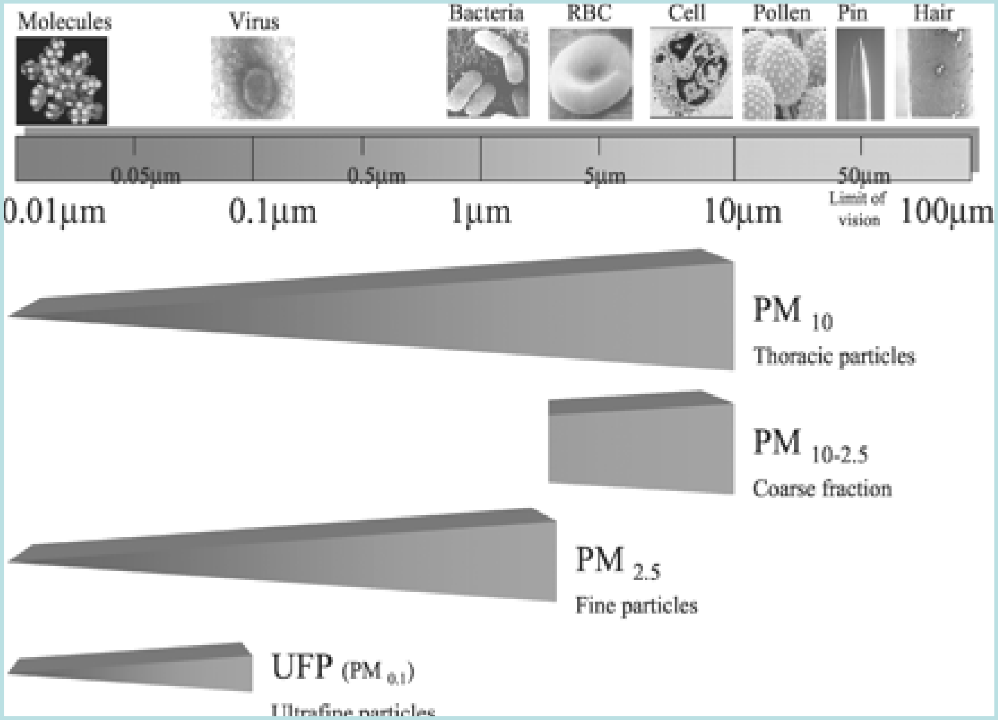
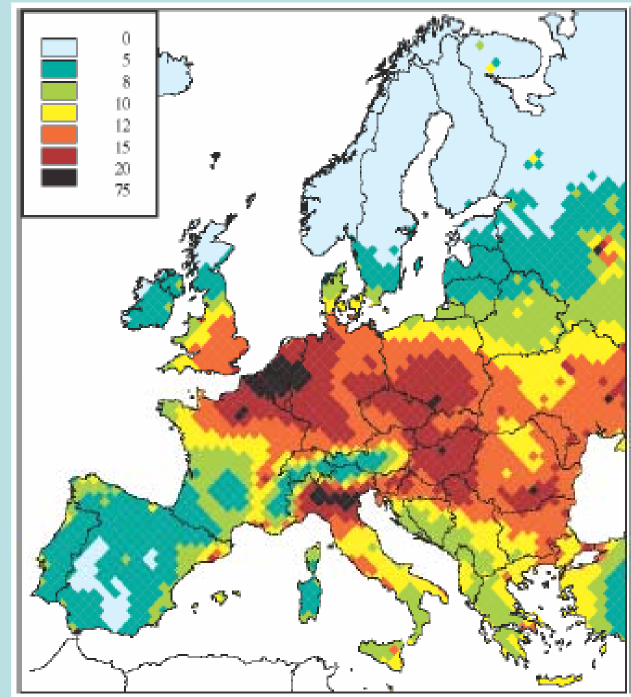
Introduction

Current situation





Annual average $PM_{2,5}$ (µg/m^3)

Air pollution → Volatile matter (NO_x, SO_2, CO, O_3)

Air pollution → Particulate matter (PM)

Introduction

Short-term PM exposure and mortality risk

Risk estimates provided by several short term studies per increment of 10 μg/m^3 in $PM_{2.5}$ or PM_{10} (1-5days)

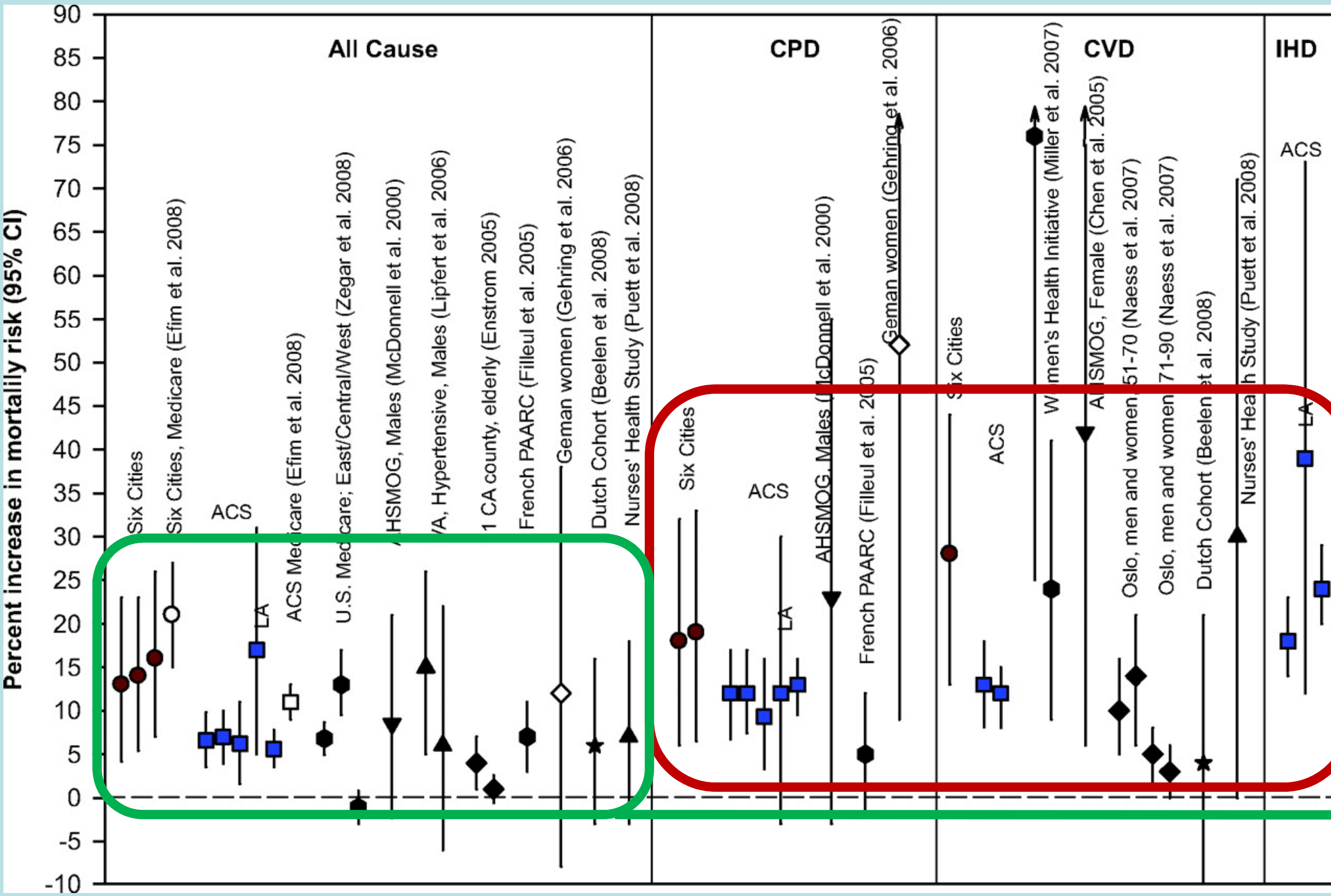
	Primary Source	Exposure Increment	Percent Increases in Mortality (95% CI)		
			All-Cause	Cardiovascular	Respiratory
Meta-estimate with and without adjustment for publication bias	Anderson et al[27] 2005	20 μg/m^3 PM_{10}	1.0 (0.8–1.2) 1.2 (1.0–1.4)	…	…
Meta-estimates from COMEAP report to the UK Department of Health on CVD and air pollution	COMEAP[31] 2006	20 μg/m^3 PM_{10} 10 μg/m^3 $PM_{2.5}$	… …	1.8 (1.4–2.4) 1.4 (0.7–2.2)	… …
NMMAPS, 20 to 100 US cities	Dominici et al[34] 2003	20 μg/m^3 PM_{10}	0.4 (0.2–0.8)	0.6 (0.3–1.0)*	…
APHEA-2, 15 to 29 European cities	Katsouyanni et al[35] 2003 Analitis et al[36] 2006	20 μg/m^3 PM_{10}	1.2 (0.8–1.4)	1.5 (0.9–2.1)	1.2 (0.4–1.9)
US, 6 cities	Klemm and Mason[37] 2003	10 μg/m^3 $PM_{2.5}$	1.2 (0.8–1.6)	1.3 (0.3–2.4)†	0.6 (−2.9, 4.2)‡
US, 27 cities, case-crossover	Franklin et al[38] 2007	10 μg/m^3 $PM_{2.5}$	1.2 (0.3–2.1)	0.9 (−.1, 2.0)	1.8 (0.2, 3.4)
California, 9 cities	Ostro et al[39] 2006	10 μg/m^3 $PM_{2.5}$	0.6 (0.2–1.0)	0.6 (0.0, 1.1)	2.2 (0.6, 3.9)
France, 9 cities	Le Tertre et al[40] 2002	20 μg/m^3 BS	1.2 (0.5–1.8)§	1.2 (0.2–2.2)§	1.1 (−1.4, 3.2)§
Japan, 13 cities, age >65 y	Omori et al[41] 2003	20 μg/m^3 SPM	1.0 (0.8–1.3)	1.1 (0.7–1.5)	1.4 (0.9–2.1)
Asia, 4 cities	Wong et al[42] 2008	10 μg/m^3 PM_{10}	0.55 (0.26–0.85)	0.59 (0.22–0.93)	0.62 (0.16–1.04)
US, 112 cities	Zanobetti et al[43] 2009	10 μg/m^3 $PM_{2.5}$	0.98 (0.75–1.22)	0.85 (0.46–1.24)	1.68 (1.04–2.33)
		10 μg/m^3 $PM_{10-2.5}$‖	0.46 (0.21–0.71)	0.32 (0.00–0.64)	1.16 (0.43–1.89)
		10 μg/m^3 $PM_{2.5}$¶	0.77 (0.43–1.12)	0.61 (0.05–1.17)	1.63 (0.69–2.59)
		10 μg/m^3 $PM_{10-2.5}$¶	0.47 (0.21–0.73)	0.29 (−0.04, 0.61)	1.14 (0.043–1.85)

(Brook et al. Circulation 2010)

0.5-1.2 % increase in daily mortality
0.4-1% increase in daily (CV) mortality
0.6-1.6 % increase in daily pulmonary mortality

Introduction

Long-term PM exposure and mortality risk



(Brook et al. Circulation 2010)

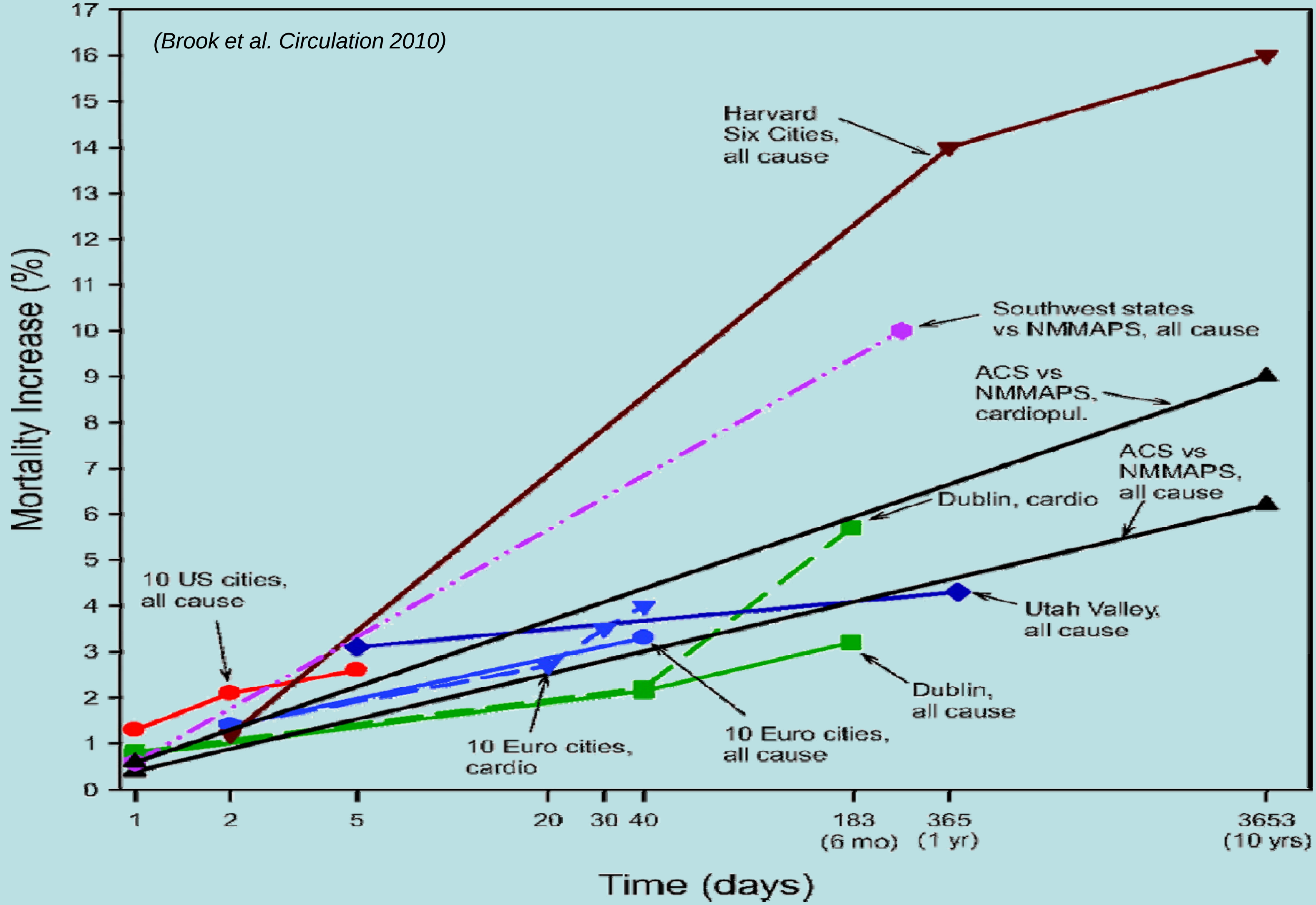
3-40% increase in Cardio-Pulmonary mortality

5-15% increase in All Causes mortality

Risk estimates provided by several long term cohort studies per increment of 10 $\mu g/m^3$ in $PM_{2.5}$ or PM_{10}

Introduction

PM exposure and mortality risk



Risk estimates per increment of 10 μg/m³ in $PM_{2.5}$ or 20 μg/m³ in PM_{10} for different time scales

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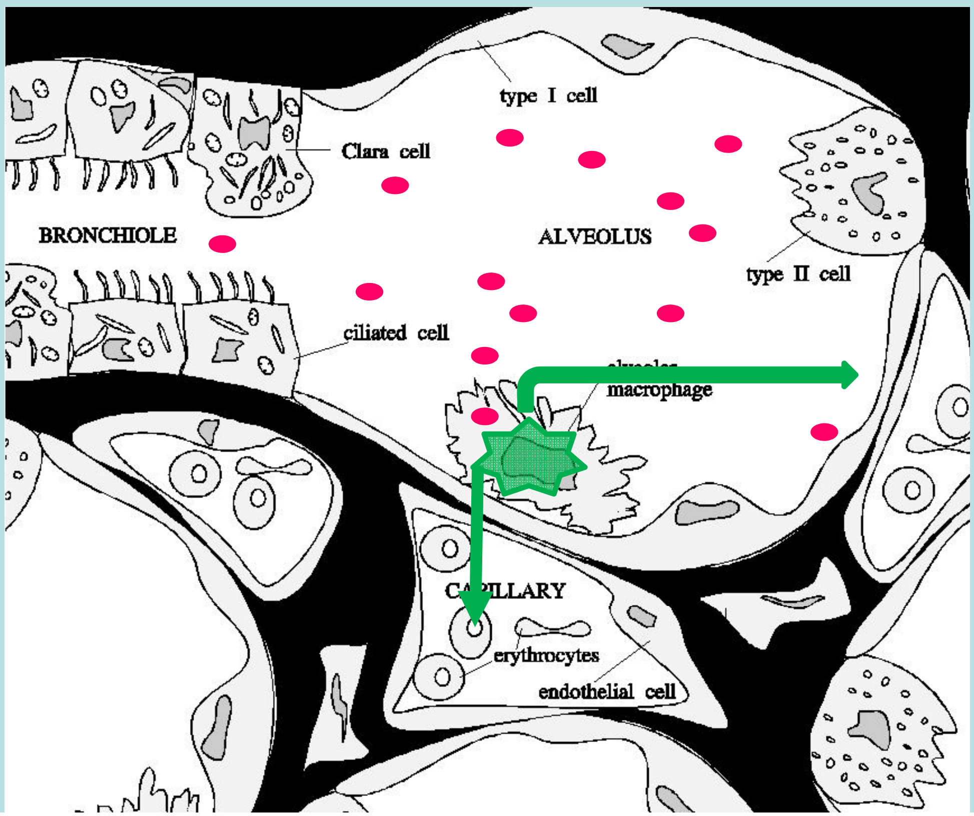
General mechanisms cardio-pulmonary response

Inhaled particles (all sizes)

↑pulmonary inflammation

↑ systemic release of mediators (systemic spill over)



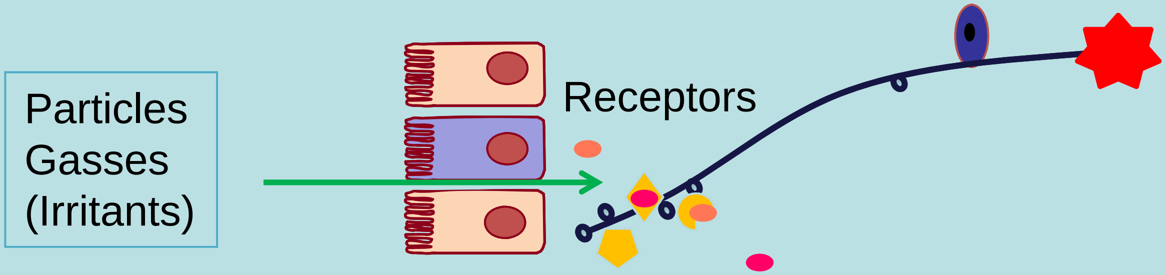
Inflammatory mediators

General mechanisms cardio-pulmonary response

Inhaled particles (all sizes)

↑pulmonary inflammation

↑ systemic release of mediators (systemic spill over)



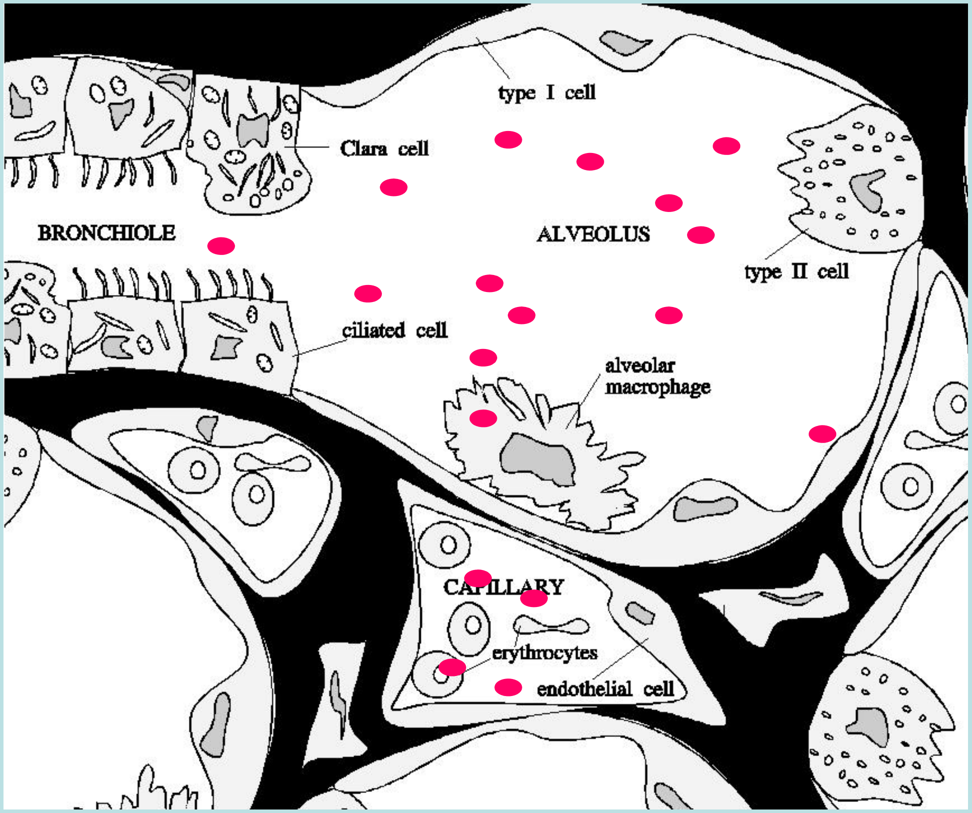
+ Stimulation of (different) irritant receptors in the lung (nerve endings – cellular)

➔ remote effects: heart rate – vascular tone – BP ….

General mechanisms cardio-pulmonary response

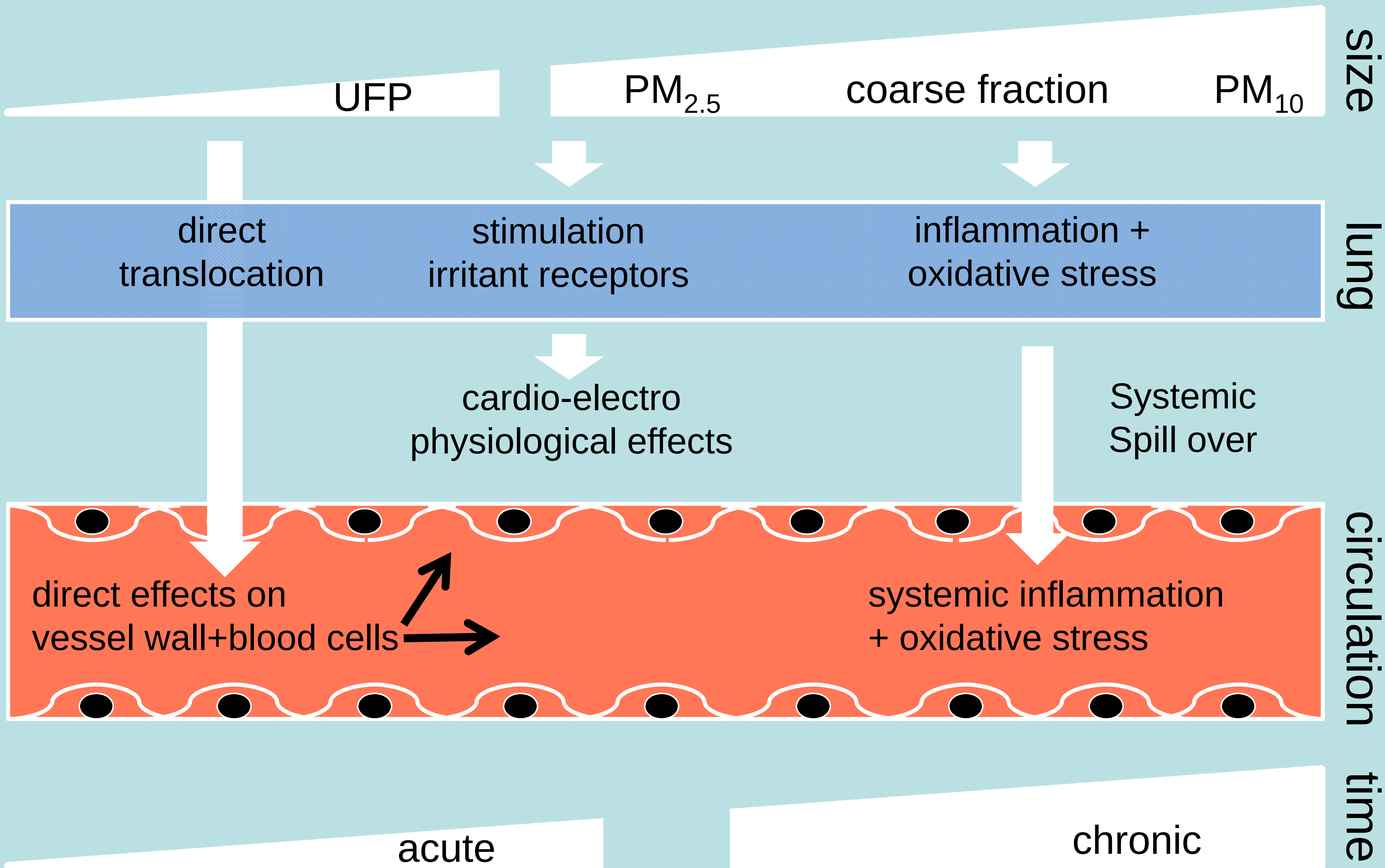
inhaled <u>ultrafine</u> particles (Ø < 0.1 µm)

- pass into the circulation
- "direct" effects on cardiovascular endpoints

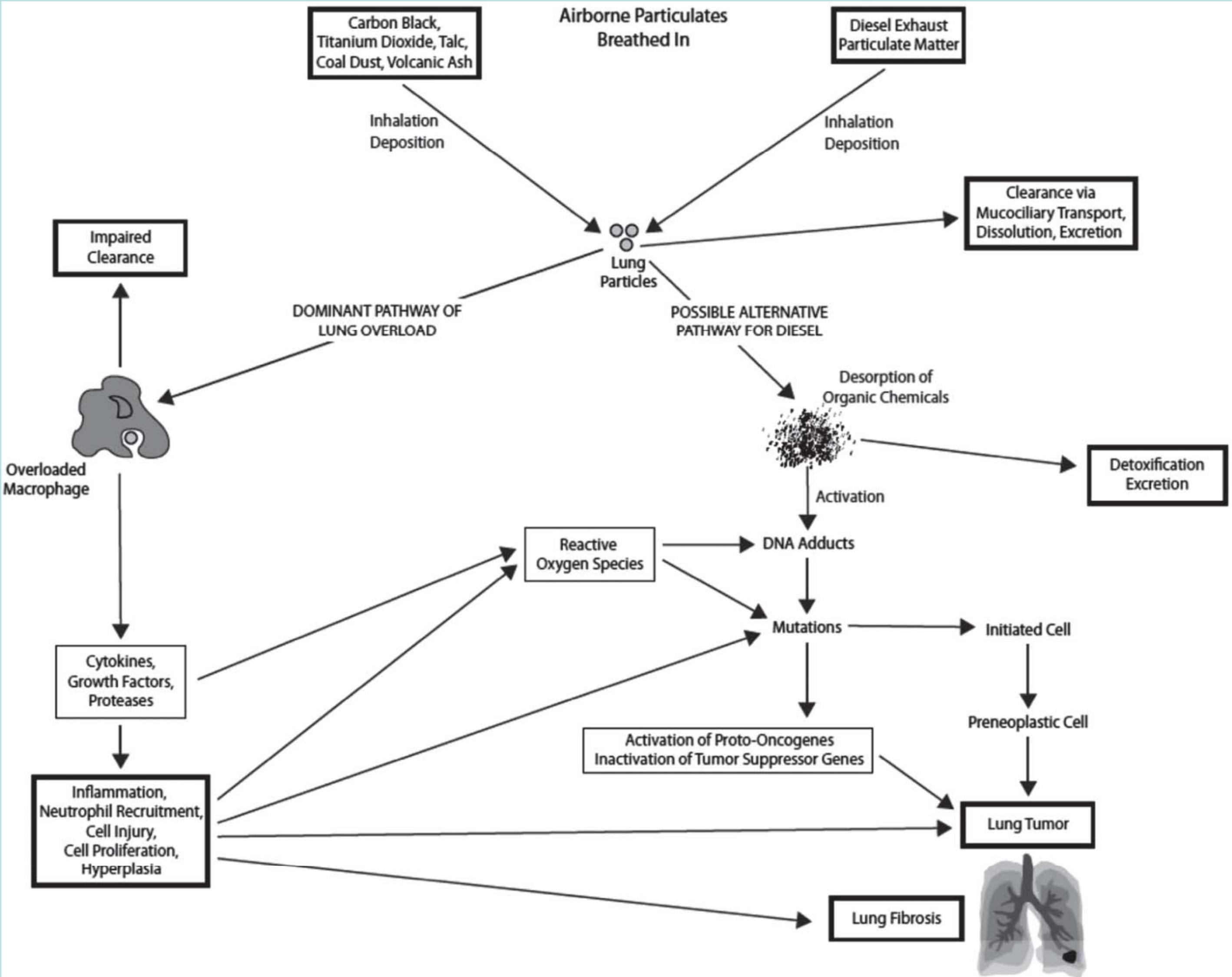


General mechanisms

Schematic overview



General mechanisms
Lung Cancer



Thomas W. Hesterberg, Inhalation Toxicology, 2012

General mechanisms
Lung Cancer

International Agency for Research on Cancer

World Health Organization

PRESS RELEASE
N° 213

12 June 2012

IARC: DIESEL ENGINE EXHAUST CARCINOGENIC

Lyon, France, June 12, 2012 -- After a week-long meeting of international experts, the International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO), today classified diesel engine exhaust as **carcinogenic to humans (Group 1)**, based on sufficient evidence that exposure is associated with an increased risk for lung cancer.

Group 1: *The agent is carcinogenic to humans.*
This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

General mechanisms
Lung Cancer

Possible toxins & carcinogens in Diesel Exhaust

- The gas phase consists of carbon monoxide, nitrogen oxides, and volatile organic compounds such as benzene and formaldehyde.
- Particles consist of elemental and organic carbon, ash, sulfate, and metals.
- Polycyclic aromatic hydrocarbons (PAH) and nitroarenes are distributed over the gas and the particle phase.

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Brugge D et al. Near-highway pollutants in motor vehicle exhaust: a review of epidemiologic evidence of cardiac and pulmonary health risks. Environ Health. 2007 Aug 9;6:23

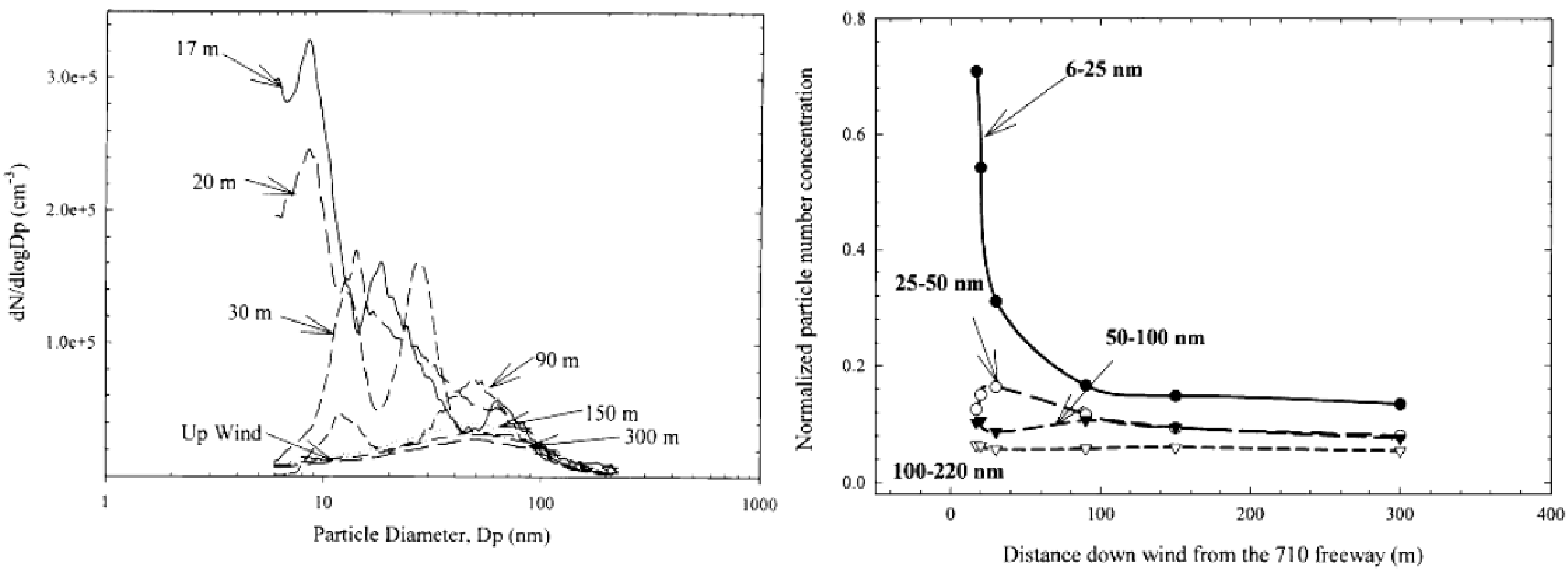


Figure 1
Ultrafine particle size distribution (top panel) and normalized particle number concentration for different size ranges (bottom panel) as a function of distance from a highway in Los Angeles. From Zhu et al. (8). Reprinted with permission from Elsevier.

Brugge D et al. Near-highway pollutants in motor vehicle exhaust: a review of epidemiologic evidence of cardiac and pulmonary health risks. Environ Health. 2007 Aug 9;6:23

Table 2: Summary of near-highway health effects studies

Citation	Location	Highway traffic intensity[a]	Pollutants measured[b]	Distance from highway	Health Outcomes	Statistical association[e]
Schwartz et al. 2005 (22)	Boston	NA	$PM_{2.5}$, BC, CO	NA	Heart rate variability	Decreases in measures of heart rate variability
Adar et al. 2007 (23)	St. Louis, Missouri	NA	$PM_{2.5}$, BC, UFP	On highway in busses	Heart rate variability	Decreases in measures of heart rate variability
Hoek et al. 2002 (24)	Netherlands	NA	BC, NO_2	Continuous [d]	Cardio-pulmonary mortality, lung cancer	1.41 OR for living near road
Tonne et al. 2007 (41)	Worchester, Mass.	NA	$PM_{2.5}$	Continuous [d]	Acute myocardial infarction (AMI)	5% increase in odds of AMI
Venn et al. 2001 (49)	Nottingham, UK	NA	NA	Continuous [d]	Wheezing in children	1.08 OR for living w/ in 150 m of road
Nicolai et al. 2003 (58)	Munich, Germany	>30,000 veh/d	Soot, benzene, NO_2	Traffic counts within 50 m of house	Asthma, respiratory symptoms, allergy	1.79 OR for asthma and high traffic volume
Gauderman et al. 2005 (65)	Southern California		NO_2	Continuous [d]	Asthma, respiratory symptoms	Increased asthma closer to freeways
McConnell et al. 2006 (57)	Southern California	NA	NA	Continuous [d]	Asthma	Large risk for children living w/in 75 m of road
Ryan, et al. 2007 (59)	Cincinnati, Ohio	> 1,000 trucks/d	PM2.5	400 m	Wheezing in children	NA
Kim et al. 2004 (60)	San Francisco	90,000 – 210,000 veh/d	PM, BC, NO_x	School sites	Childhood asthma	1.07 OR for high levels of NO_x
Wjst et al. 1993 (68)	Munich, Germany	7,000–125,000 veh/d	NO_x, CO	School sites	Asthma, bronchitis	Several statistical associations found
Brunekreef et al. 1997 (69)	Netherlands	80,000 – 152,000 veh/d	PM_{10}, NO_2	Continuous[d]	Lung function	Decreased FEV with proximity to high truck traffic
Janssen et al. 2003 (74)	Netherlands	30,000–155,000 veh/d	$PM_{2.5}$, NO_2, benzene	< 400 m [c]	Lung function, respiratory symptoms	No association with lung function
Peters et al. 1999 (82)	Southern California	NA	PM_{10}, NO_2	NA	Asthma, bronchitis, cough, wheeze	1.54 OR of wheeze for boys with exposure to NO_2
Brauer et al. 2007 (67)	Netherlands	Highways and streets	$PM_{2.5}$, NO_2, soot	Modeled exposure	Asthma, allergy, bronchitis, respiratory symptoms	Strongest association was with food allergies
Visser et al. 2004 (91)	Amsterdam	> 10,000 veh/d	NA	NA	Cancer	Multiple associations
Vineis et al. 2006 (87)	10 Eurpoean countries	NA	PM_{10}, NO_2, SO_2	NA	Cancer	1.46 OR near heavy traffic, 1.30 OR for high exposure to NO_2
Gauderman et al. 2007 (73)	Southern California	NA	PM_{10}, NO_2	Continuous[d]	Lung Function	Decreased FEV for those living near freeway

[a]As defined in article cited (veh/d = vehicles per day; veh/h = vehicles per hour).
[b]UFP = ultrafine particles; FP = fine particles; $PM_{2.5}$ = particles with aerodynamic diameter ≤ 2.5 um; PM_{10} = particles with aerodynamic diameter ≤ 10 um; BC = black carbon; PPAH = particle-bound polycyclic aromatic hydrocarbons; VOCs = volatile organic compounds
[c]Pollutant measurements were made along a transect away from the highway
[d]Proximity of each participant to a major road was calculated using GIS software
[e]Statistical association between proximity to highway or exposure to traffic-generated pollutants and measured health outcomes
NA = not applicable; measurements were not made.

Brugge D et al. Near-highway pollutants in motor vehicle exhaust: a review of epidemiologic evidence of cardiac and pulmonary health risks. Environ Health. 2007 Aug 9;6:23

Conclusions

- Growing evidence that freshly-emitted air pollutants (downwind) from major highways, motorways, and freeways include elevated levels of ultrafine particulates (UFP), black carbon (BC), oxides of nitrogen (NOx), and carbon monoxide (CO).
- People living (or spending substantial time) within about 200 m of highways are exposed … Evidence of the health hazards …
  - Development of asthma and reduced lung function in children
  - Particulate matter (PM) that show associations with cardiac and pulmonary mortality
  - Less work has tested the association between lung cancer and highways

Lindgren A *et al.* Traffic-related air pollution associated with prevalence of asthma and COPD/chronic bronchitis. A cross-sectional study in Southern Sweden
International Journal of Health Geographics 2009, 8:2 doi:10.1186/1476-072X-8-2

Associations residential traffic &

asthma - COPD in adults in S Sweden.

(n = 9319, 18–77 years)

Geographical Information System (GIS) - residential addresses to road database & emission database (NOx.)

Exposure: cars/minute within 100 m (none to >10 cars/minute)

Result: OR Asthma: 1.40 (95% CI = 1.04–1.89)

COPD 1.64 (95%CI = 1.11–2.4)

Conclusion

Living close to traffic is associated with prevalence of asthma & COPD

Lindgren A *et al.* Traffic-related air pollution associated with prevalence of asthma and COPD/chronic bronchitis. A cross-sectional study in Southern Sweden
International Journal of Health Geographics 2009, 8:2 doi:10.1186/1476-072X-8-2

Table 5: COPD diagnosis and chronic bronchitis symptoms in relation to traffic.

		COPD Diagnosis			Chronic bronchitis symptoms		
		n	n, (%)	OR [a]	n	n, (%)	OR [a]
Heavy traffic	No	6041	243(4.0%)	1.00	6041	401(6.6%)	1.00
	Yes	3275	172(5.3%)	1.36(1.10–1.67)	3275	234(7.1%)	1.11(0.94–1.31)
Heaviest road within <100 m	no heavy road	3755	153(4.1%)	1.00	3755	222(5.9%)	1.00
	<2 cars/min	2235	95(4.3%)	1.04(0.80–1.35)	2235	159(7.1%)	1.21(0.98–1.50)
	2–5 cars/min	1820	71(3.9%)	0.96(0.72–1.28)	1820	137(7.5%)	1.30(1.04–1.62)
	6–10 cars/min	886	60(6.8%)	1.57(1.15–2.14)	886	67(7.6%)	1.24(0.93–1.65)
	>10 cars/min	578	34(5.9%)	1.64(1.11–2.41)	578	48(8.3%)	1.53(1.10–2.13)
NO_x ($\mu g/m^3$)	0–8	1855	74(4.0%)	1.00	1855	110(5.9%)	1.00
	8–11	1855	68(3.7%)	0.89(0.63–1.24)	1855	118(6.4%)	1.05(0.81–1.38)
	11–14	1855	87(4.7%)	1.19(0.86–1.64)	1855	121(6.5%)	1.12(0.86–1.46)
	14–19	1858	83(4.5%)	1.03(0.74–1.42)	1858	122(6.6%)	1.06(0.81–1.39)
	>19	1851	101(5.5%)	1.43(1.04–1.95)	1851	162(8.8%)	1.55(1.21–2.00)
			p-trend	0.010		p-trend	<0.0001

[a] Adjusted for age, sex, and smoking. [OR(95%CI)].

Traffic-related pollution and children

McConnell *et al.* Traffic, susceptibility, and childhood asthma. *Env Health Persp* 2006, 114, 766-72

- Cross-sectional study (CHS), southern California:
  - 5,341 children (5-7 y) from 13 communities (2003)
  - Respiratory Questionnaire (ISAAC)
- <u>Exposure:</u>
  - Residence proximity to nearest major road (geocoding)
  - Estimate of exposure to fresh traffic-modeled pollutants
- <u>Adjustments:</u> maternal smoking, ETS, housing characteristics

➢ O.R. lifetime asthma, prevalent asthma or wheeze
  - Residence <75 m major road: 1.29, 1.50, 1.40 (*vs*>300 m)

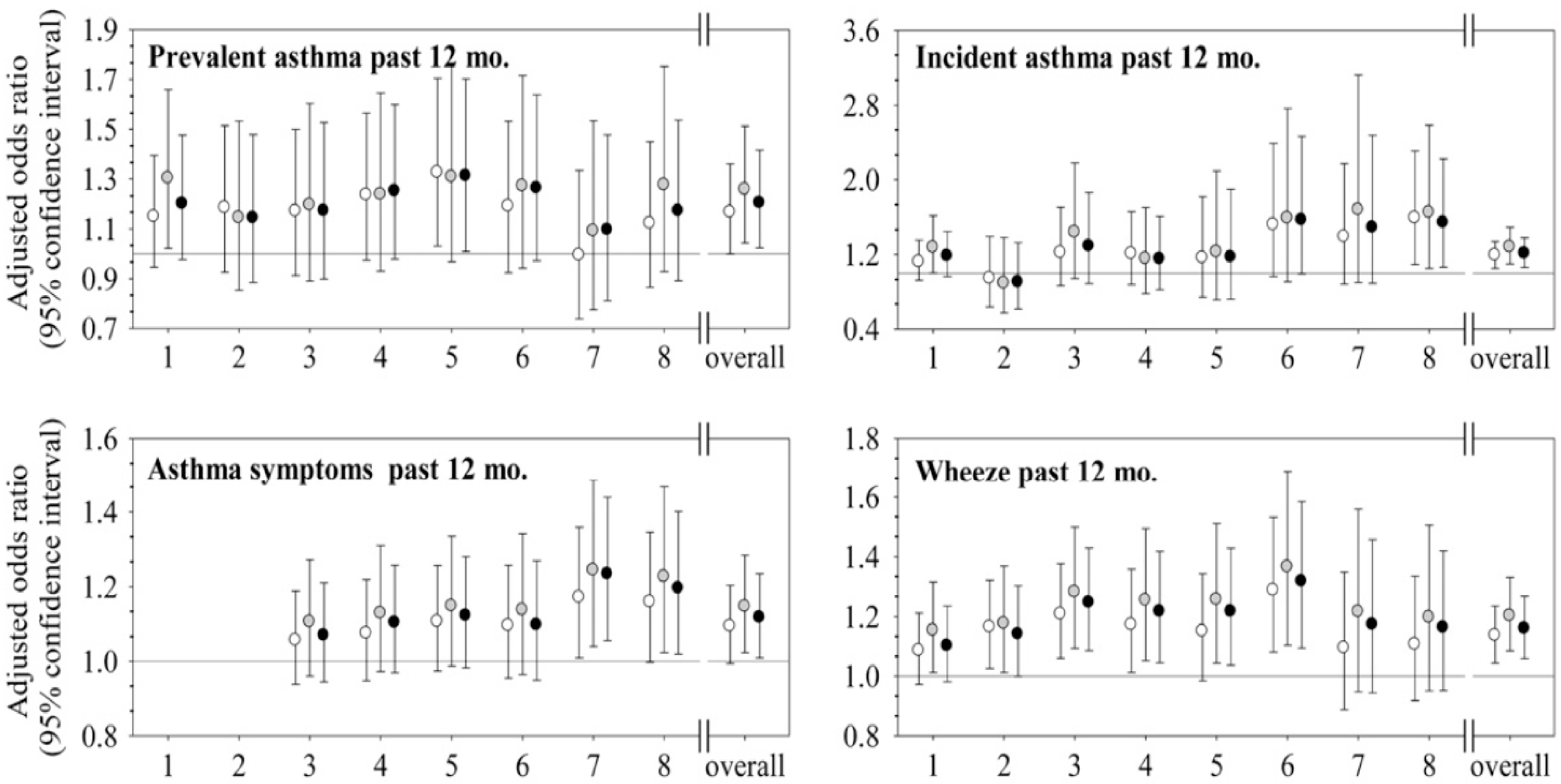
Traffic-related pollution and children

Gehring *et al.* Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *Am J Respir Crit Care Med* 2010, 181, 596-603

- Prospective birth cohort study (PIAMA), Nl:
  - 3,963 newborns (1996-7) + follow-up up to 8 y (n=3,863)
  - Questionnaires + specific IgE (n=1,700) + BHR (n=936)
- Exposure (birthplace home address):
  - $PM_{2.5}$, soot and NO_2 at 40 sites (4x2weeks)
  - Traffic intensity (GIS)
- Adjustments: maternal smoking, education, breastfeeding, gas cooking, moving house, …

➢ asthma incidence & prevalence related to air pollution

Gehring *et al.* Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *Am J Respir Crit Care Med* 2010, 181, 596-603



Annual asthma prevalence was 3 to 6%
12 to 23% for asthma symptoms.
Annual incidence of asthma was 6% at age 1 and 1 to 2% at later ages.

○	NO_2	IQR 10.4 µg/m^3	[18.5-28.9]
◉	$PM_{2.5}$	IQR 3.2 µg/m^3	[14.9-18.1]
●	soot	IQR 0.57.10^{-5} m^{-1}	[1.35-1.92]

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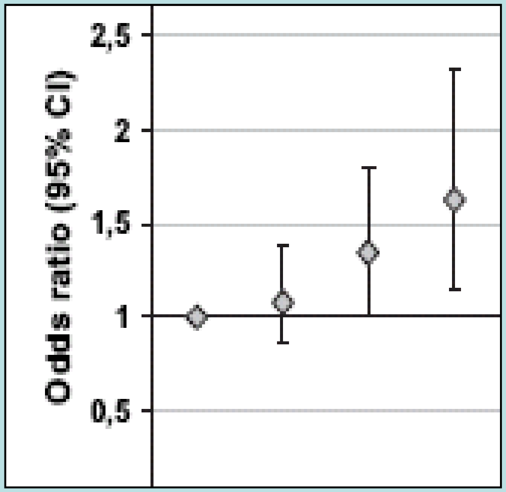
Cardiovascular morbidity

Hoffmann *et al.* Residential exposure to traffic is associated with coronary atherosclerosis. *Circulation* 2007, 116, 489-96

- Prospective cohort study, Germany:
  - 2000 - : 4494 persons, 45-74 y
  - Coronary artery calcification (CAC) by electron-beam CT
- Exposure: distance of residence to major roads
- OR for high CAC (> 75^{th} percentile):
  - > 200 m from major road : 1 (ref)
  - 101-200 m : 1.08
  - 51-100 m : 1.34
  - < 50 m : 1.63



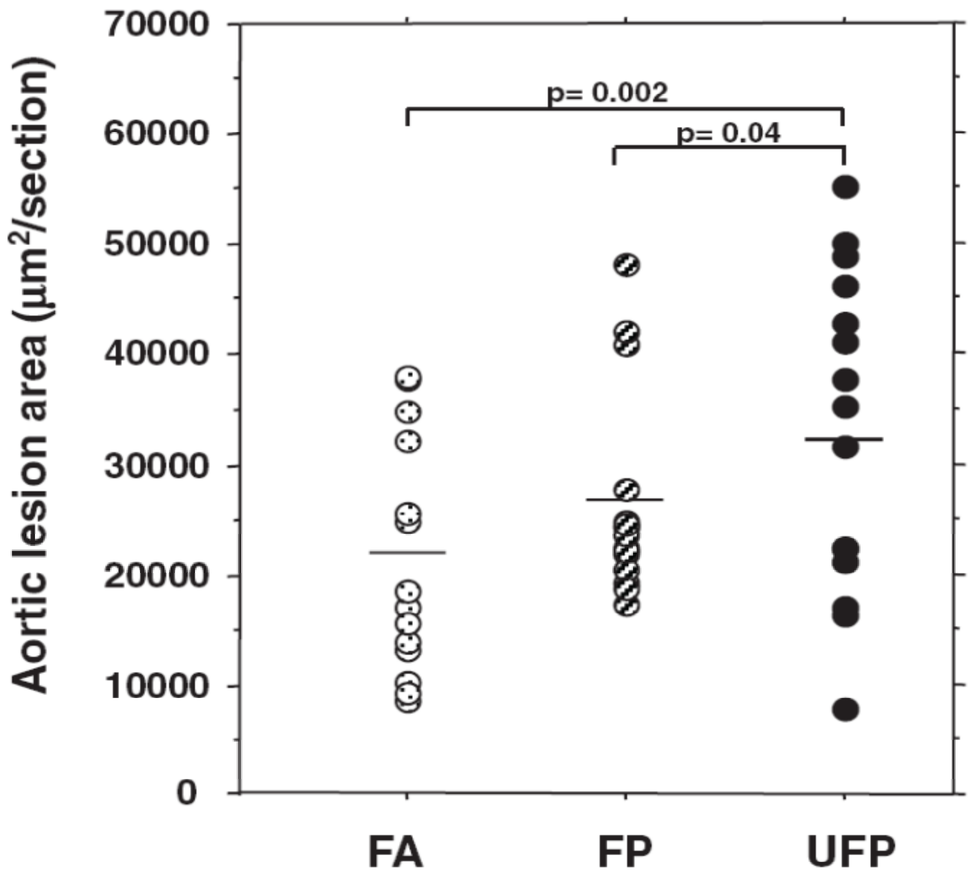
Cardiovascular morbidity

Araujo JA *et al.* Ambient particulate pollutants in the ultrafine range promote early atherosclerosis and systemic oxidative stress. Circ Res. 2008 Mar 14;102(5):589-96

- Experimental study
  - compared the pro-atherogenic effects of ambient particles of <0.18 microm (ultrafine particles UFP) with particles of <2.5 microm (fine FP) in genetically susceptible (apolipoprotein E-deficient) mice (particles from air of LA)
- outcome
  - UFP significantly larger early atherosclerotic lesions ⇔ PM(2.5) or filtered air.
  - UFP inhibition of the anti-inflammatory capacity of plasma high-density lipoprotein and greater systemic oxidative stress (increase in hepatic malondialdehyde levels and upregulation of Nrf2-regulated antioxidant genes)

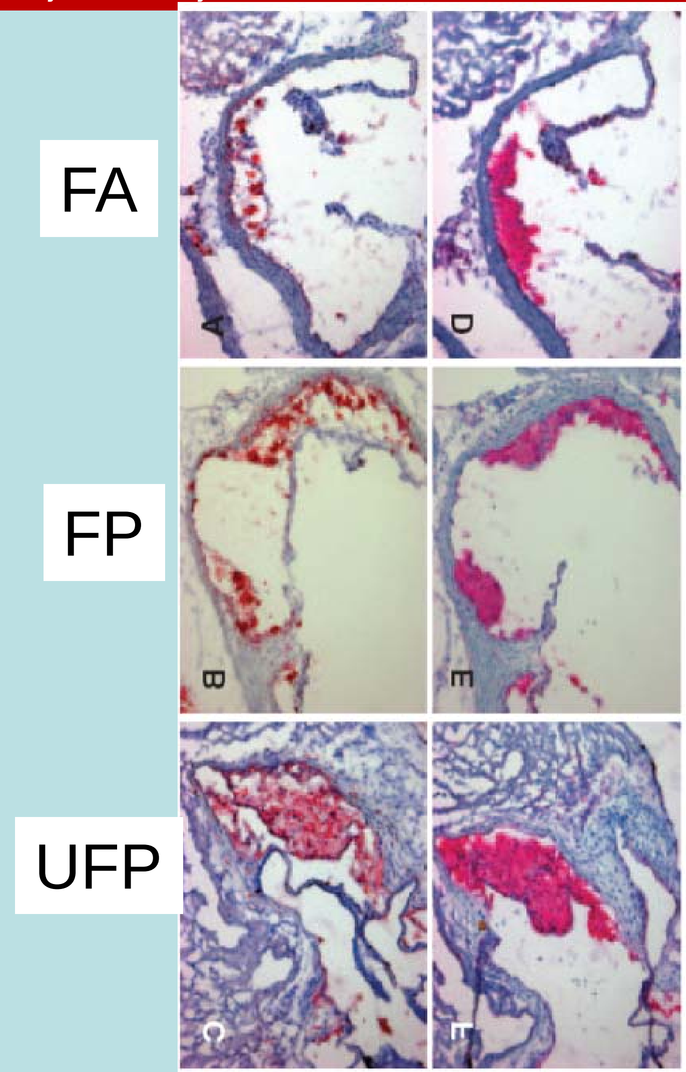
Cardiovascular morbidity

Araujo *et al. Circ Res* 2008, 102, 589-96



PM <0.18 µm n/cm³	~ 5,000	$3.88x10^5$	$5.59x10^5$
	0 mg/m³	0.4 mg/m³	0.1 mg/m³

5h/d 3d/wk x3 (75 h)



DOI: 10.1161/CIRCRESAHA.107.164970

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General mechanisms
Lung Cancer

- Handful of studies associated long-term exposure to urban pollution to increase the risk of lung cancer.
- The risk associated with air pollution is about 10–20% for each 10 mg/m3 increase in PM10 or PM2.5.
- European Prospective Investigation into Cancer and Nutrition:
  - **nonsignificant association** between **lung cancer** incidence and **residence near heavy traffic** roads (1.46, CI 0.89–2.40)
  - **significant interaction** between **distance from heavy traffic road** and **polymorphisms in genes coding** for **repair**
- An ecological study suggests that the differences in lung cancer mortality within Europe could be explained by exposure to particulate matter pollution.
- A meta-analysis (2010) show a small **consistent association** between occupational exposure to DME and lung cancer risk, and significant exposure–response trends.

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(Particulate) air pollution and health?

- Complex interaction
  - Multiple possible health effects
    - Lung: Asthma – COPD
    - Lung cancer
    - Systemic – Cardiovascular effects: clotting – arthrosclerosis – BP – HRate
    - Dependent on timing of exposure (children – adults ..)
  - Multiple particle
    - Size (UFP – FP – Coarse)
    - Composition
    - Fresh vs old
  - Multiple confounders
    - Pollutant gasses
    - Smoking
    - Indoor PM

(Particulate) air pollution and health?

- Complex interaction
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    - Lung: Asthma – COPD
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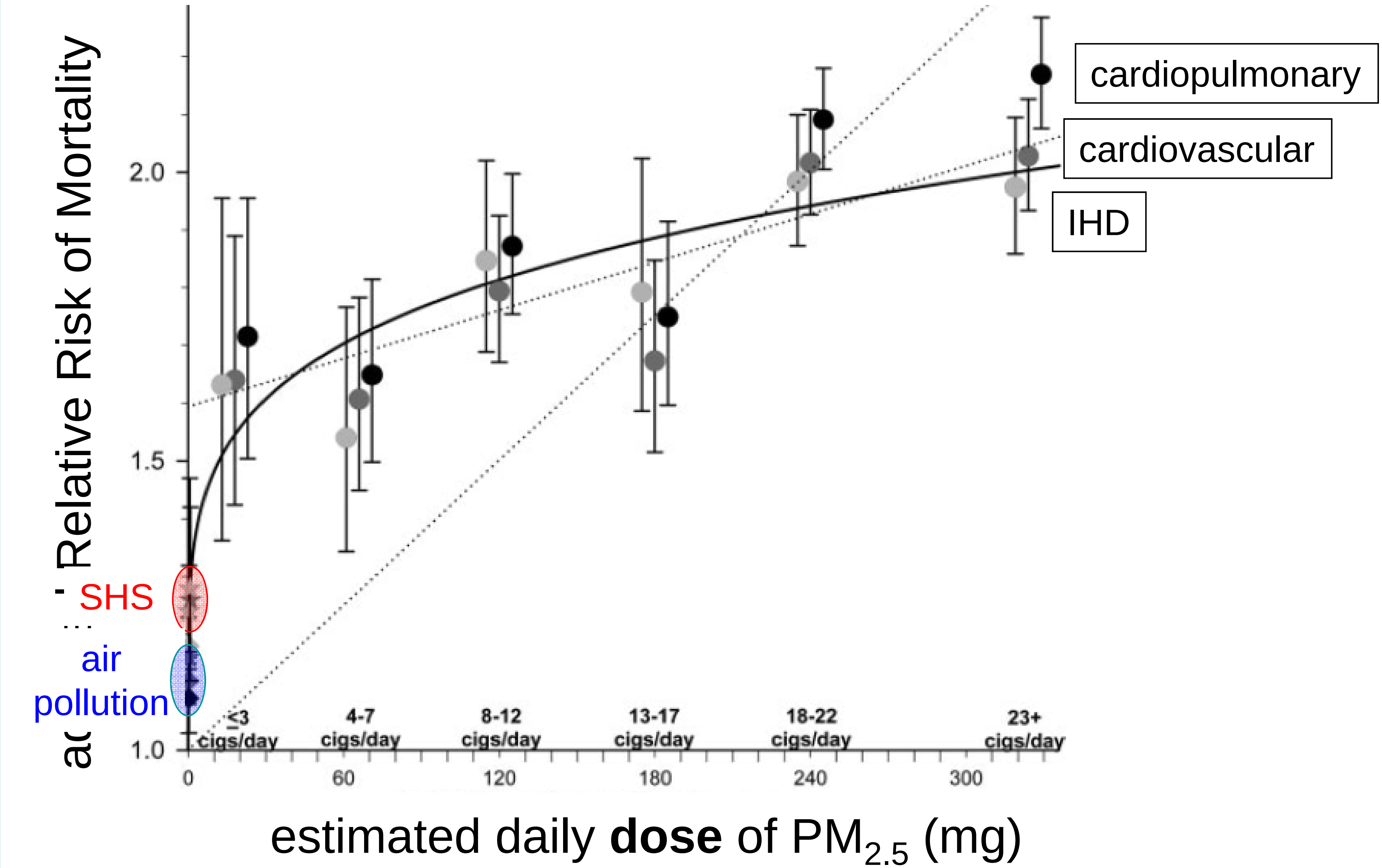
    - Systemic – Cardiovascular effects: clotting – arthrosclerosis – BP – Heart rate
    - Dependent on timing of exposure (children – adults ..)
  - Multiple particle
    - Size (UFP – FP – Coarse)
      - Soot (or Black Carbon) strongly associated with respiratory diseases such as Asthma & COPD
      - Near Road - Traffic related studies - show strong association with :
        - Pulmonary effects in children
        - CV-effects
    - Composition (source)
    - Fresh vs old
  - Multiple confounders
    - Pollutant gasses
    - Smoking
    - Indoor PM

How do ambiant particles compare to smoking
Pope *et al.* Circulation 2009, 120, 941-8



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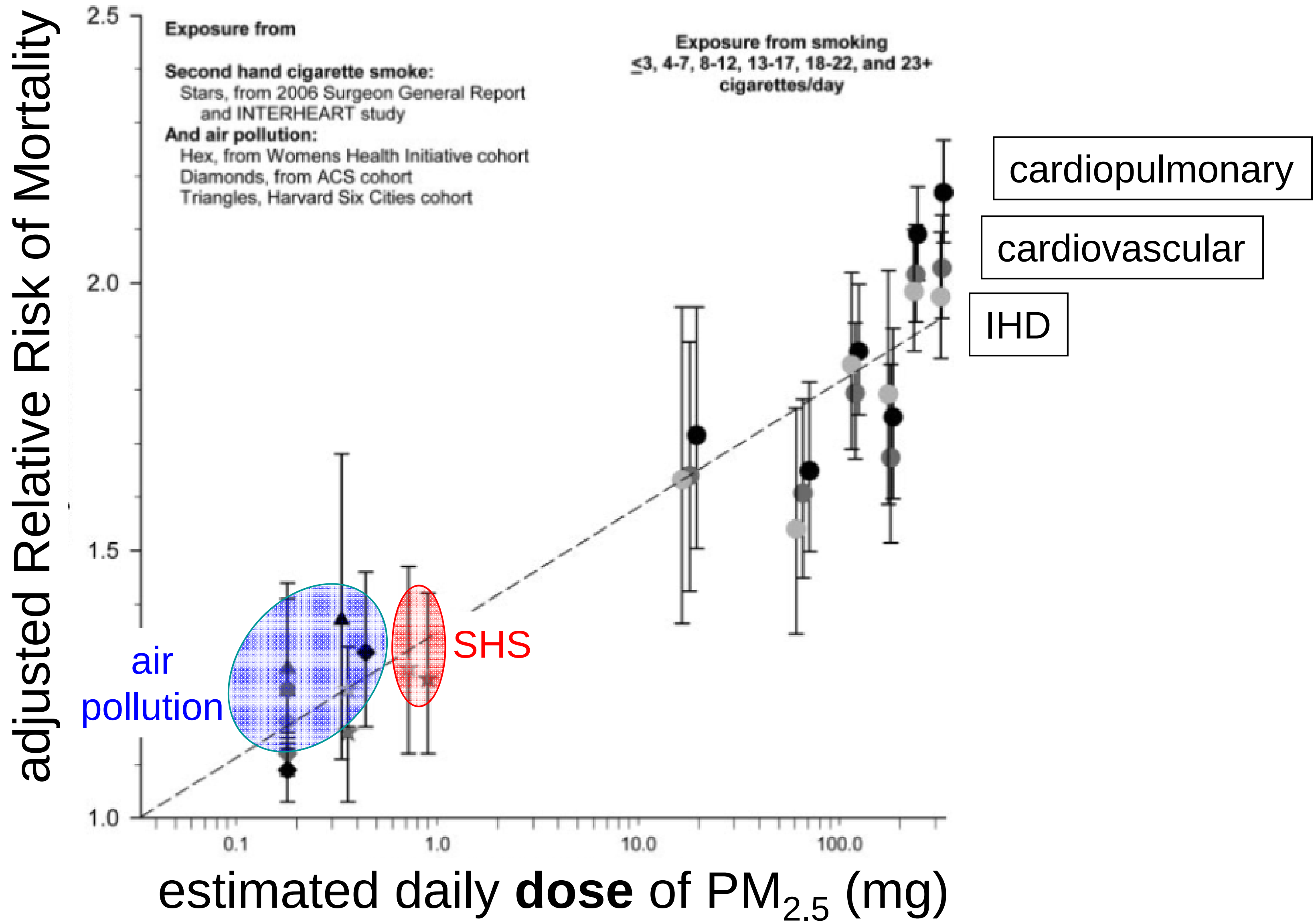

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Thank you for your attention