


Fine particulate matter: effects on mortality and cardiovascular and respiratory morbidity
Particules fines : effets sur la mortalité, effets sur la morbidité cardiovasculaire et respiratoire

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Collège de France & Inserm

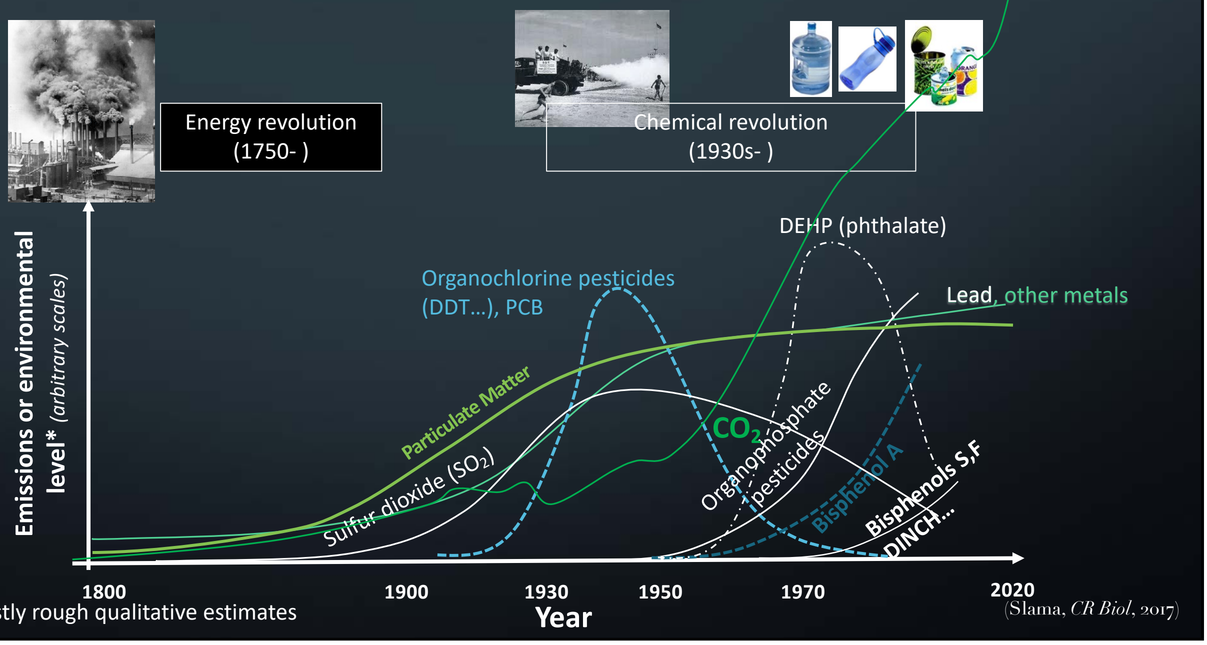
The relations between human health and the environment in the Anthropocene

Lecture #3 – 13 April 2022

COLLÈGE DE FRANCE 1530

1

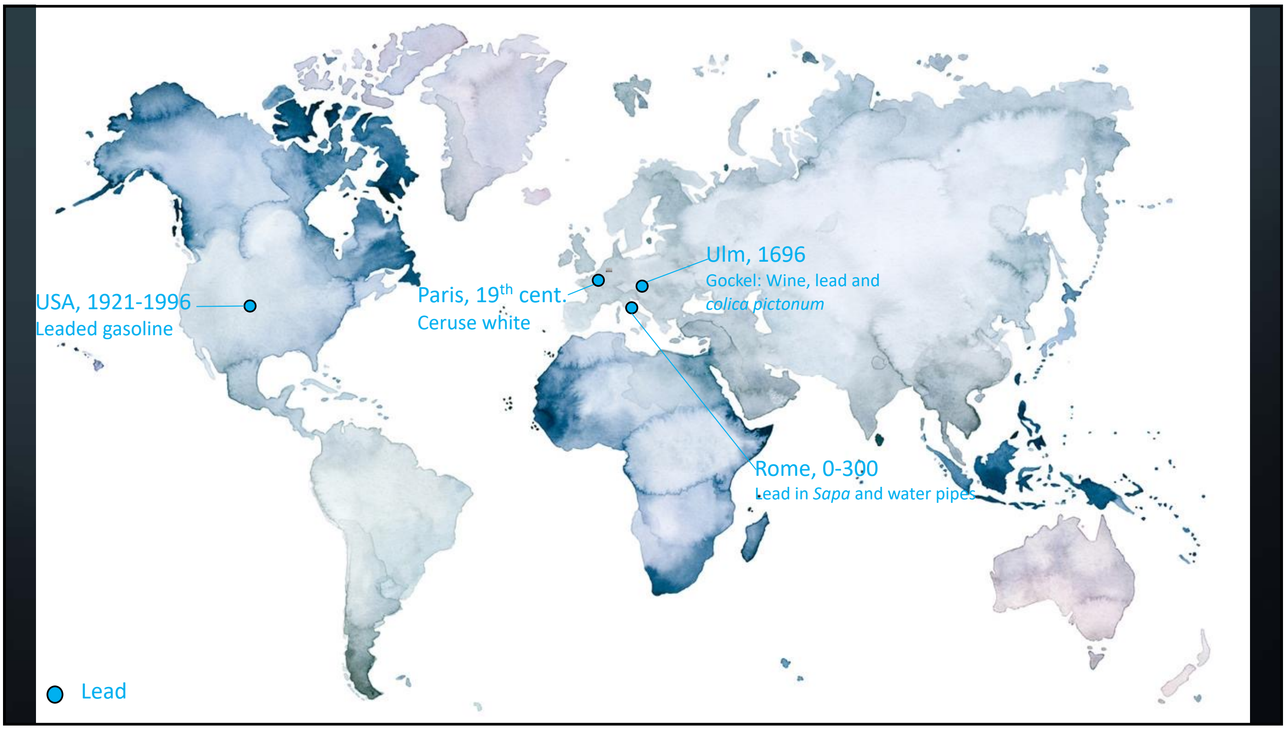
The Anthropocene seen from the perspective of environmental pollution



*Mostly rough qualitative estimates

(Slama, *CR Biol*, 2017)

2



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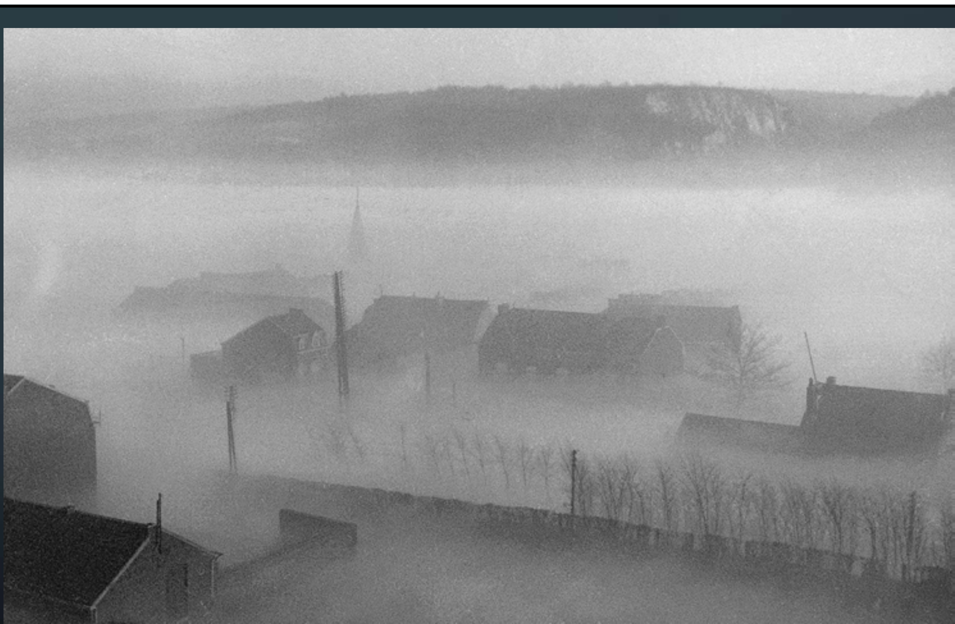


Meuse valley, ca. 1930, coll. Albert Humblet

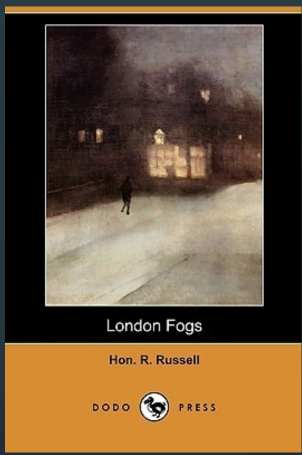
4

Dec. 20, 1873.] THE BRITISH MEDICAL JOURNAL.

ACCIDENTS IN THE FOG.

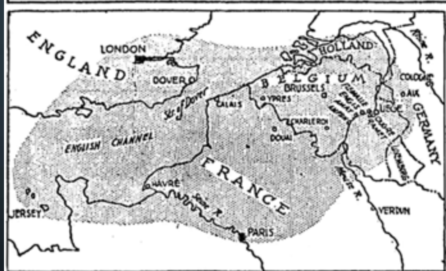
THE unusually high reading of the barometer (over 30.50 in.), which prevailed from the 6th to the 13th instant, were accompanied by a fog in the metropolis from the 9th to the 13th, which was at times excessively dense. In the Cattle Show, the horned cattle suffered severely from difficulty of breathing, but the sheep and pigs were less affected. Persons in good health who were living in the fog suffered much bodily discomfort, and smarting of the conjunctivæ was frequently accompanied by severe frontal headache. To invalids, however, and especially to those suffering from disease of the lung, the atmosphere was most distressing. Many fatal accidents on the river and in the streets were reported in the daily journals. The following house-surgeons have favoured us with accounts of the accidents attended at their hospitals. Mr. J. H. Morgan (St. George's) saw only two trivial accidents resulting from the fog: one, a contusion of the eye from a fall over the railings in Hyde Park; the other, a slight burn in the face from a blow with a torch. Mr. G. B. Browne (University College Hospital) reports that only three accidents were admitted by him; two in which the patients were run over, with two broken ribs in one case, and a case of bad burn in the face from a blow with a lighted torch. Mr. J. Leonard (Charing Cross) reports that from thirty to forty injuries arising in the fog were attended to at his hospital, but that they were mostly of little moment. The death-rate amongst the in-patients suffering from heart and lung-diseases was greatly increased. Mr. J. L. Morley (Guy's) reports that no more accidents than usual have been admitted during the past fortnight. Only one serious case arose from the fog; it was that of a man, forty years of age, engaged in putting fog-signals on the rails. An engine knocked him down and crushed his left foot. The leg was amputated by Mr. Howse in the upper third immediately upon his admission. The patient had also a badly comminuted fracture of the left humerus; also rupture of the crucial ligaments and inner portion of the capsule of the right knee-joint, and three or four scalp-wounds. He is doing very well, and is under carbolic treatment. Mr. E. Jepson (St. Bartholomew's) writes, that "only two accidents due to the fog were admitted. A man fell thirty-six feet from the top of a house; and another man drove his cart into the East India Docks. Both patients are doing well. The medical patients, with affections of the lung, suffered very much."

Br Med J, Dec. 20, 1873, p.731



« smoke in London has continued probably for many years to shorten the lives of thousands »
(F.A. Rollo Russel, London fogs, 1880)

"Poison Fog" Terrorizes Northwestern Europe



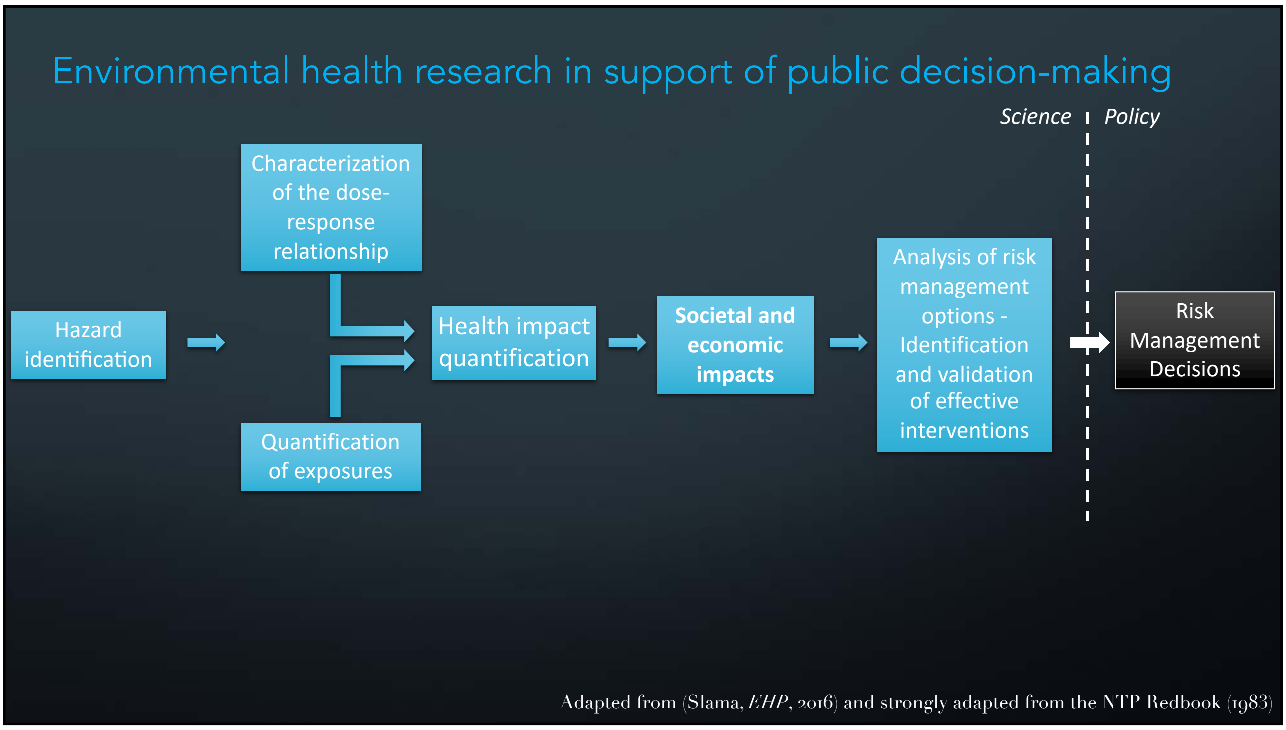
Shaded portion of map indicates region where impenetrable pall of fog is causing mysterious strangling malady in northern France, Belgium, Holland, and England. Sixty-four deaths have been caused in the Meuse valley, Belgium, near Liege. Scientists are baffled by the mysterious epidemic, and the Belgian government is preparing to rush 20,000 gas masks to the Meuse district for distribution among the inhabitants.

Chicago Daily Tribune, 6 Dec. 1930

5

Punch magazine (UK, 1880)

6



7

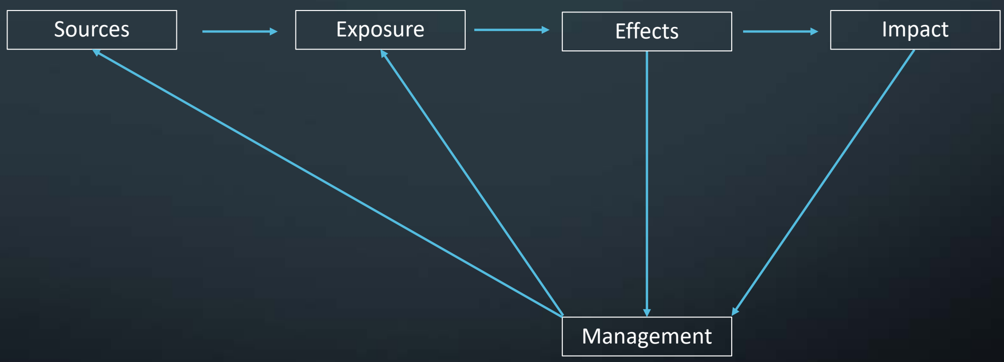
Lecture overview

A. Nature of atmospheric pollution
B. Effects (1): Peaks and valleys. *Before-after* studies
C. Effects (2): A new microscope - *Time-series* studies
D. Effects (3): Cohorts - making long-term effects visible
E. Effects (4): Overview of cardiovascular and respiratory effects
F. Effects (5): Other health targets of atmospheric pollutants
G. Social inequalities in exposure
H. Health and societal impact
I. Evaluation of risk management options
J. Risk management

Sources
Effects

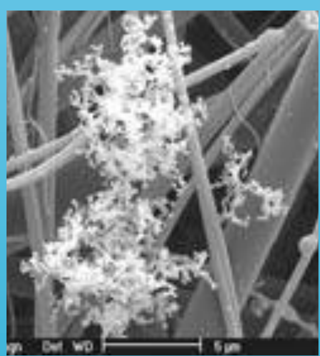
Exposure
Impact
Management options
Management

9



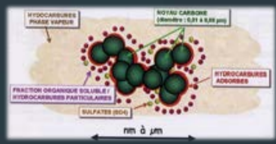
10

A. Nature and sources of atmospheric pollutants



11

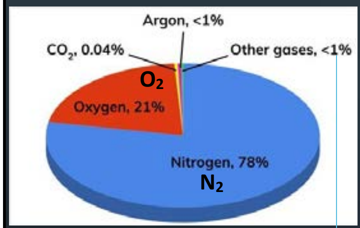
There's something in the air…



Aerosols

Mixture of solid or liquid particulate matter with gas

Gas

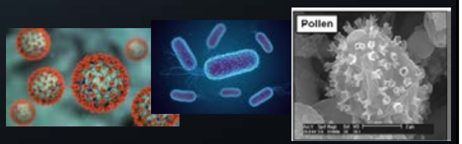


Inorganic gases: CO, nitrogen oxides (NO, NO_2), sulphur dioxide (SO_2), O_3.
Volatile organic compounds (VOCs): Benzene, formaldehyde, polycyclic aromatic hydrocarbons (PAH)…
Usually in the concentration of 1 part per million

Suspended particulate matter

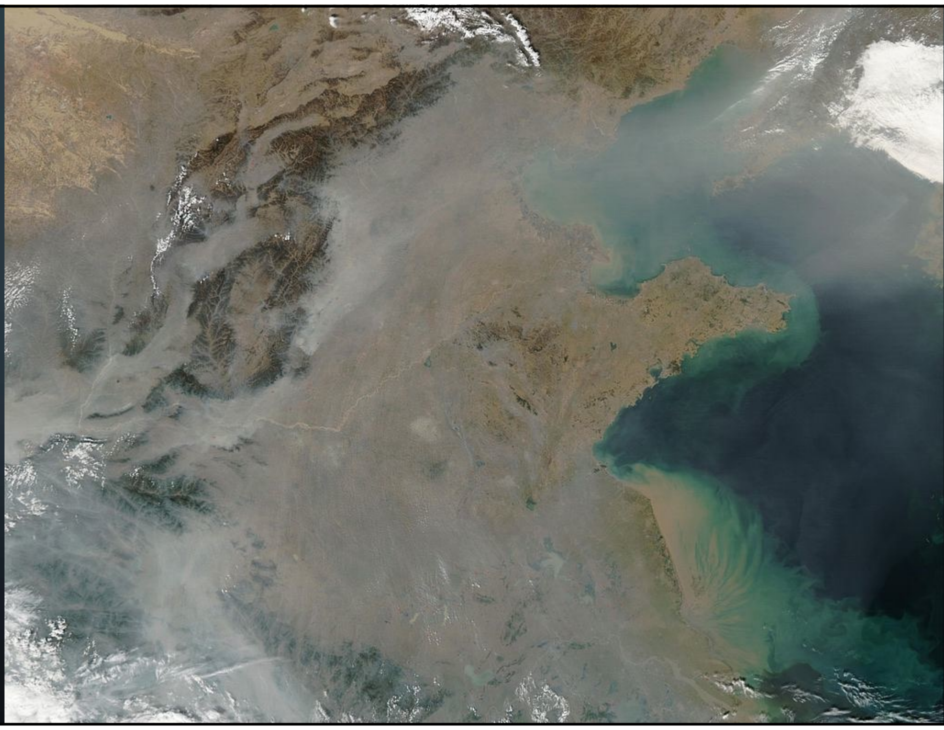
(below ca. 40-50 µ aerodynamical diameter)

Bioaerosols



Virus Bacteria Pollen

12



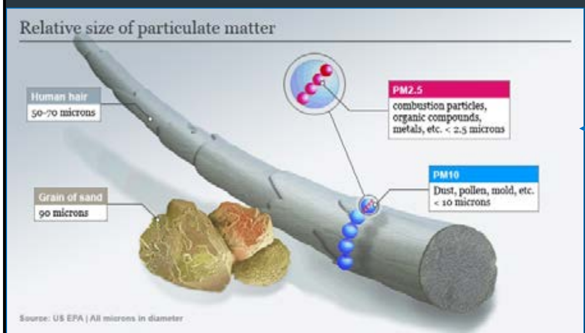
13

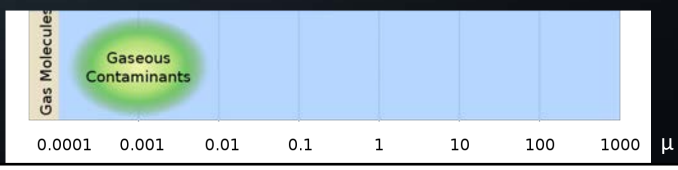
Characterizing atmospheric pollutants

- Physical properties
  - Gases vs. aerosols
  - Size, mass, surface
  - Sedimentation time
- Chemical and biological nature
- Origin
  - Natural (volcano, erosion…) *vs.* man-made (combustion by-products in engines, pesticide aerosols…)
  - Primary *vs.* secondary compounds (e.g., ozon)

14

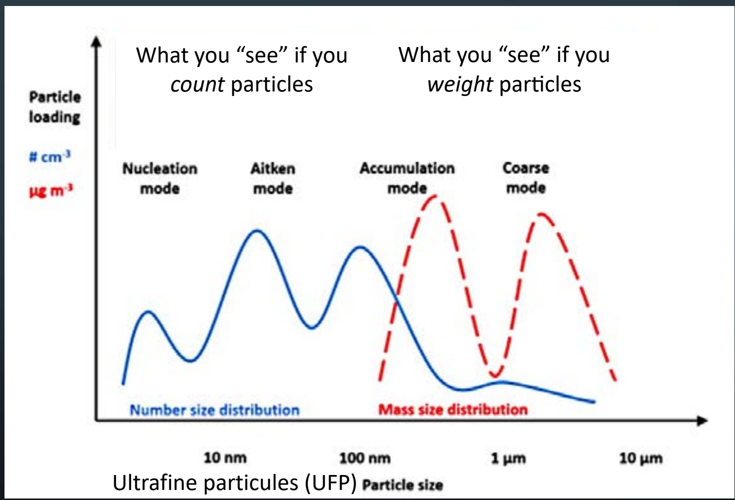
Atmospheric contaminants ranked by size



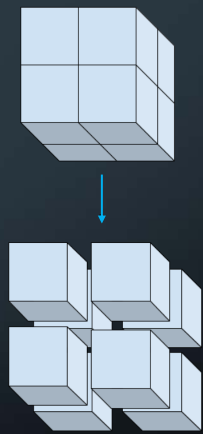


15

Weighing or counting particles?



Ultrafine particules (UFP)
Very limited contribution to PM mass

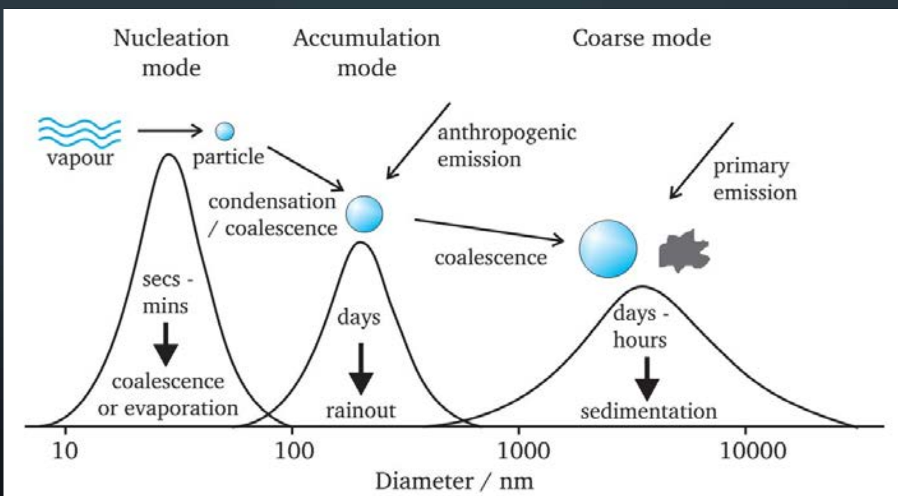


Mass: m
Surface: S
Particle nb: 1

Mass: m
Surface: **2**xS
Particle nb: **8x1**

16

The atmospheric half-life of particulate matter



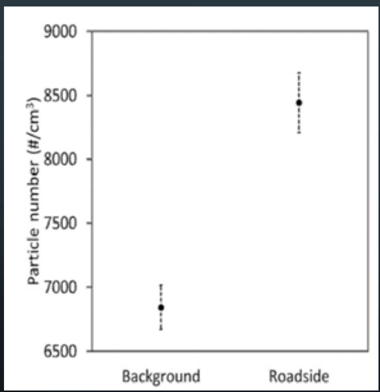
$$v = \frac{d^2 (p - L) \times g}{18\, n}$$

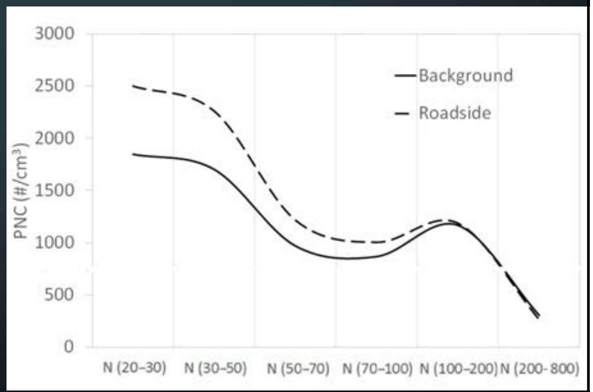
v = sedimentation rate or velocity of the sphere
d = diameter of the sphere
p = particle density
L = medium density
n = viscosity of medium
g = gravitational force

Stoke's law

17

Particle number (size range, 20-800 nm)





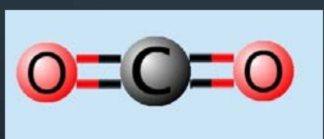
(Strasbourg, France, winter 2019)

(Chatain, *Atmosphere*, 2021)

18

Long-term consequences…

CO_2 (greenhouse gas)



Atmospheric half-life:
circa 100 years (from 5 to 200 years)

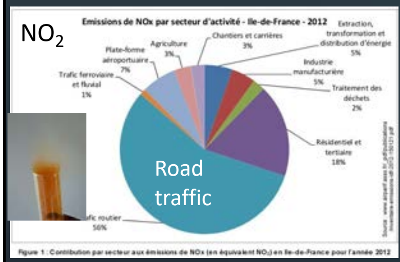
Particulate matter (PM)

Atmospheric half-life:
Hours to days

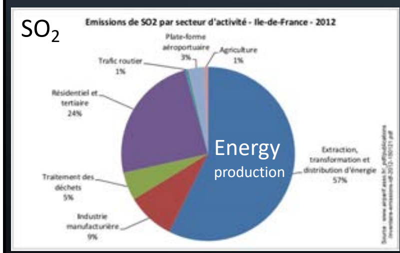
19

Sources of some primary air pollutants
(Ile de France, 2012)

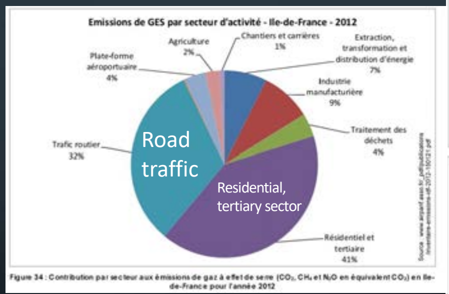
NO_2



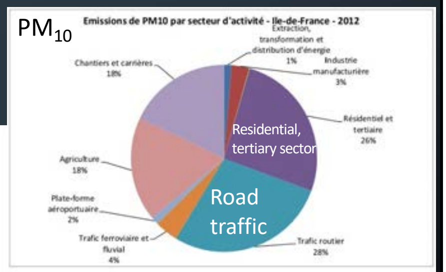
SO_2



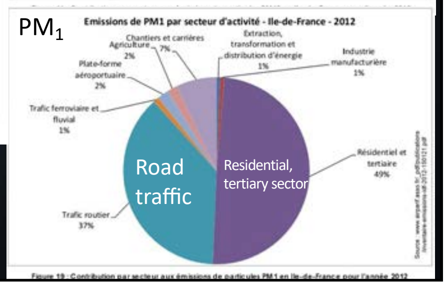
Grenhouse gases



PM_{10}

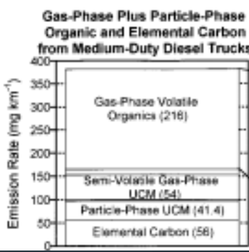


PM_1



(Airparif, 2016)

20



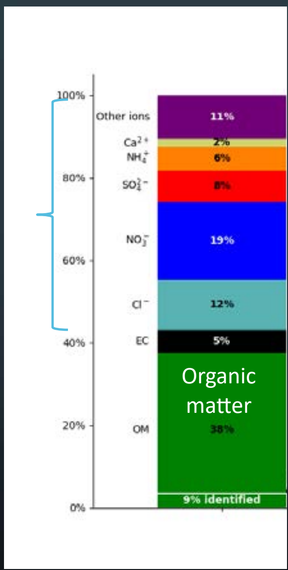
Road
traffic

Chemical composition of diesel engine exhaust

(Schauer, *Env Sci Technol*, 1999)

21

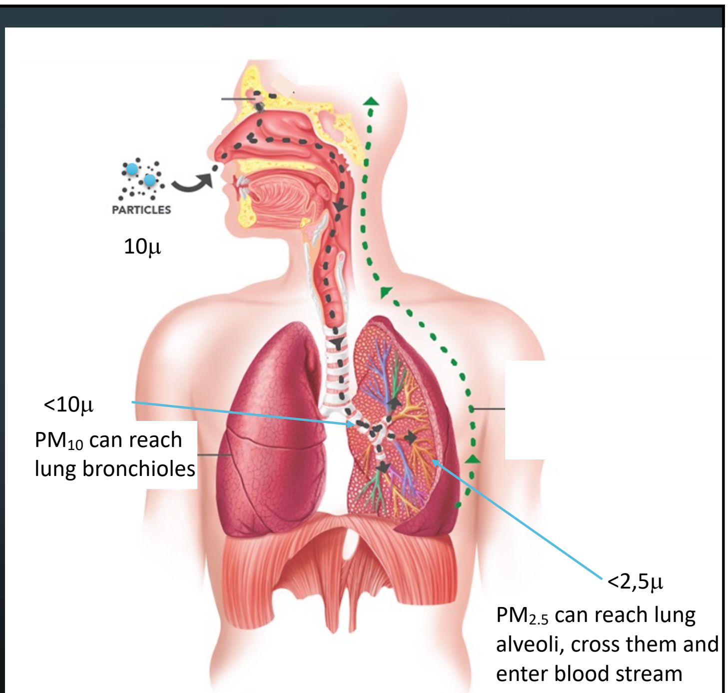
Chemical composition of PM_{10}



(Jaffrezo, IGE Grenoble, personal communication)

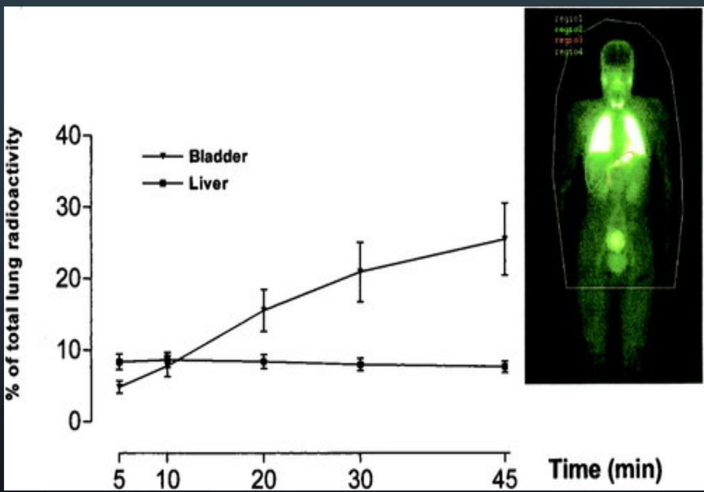
22

Translocation of particulate matter into the body



(California Air Ressource Board)

23



(Nemmar, *Circulation*, 2002)

Table 1. Ag concentrations and estimated content in tissues/organs of rats exposed to ultrafine EAg particles for 6 hr.[a]

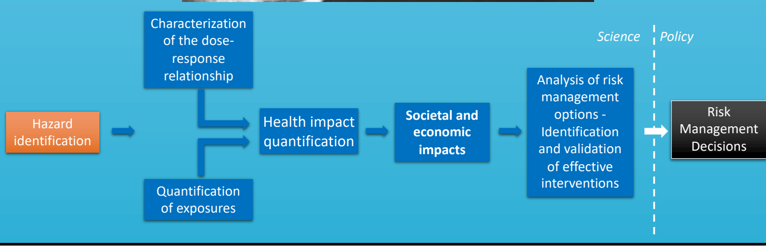
Tissues/organs		Time after exposure: Immediately (30 min–2 hr)	Day 1	Day 4	Day 7
Lung	Concentration[b]	2,375(171)	904(31)	199(41)	98(19)
	Content[c]	1,716(169)	656(31)	152(35)	75(14)
Liver	Concentration	33(13)	24(5.1)	5.6(1.8)	3.0(1.1)
	Content	156(60)	113(24)	29(10)	16(7)
Kidney	Concentration	ND	39(8.1)	4.7(4.4)	ND
	Content	ND	45(10)	5(5)	ND
Heart	Concentration	ND	2.8(0.5)	0.7(0.1)	ND
	Content	ND	1.5(0.3)	0.4(0.1)	ND
LALN (tracheobronchial lymph nodes)	Concentration	ND	21(7.7)	72(63)	ND
	Content	ND	0.6(0.3)	1.7(1.4)	ND
LALN (mediastinal tissues including mediastinal lymp nodes)	Concentration	ND	6.8(0.7)	1.6(0.1)	ND
	Content	ND	2.1(0.4)	0.5(0.1)	ND
Nasal cavity, anterior	Concentration	59.2(22.6)	13.9(2.2)	ND	ND
	Content	13(6.5)	1.8(0.5)	ND	ND
Nasal cavity, posterior	Concentration	96(20.4)	68.3(4.5)	ND	ND
	Content	16.3(5.6)	8.8(1.3)	ND	ND
Brain olfactory portion	Concentration	1.9(1.1)	3.1(1.3)	ND	ND
	Content	0.3(0.02)	0.4(0.2)	ND	ND
Brain rest	Concentration	1.4(0.5)	1.2(0.2)	ND	ND
	Content	1.6(0.6)	1.3(0.1)	ND	ND
Blood	Concentration	8.9(6.2)	6.2(0.8)	2.9(1.5)	1.0(0.2)
Unexposed					
Lung	Concentration	< 1.2(0.2)			
	Content	< 0.9(0.1)			
Blood	Concentration	< 0.6(0.1)			

ND, not done.
[a] $n = 4$ for each examination (for unexposed lungs $n = 8$). [b] Concentration: ng/g wet weight, mean (SD). [c] Estimated content: concentration × organ weight; ng, mean (SD).

(Takenaka, *Env Health Perspect*, 2001)

24

B. Effects (1): Peaks and valleys (1820-1952). Before-after studies – *when pollution was visible*



25

Meuse Valley, 1930

Donora (Pennsylvania), 1948

London, 1952

26

London (Dec. 1952) smog episode

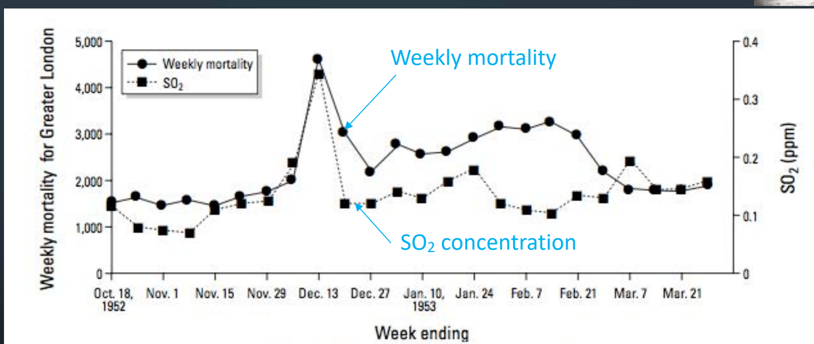


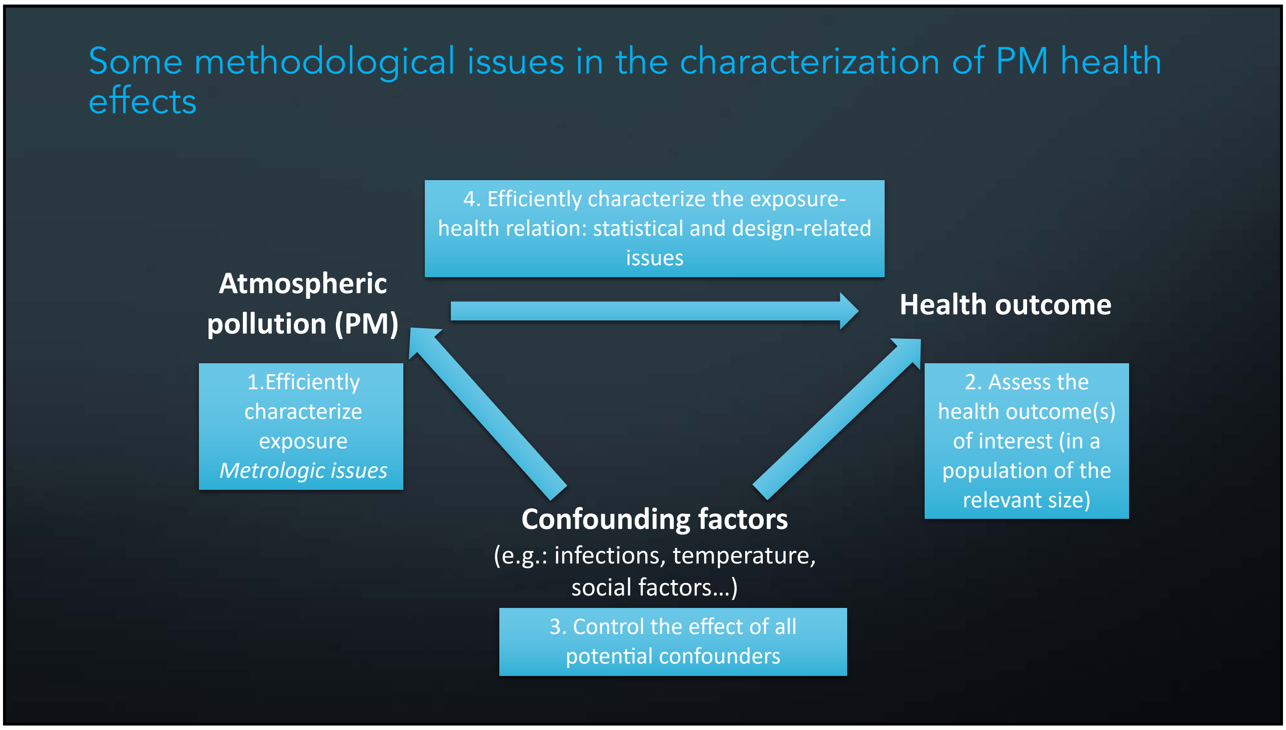
Figure 1. Approximate weekly mortality and SO_2 concentrations for Greater London, 1952–1953.

Number of excess deaths (greater London) :

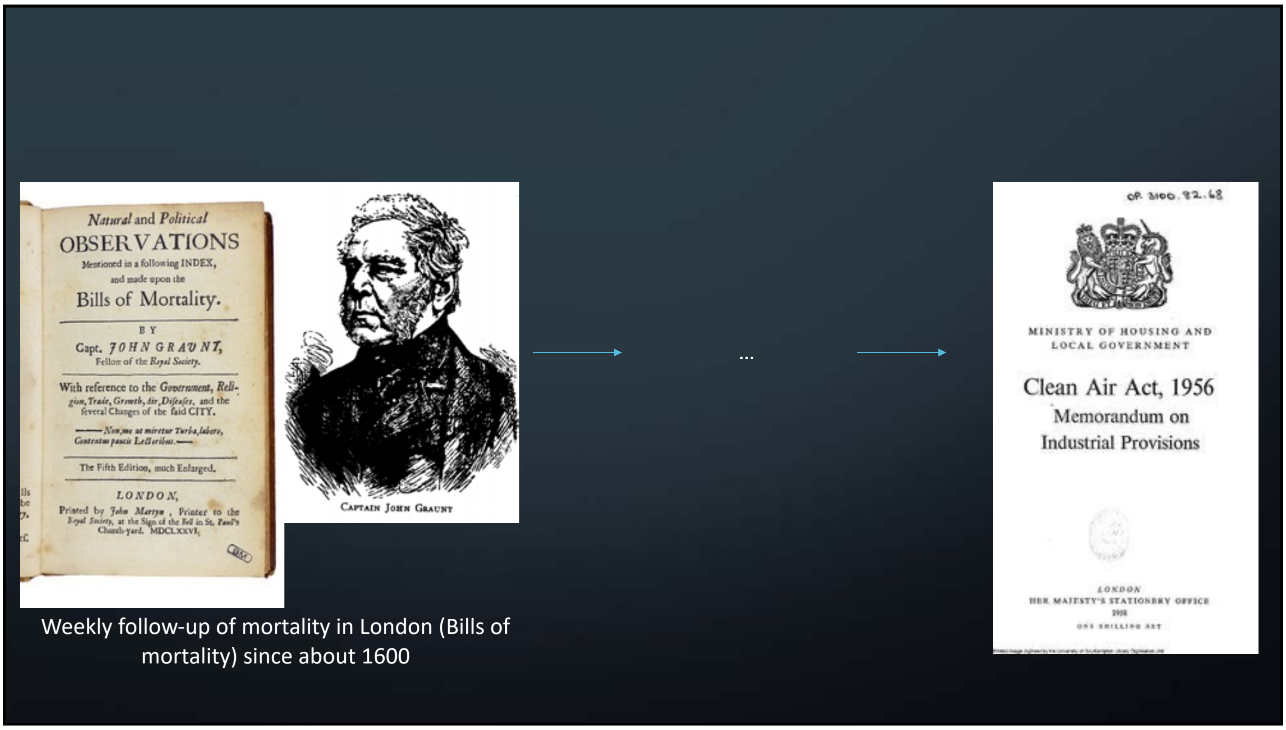
- 5,000 in Dec. 1952
- 12,000 for the period from Nov. 1952 to Feb. 1953

(Bell, *Env Health Perspect*, 2001, 2004)

27

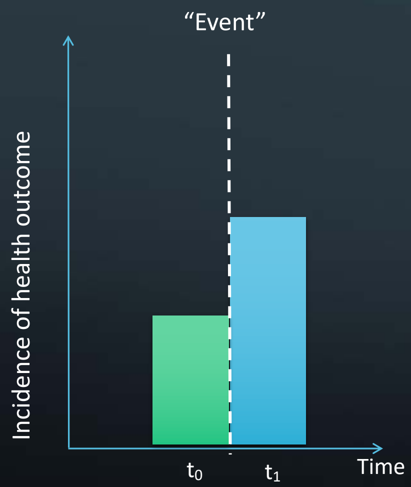

Some methodological issues in the characterization of PM health effects
4. Efficiently characterize the exposure-health relation: statistical and design-related issues
Atmospheric pollution (PM)
Health outcome
1.Efficiently characterize exposure
Metrologic issues
2. Assess the health outcome(s) of interest (in a population of the relevant size)
Confounding factors
(e.g.: infections, temperature, social factors…)
3. Control the effect of all potential confounders

28


Natural and Political
OBSERVATIONS
Mentioned in a following INDEX, and made upon the
Bills of Mortality.
BY
Capt. JOHN GRAUNT,
Fellow of the Royal Society.
The Fifth Edition, much Enlarged.
LONDON,
Captain John Graunt
Weekly follow-up of mortality in London (Bills of mortality) since about 1600
…
MINISTRY OF HOUSING AND LOCAL GOVERNMENT
Clean Air Act, 1956
Memorandum on Industrial Provisions
LONDON
HER MAJESTY'S STATIONERY OFFICE

29

Study design : Before-after study (*natural experiment*)



Temporal ecological study

Unit of analysis:

The community (city, district…) considered at a given time point (e.g., day)

Analysis:

Comparison of the incidence of the health outcome (e.g., deaths) in the studied community in the 2 periods of interest (after-before). Possibly: comparisons with the same periods 1-2 years before

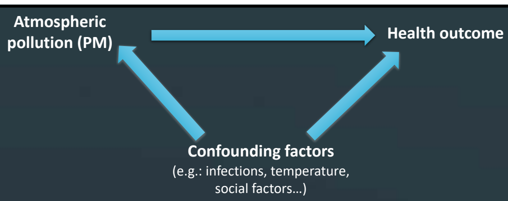
Exposure assessment:

No direct assessment required. Time as a proxy of exposure changes. Aggregated at the community level

Only **short-term effects** (hour to week) can be efficiently characterized.

Only the effect of the average change in exposure across the study population is seen

30



- Only factors with short-term variations (within a few days) that also influence mortality can confound the before-after comparison
- Candidates: temperature, infections
- All factors that do not vary on the short term need not be controlled (e.g., genes, smoking rate…)

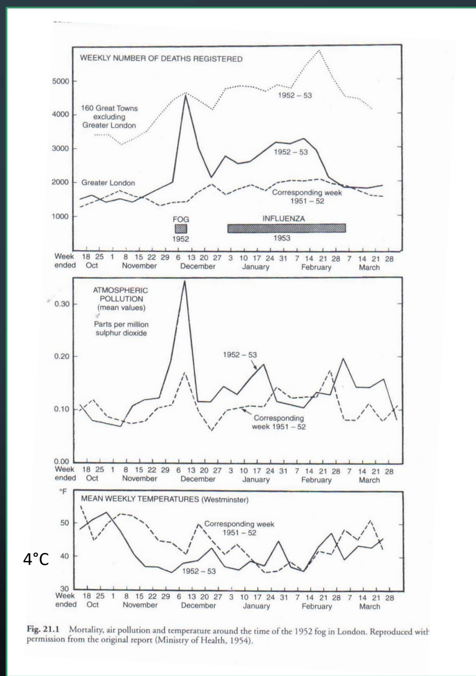
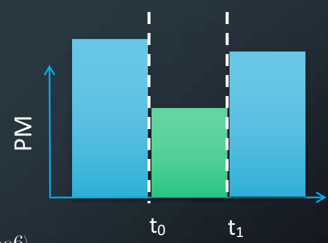


Fig. 21.1 Mortality, air pollution and temperature around the time of the 1952 fog in London. Reproduced with permission from the original report (Ministry of Health, 1954).

31

A century of natural experiments on air pollution effects

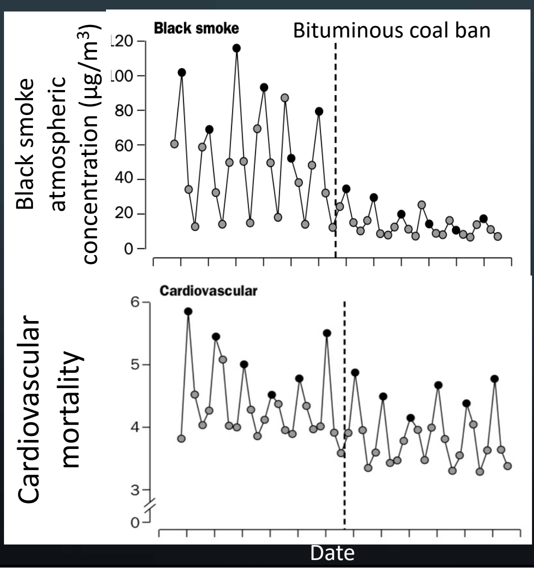
- 1930: Meuse valley (Belgium) (Nemery, *Lancet*, 2001)
- 1948: Donora (Pennsylvania)(Jacobs, *Am J Pub Health*, 2018)
- 1952 : London (Bell, *Env Health Perspect*, 2001, 2004)
- 1985: Utah Valley steel mill strike (Pope CA, *Am J Pub Health*, 1989 ; *JEAEE*, 1996)
- 1996: Atlanta Olympic games (Friedman, *JAMA*, 2001) ; Beijing (Rich, *JAMA*, 2012; *EHP* 2015)
- 1990: Dublin bituminous coal sale ban (Clancy, *Lancet*, 2002)
- 1990s: German reunification and respiratory health in former DDR (Heinrich, *Epidemiology*, 2002)

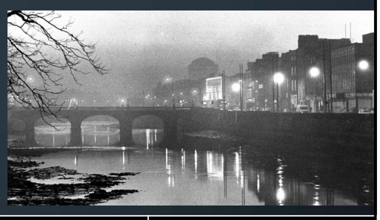


Bitterfeld, DDR

32

Dublin bituminous coal sale ban (1 Sept 1990)



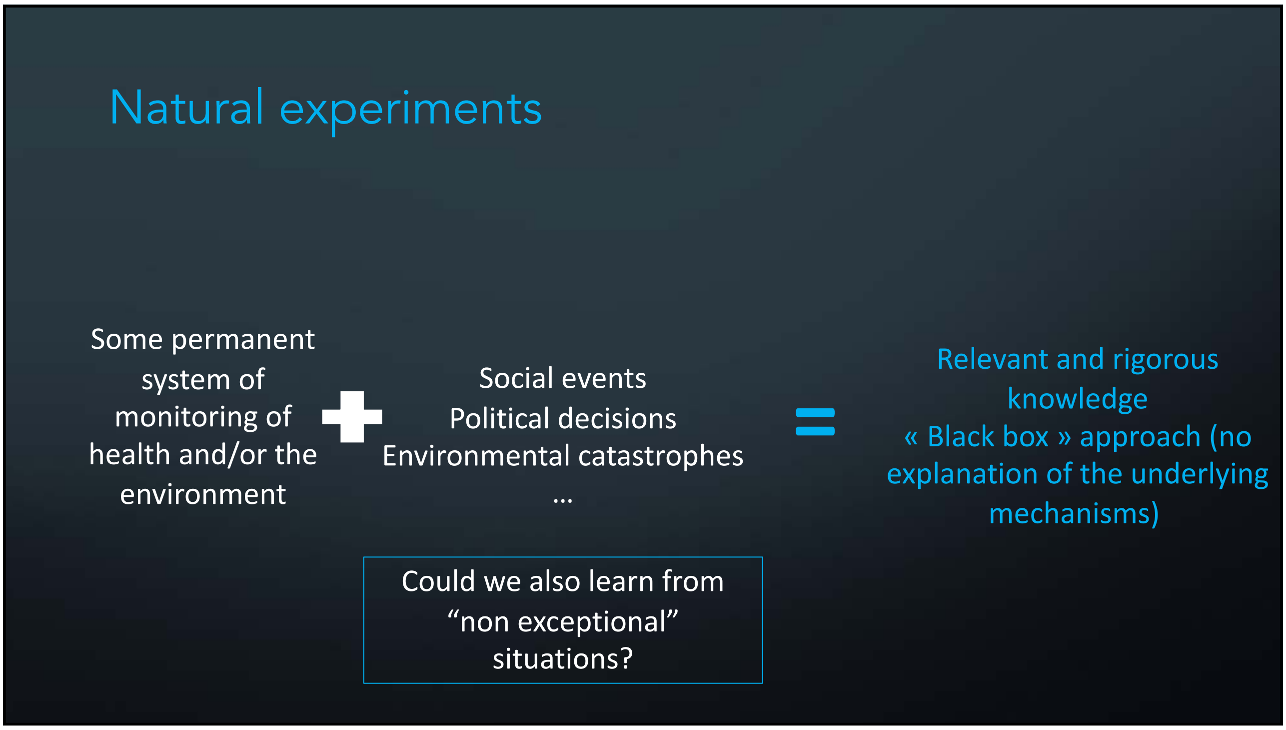


	Variation *(after-before*)*
Black smoke concentration	-70%

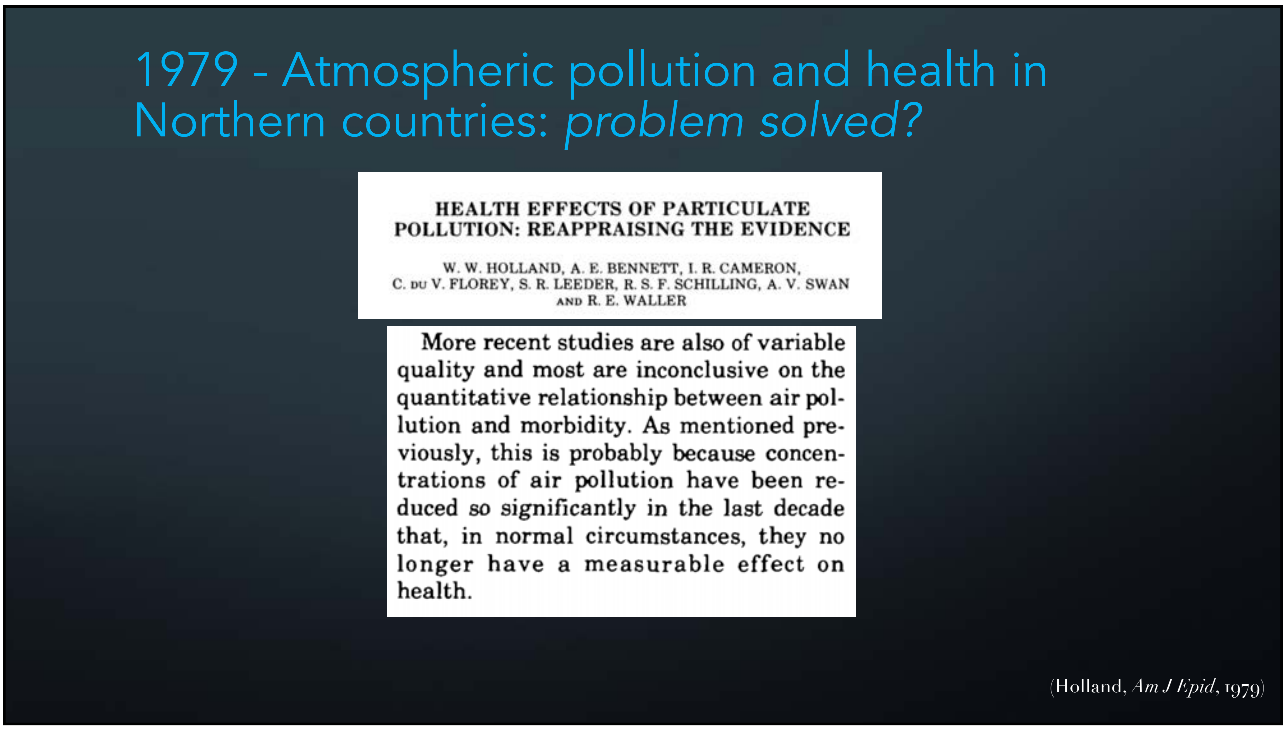
*Change between the 7 year average *after* and the 7 year *before* the intervention

(Clancy, *Lancet*, 2002)

33

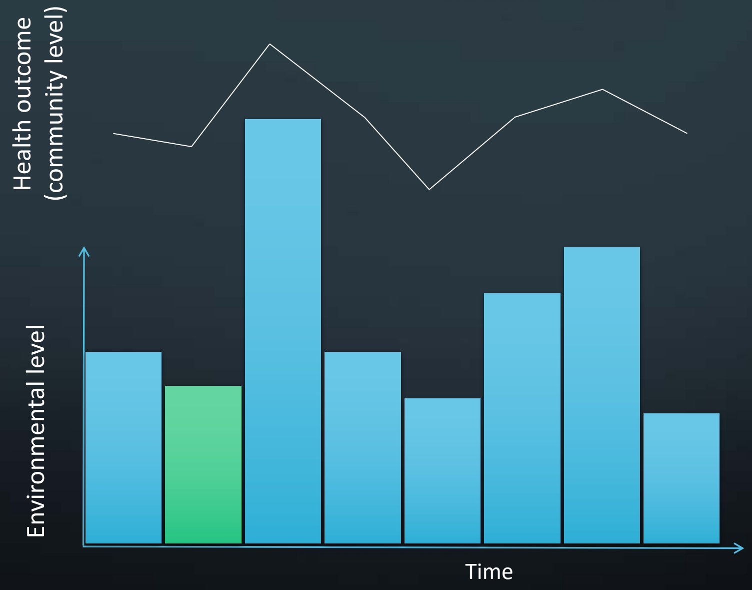

Natural experiments
Some permanent system of monitoring of health and/or the environment
Social events
Political decisions
Environmental catastrophes
…
Relevant and rigorous knowledge
« Black box » approach (no explanation of the underlying mechanisms)
Could we also learn from "non exceptional" situations?

34


1979 - Atmospheric pollution and health in Northern countries: *problem solved?*
HEALTH EFFECTS OF PARTICULATE POLLUTION: REAPPRAISING THE EVIDENCE
W. W. HOLLAND, A. E. BENNETT, I. R. CAMERON, C. DU V. FLOREY, S. R. LEEDER, R. S. F. SCHILLING, A. V. SWAN AND R. E. WALLER
More recent studies are also of variable quality and most are inconclusive on the quantitative relationship between air pollution and morbidity. As mentioned previously, this is probably because concentrations of air pollution have been reduced so significantly in the last decade that, in normal circumstances, they no longer have a measurable effect on health.
(Holland, *Am J Epid*, 1979)

35

Before after studies: *and after?*



Time series analyses

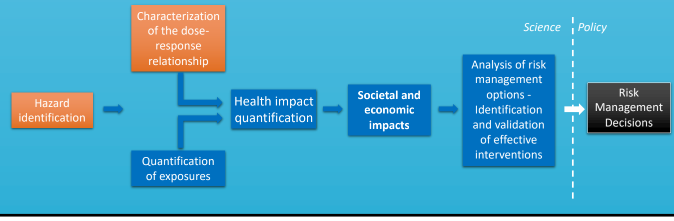
Principle:
The before-after comparison could be generalized to lower day-to–day variations in air pollution levels.

Expected increase in statistical power

(because power depends on the total number of disease cases), assuming that there are also strong daily variations in air pollution.

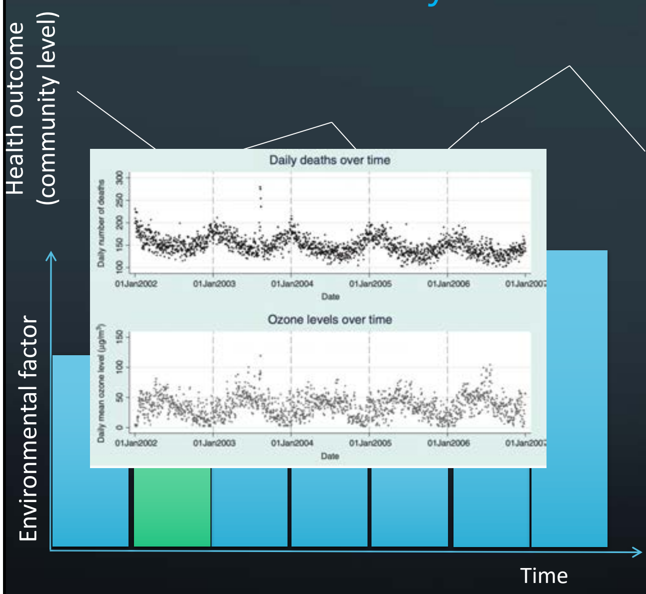
36

C. Effects (2): A new microscope - Time series analyses of air pollution effects



37

Time-series analyses



Unit of analysis:
The community (city, district…) considered at a given time point (e.g., day) throughout a study period (typically, several years)

Health outcome: Assessed at the community level

Exposure assessment:
Aggregated at the community level (e.g., central monitoring station)

Analysis:
Regression analysis of the association of daily counts of the health outcome as a function of exposure 0, 1, a few days before, adjusted for relevant confounders in a regression (e.g., *Poisson*) model.

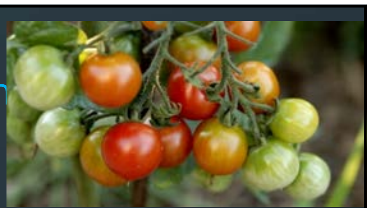
Confounding bias:
Only factors with short-term variations can induce confounding bias. Their effect can be corrected if information on the variation of their impact over time is available (e.g., deaths by flu). Mid and long-term trends are usually corrected for using a flexible coding.

Only **short-term effects** (hour to week) can be efficiently characterized. *Only the effect of the average change in exposure across the study population is seen*

See Baskharan, *Int J Epidemiol*, 2013 for a review

38

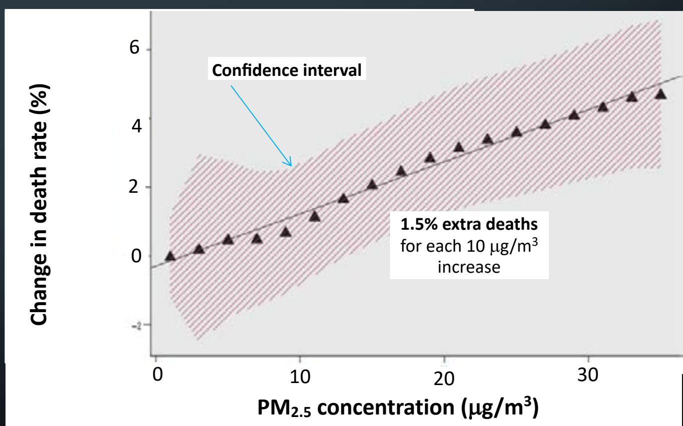
Particulate matter and mortality: a tim



J. Schwartz, Harvard

Table 1. Mean daily deaths in six U.S. cities and mean concentrations of $PM_{2.5}$ overall, and from the three source categories showing evidence of an association with daily deaths in Laden et al. (*8*).

City	Deaths	$PM_{2.5}$ (μg/m³)	Traffic (μg/m³)	Coal (μg/m³)	Residual oil (μg/m³)	Dates (month/year)
Boston	59	16.5	4.8	8.3	0.5	5/79–1/86
Knoxville	12	21.1	4.4	6.8	—	1/80–12/87
St. Louis	55	19.2	2.9	5.6	—	9/79–1/87
Steubenville	3	30.5	1.5	19.2	0.9	4/79–9/87
Madison	11	11.3	3.1	4.9	—	3/79–12/97
Topeka	3	12.2	2.1	7.0	—	9/79–10/88

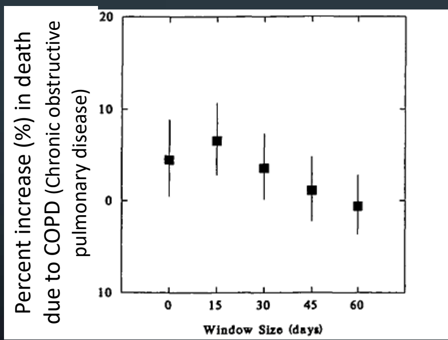


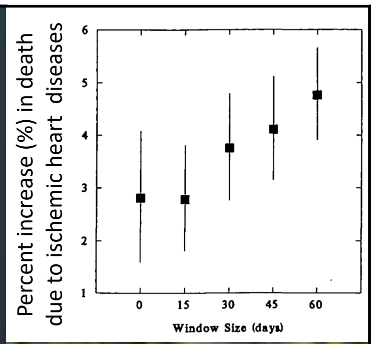
(Schwartz, *EHP*, 2002)

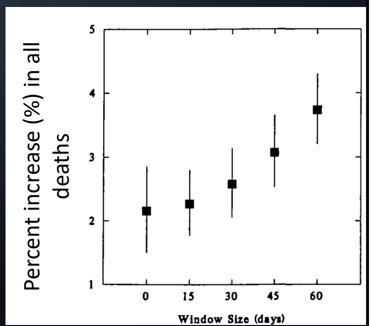
39

Tackling the « harvesting » issue (1):

Increase in mortality (%) associated with a 10 µg/m^3 increase in $PM_{2.5}$ averaged over various durations (0 to 60 days)







For deaths due to other causes than BPCO, the mid-term effect appears to be larger than the short-term effect of PM, which is not in favour of a strong harvesting effect for these causes of death.

(Schwartz, *Am J Epid*, 2000)

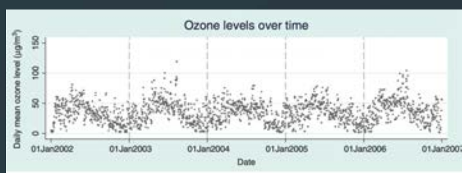
40

Time
(short and long term)

Exposure

Behaviours

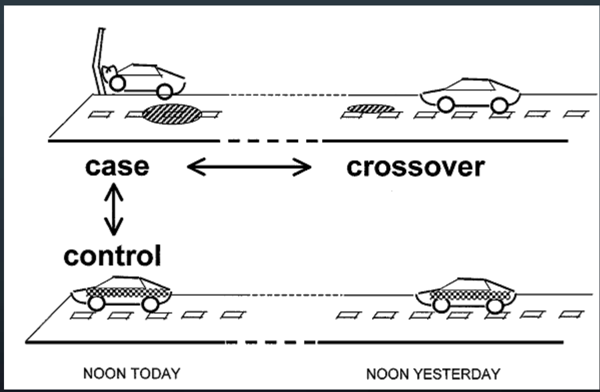
Space



42

Methodological issue

The case-crossover design: a within-subject comparison to study short-term effects of exposures



(Maclure, *Annu Rev Pub Health*, 2000)

43

Exposure to traffic and myocardial infarction (MI): a case-crossover analysis

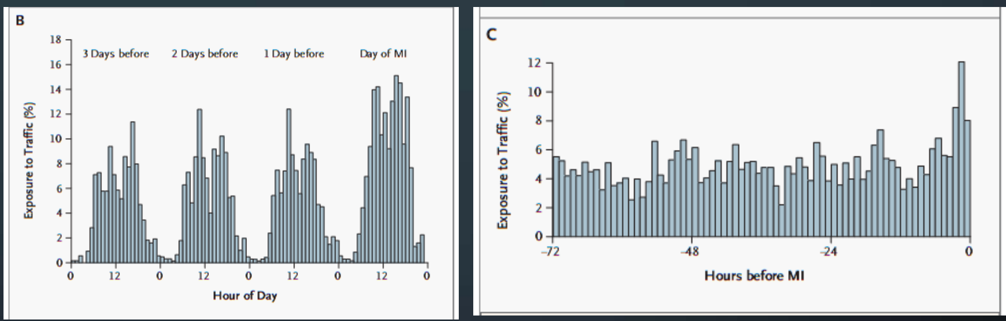


Figure 1. The Onset of 691 Nonfatal Myocardial Infarctions (MI) in Relation to Exposure to Traffic, According to the Amount of Time Spent in Traffic, February 1999 to July 2001, in the Region of Augsburg, Germany.
Panel A shows the distribution of times of onset of the myocardial infarctions over the day of the event, Panel B the time subjects spent in traffic on the day of the event and during the three days before it, and Panel C the time spent in traffic during the 72 hours preceding the onset of the myocardial infarction. The percentages are the proportions of subjects with exposure during the hour in question. Data are from the KORA Myocardial Infarction Registry.

(Peters, *NEJM*, 2004)

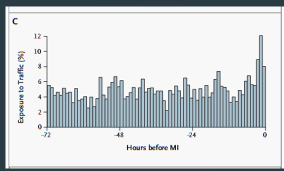
44

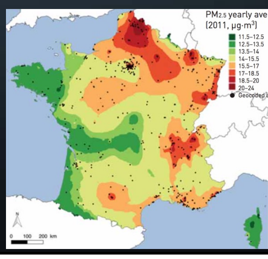
Time
(short and long term)

Exposure

Behaviours

Space

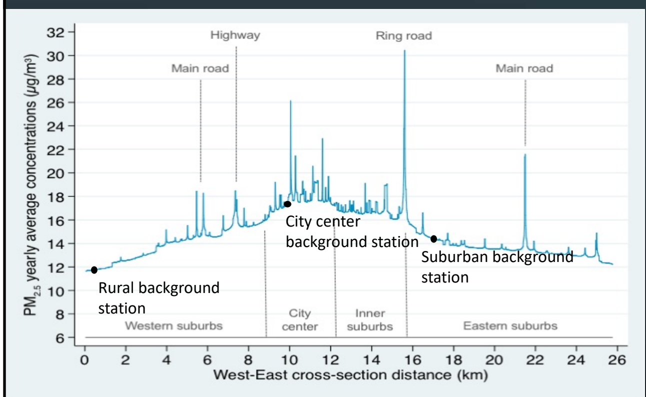


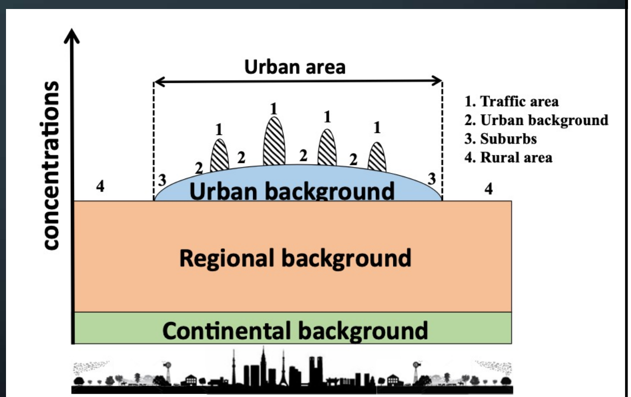


If one wants to study long-term effects of exposure, one needs to average exposure over time.
The main easily accessible source of variability in exposure is **space**.

45

Making use of spatial exposure contrasts

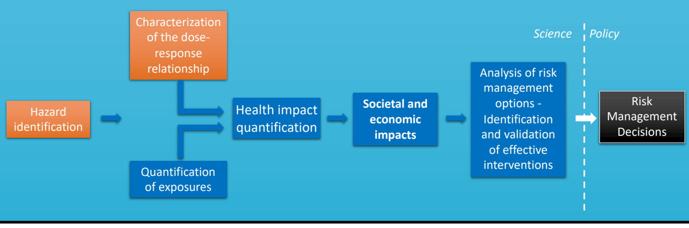




(Adapted from Morelli, *Env Int*, 2019)

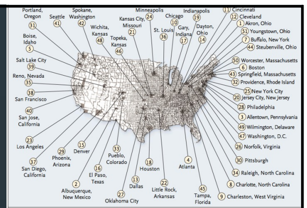
46

D. Effects (3): Cohorts - making long-term effects visible



47

PM2.5 level and life expectancy in US cities: an analysis at the city level



Life expectancy in 1978-82 against mean $PM_{2.5}$ level at the same period, 51 US metropolitan areas

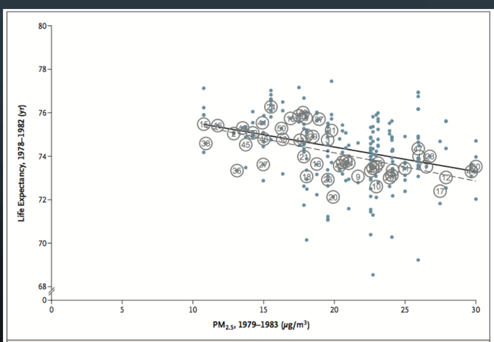
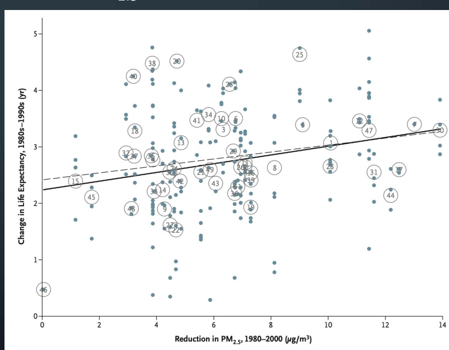


Figure 2. Cross-Sectional Life Expectancies for 1978–1982, Plotted against $PM_{2.5}$ Concentrations for 1979–1983.

Change in life expectancy from 1980 to 2000 against *change* in mean $PM_{2.5}$ level from 1980 to 2000

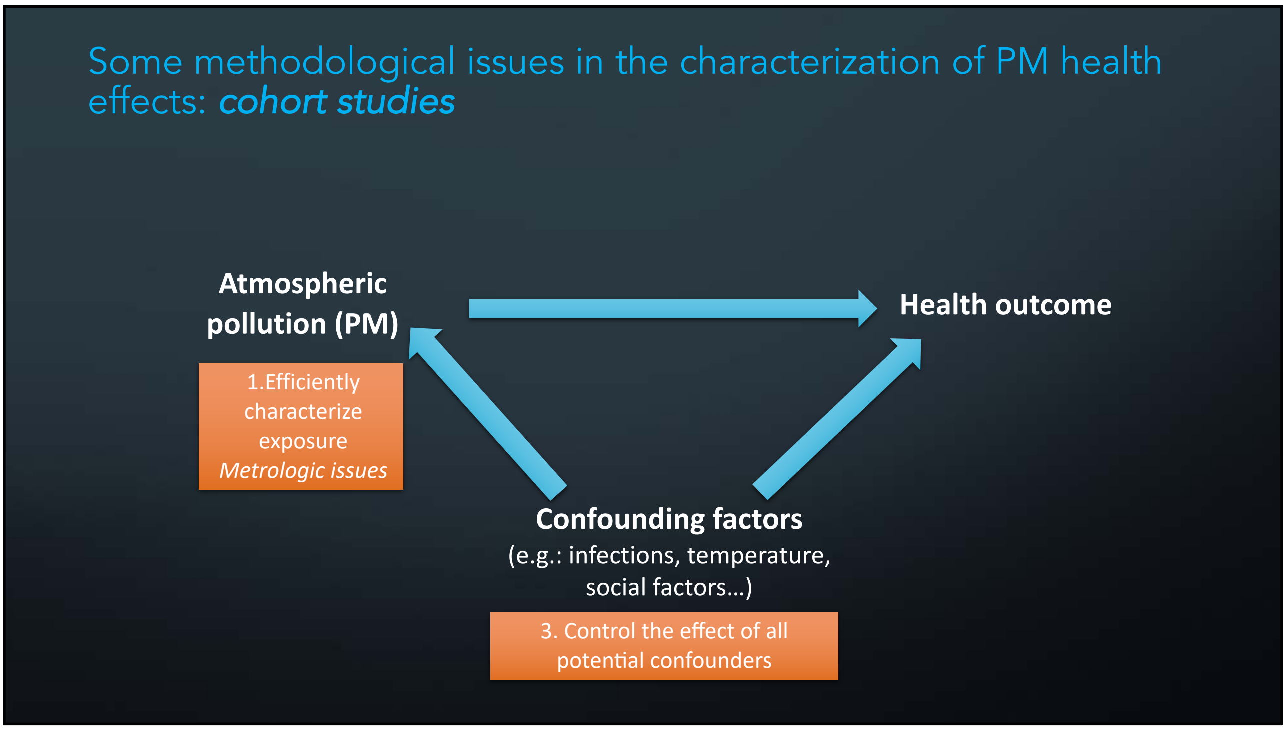


Slope: life expectancy change of 0.6 year for each 10 µg/m^3 decrease in $PM_{2.5}$

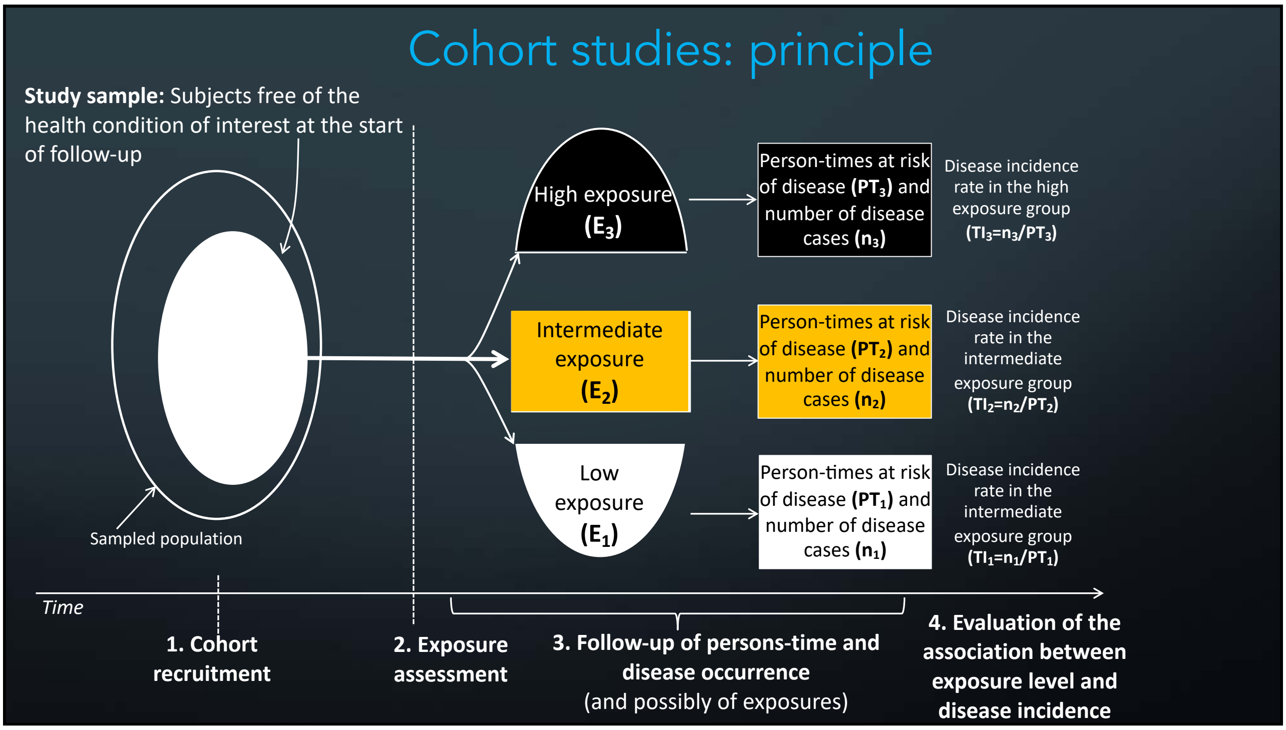
Adjusted for change in income, population, lung-cancer mortality rate, urban residence, black and Hispanic population rates…

(Arden Pope et al., *NEJM*, 2009)

48


Some methodological issues in the characterization of PM health effects: *cohort studies*
Atmospheric pollution (PM)
Health outcome
1.Efficiently characterize exposure
Metrologic issues
Confounding factors
(e.g.: infections, temperature, social factors…)
3. Control the effect of all potential confounders

49


Cohort studies: principle
Study sample: Subjects free of the health condition of interest at the start of follow-up
Sampled population
High exposure
(E_3)
Intermediate exposure
(E_2)
Low exposure
(E_1)
Person-times at risk of disease (PT_3) and number of disease cases (n_3)
Person-times at risk of disease (PT_2) and number of disease cases (n_2)
Person-times at risk of disease (PT_1) and number of disease cases (n_1)
Disease incidence rate in the high exposure group
($TI_3=n_3/PT_3$)
Disease incidence rate in the intermediate exposure group
($TI_2=n_2/PT_2$)
Disease incidence rate in the intermediate exposure group
($TI_1=n_1/PT_1$)
Time
1. Cohort recruitment
2. Exposure assessment
3. Follow-up of persons-time and disease occurrence
(and possibly of exposures)
4. Evaluation of the association between exposure level and disease incidence

50

Methodological issue

Methodological issue: Assessment of environmental exposures in human studies

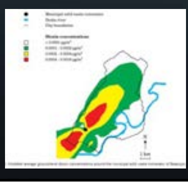
Sources (emissions) → Environmental levels → Personal exposures → Internal dose → Dose to the target organs → Effects

Sources (emissions): Data on sources (e.g. localisation of factories, roads)

Emission cadastres

Environmental levels: Dosimeter

Environmental model or measurements



Personal exposures: Questionnaire X Environmental model or data

Dosimeter

Job-exposure matrix (occupational setting)

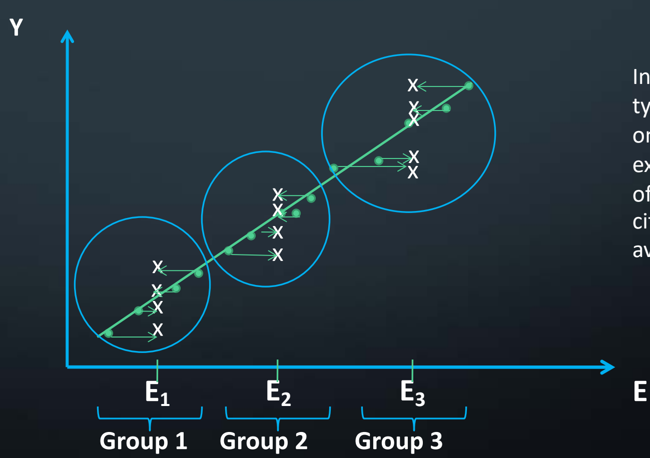
Internal dose: Exposure biomarker (biospecimen + biochemical assay)

Dose to the target organs: Exposure (bio)marker X TD-TK modelling

51

Illustration of Berkson-type error

- • Real exposure (unknown)
- — Real dose-response relation (unknown)
- x Measured exposure (with Berkson-type error)

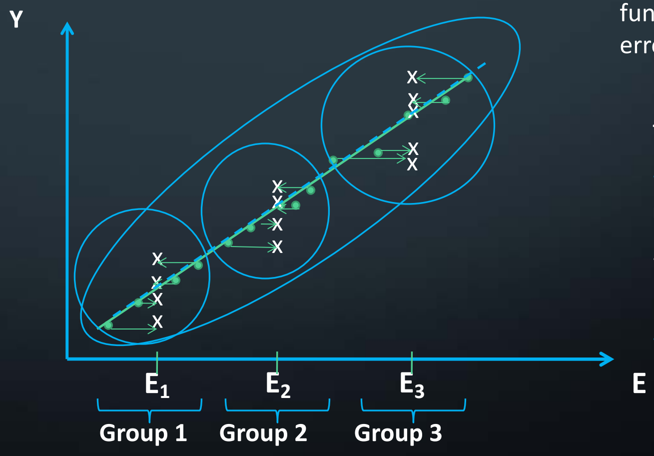


In the case of Berkson-type error on exposure E, one typically estimates exposure of all subjects of a given group (e.g., a city) by the group average.

52

Illustration of Berkson-type error

- Real exposure (unknown)
- Real dose-response relation (unknown)
- x Measured exposure (with Berkson-type error)
- - - - Estimated dose-response function (with Berkson-type error)



Consequences of Berkson-type error:

-No bias in the dose-response relation

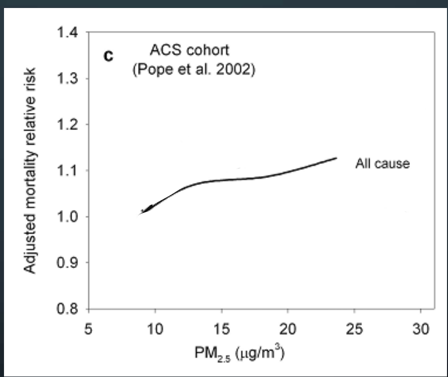
-Increased random variation in the dose-response slope

-Decreased statistical power

53

Cohort studies of air pollution effects: *results* (relative risks of death)

American Cancer Society (ACS) cohort
N=319,000 subjects



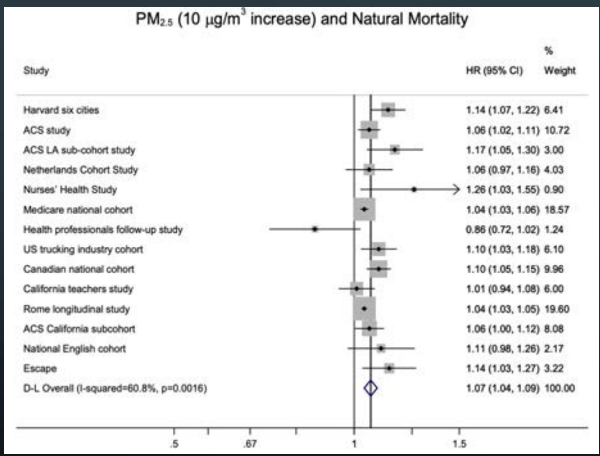
For each increase by 10 µg/m^3 in $PM_{2.5}$ average exposure:
- 6% increase in all-cause mortality risk
- 9% increase in risk of death by cardiovascular cause

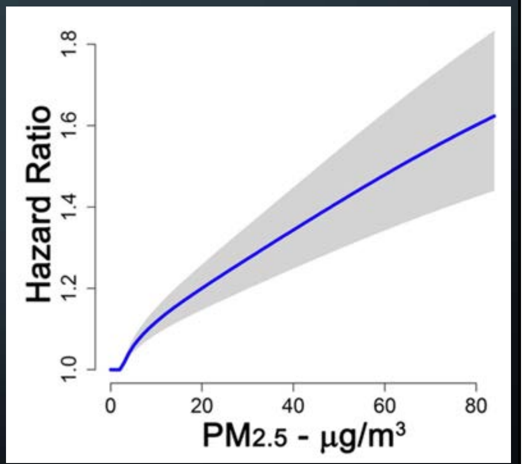
Adjusted for age, sex, race, smoking, alcohol consumption, body mass index, occupational exposure and diet

(Pope, *JAMA*, 2002)

54

PM$_{2.5}$ and all-cause mortality: meta-analyses



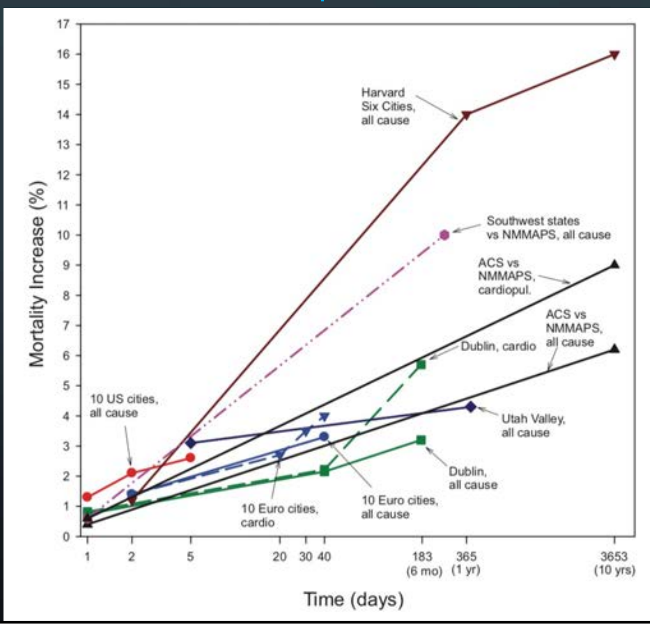


(WHO, 2014)

(Burnett, *PNAS* 2018)

55

How do estimates of short-term and long-term effects of PM exposure on mortality compare?

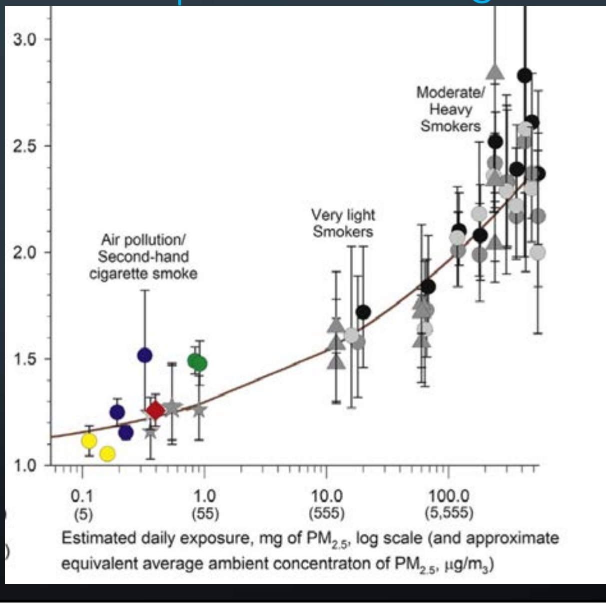


Estimates of percent change in mortality associated with an increment of 10 µg/m^3 in PM$_{2.5}$ or 20 µg/m^3 in PM$_{10}$ or black smoke for different time scales

(Brook, *Circulation*, 2010)

56

Relative risks of cardiopulmonary mortality and long-term exposure to PM from air pollution and cigarette smoke



Colour estimates correspond to studies of air pollution effects, gray symbols to studies of tobacco effects.

(Pope, *Env Res*, 2020)

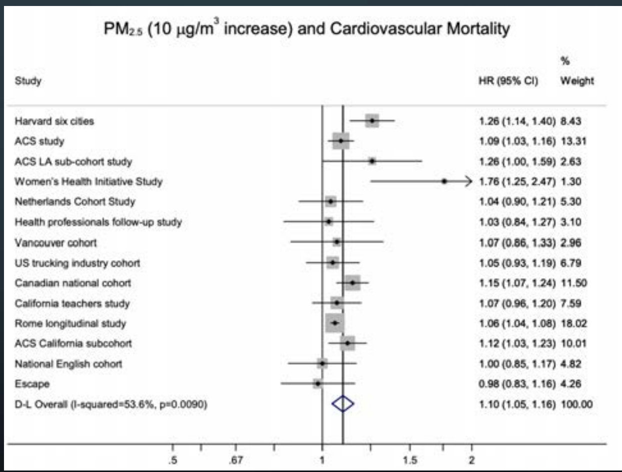
57

E. Cardiovascular and respiratory effects of air pollution exposure

58

Cohort studies of air pollution effects: *Relative risks of cardiovascular morbidity and mortality*

Individual scale (cohorts)

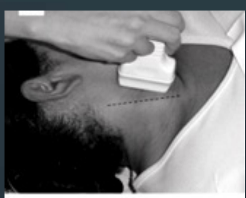


(WHO, 2014)

59

PM exposure and *intima media* thickness

Individual scale (cohorts)



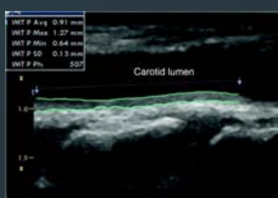


Table 2. CIMT percent difference associated with a 1-IQR increase (0.26 µg/m³) in average exposure to black carbon during the year before the first CIMT measurement.

Modeling approach	Percent difference (95% CI)	No. of participants	No. of observations
Model			
Parsimonious model (model 1)[a]	0.9 (0.2, 1.5)	380	977
Fully adjusted model (model 2)[b]	1.1 (0.4, 1.7)	378	968

(Wilker, *EHP*, 2013)

60

Cohort studies of air pollution effects: *Effets on intermediary markers of cardiovascular health*

Individual scale (cohorts)

Primary Sources	Exposure Type, Place, Subjects	PM Associations
Peters et al. 1997[311] Peters et at. 2001[312]	1985 pollution episode, Augsburg, Germany, adults	Increased blood plasma viscosity and CRP
Seaton et al. 1999[313]	Estimated personal exposure to PM_{10}, Belfast and Edinburgh, United Kingdom, elderly adults	Increased CRP, reduced red blood cells
Tan et al. 2000[314]	Elevated PM_{10} levels during forest fire episodes, Singapore, 19–24-yr-old healthy men	Elevated PMN band cells
Salvi et al. 1999[315] Salvi et al. 2000[316]	Diesel exhaust, exposure chambers, healthy nonsmoking young adults	Elevated neutrophils, lymphocytes, mast cells, endothelial adhesion molecules, IL-8, GRO-α in airway lavage, bronchial tissue, and/or bronchial epithelium; also increased neutrophils and platelets in peripheral blood.
Pekkanen et al. 2000[317]	Ambient air pollution including PM_{10}, London, male and female office workers	Higher plasma fibrinogen concentrations
Ghio et al. 2000[318] Harder et al. 2001[319] Gong et al. 2003[320] Ghio et al. 2003[321] Huang et al. 2003[322] Ghio and Huang 2004[103]	Exposure to concentrated ambient particles (CAPs) in exposure chambers, volunteer adults	Somewhat mixed results, but small increases in neutrophils and fibrinogen consistent with mild inflammatory responses to PM.
Sorensen et al. 2003[323]	Personal monitoring of $PM_{2.5}$ and carbon black, Copenhagen, young adults	Small increases in markers of oxidative stress
Adamkiewicz et al. 2003[324]	Ambient $PM_{2.5}$, Steubenville, OH, elderly adults	Increase in airway inflammation as measured by exhaled nitric oxide
Pope et al. 2004[305]	Ambient $PM_{2.5}$, Utah, elderly adults	Elevated CRP
Ruckerl et al. 2006[325]	Ambient PM, Erfurt, Germany, 57 males with CHD	Elevated CRP

CHD = coronary heart disease; CRP = C-reactive protein; PMN = polymorphonuclear leukocytes.

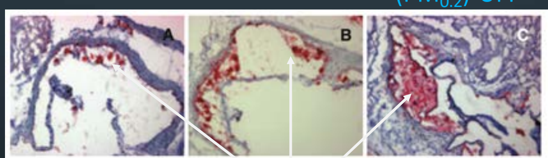
(Pope, *JAMA*, 2002)

61

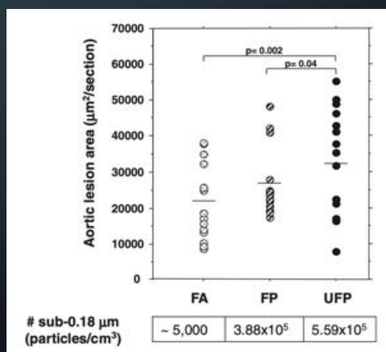
Particulate matter and atherosclerosis in an animal model

Individual scale (in vivo toxicology)

Filtered air (FA) — $PM_{2.5}$ (FP) — Ultrafine particles ($PM_{0.2}$)-UFP



Atherosclerotic lesions

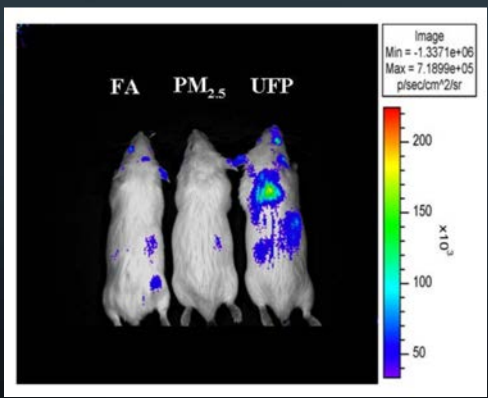


(Araujo, *Circulation Res*, 2008)

62

PM generate oxidative stress

Individual scale (in vivo toxicology)

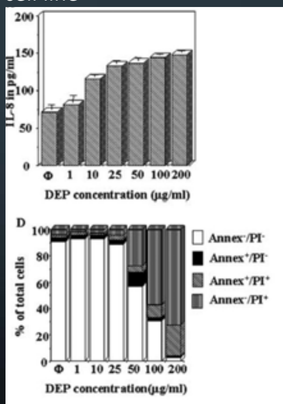


(Araujo, *Part Fib Tox*, 2009)

Cellular scale (in vitro toxicology)

Effects of Diesel exhaust particles (DEP) on a THP-1 macrophage cell line

Interleukin 8



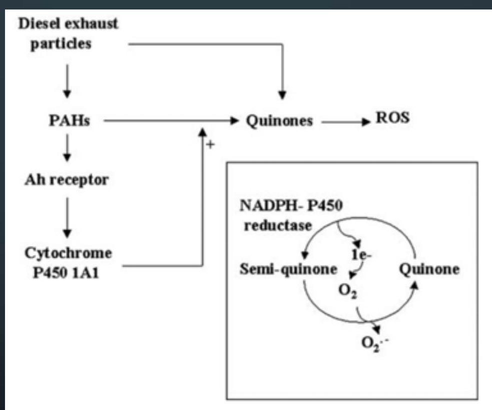
DEP: Diesel exhaust particles

HO-1: Heme oxidase expression

(Li N, *Clin Immun*, 2003)

63

PM generate oxidative stress: a possible cellular mechanism implying PAHs (Polycyclic Aromatic Hydrocarbons)

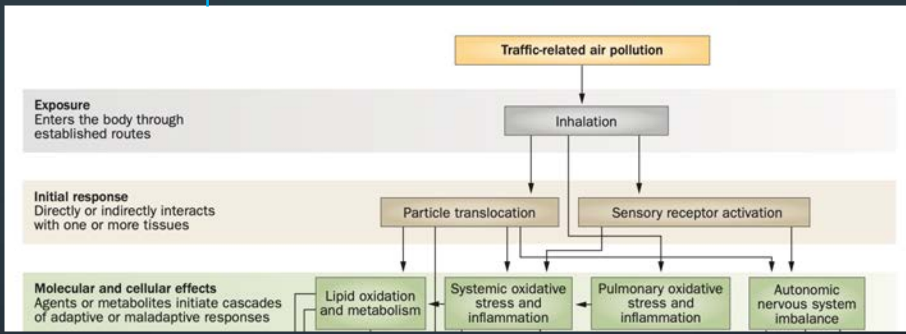


ROS: Reactive oxygen species

(Li N, *Clin Immun*, 2003)

64

Mechanisms of air pollution effects on cardiovascular diseases



(Cosselman, *Nat Rev Card*, 2015)

65

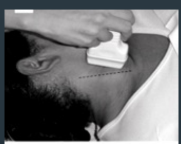
PM and ischemic diseases: Body of evidence from populations to particles

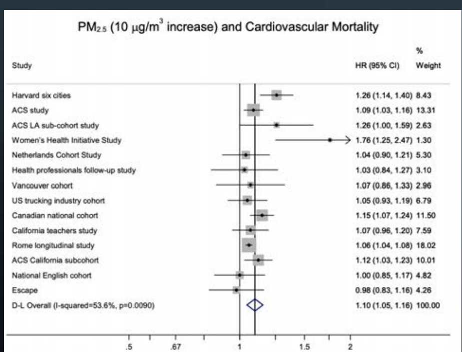
Individual scale (cohorts)

Individual scale (in vivo toxicology)

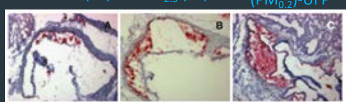
Cellular scale (in vitro toxicology)

Molecular scale





Filtered air (FA) $PM_{2.5}$ (FP) Ultrafine particles ($PM_{0.2}$)-UFP

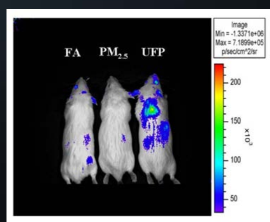


Lipid metabolism

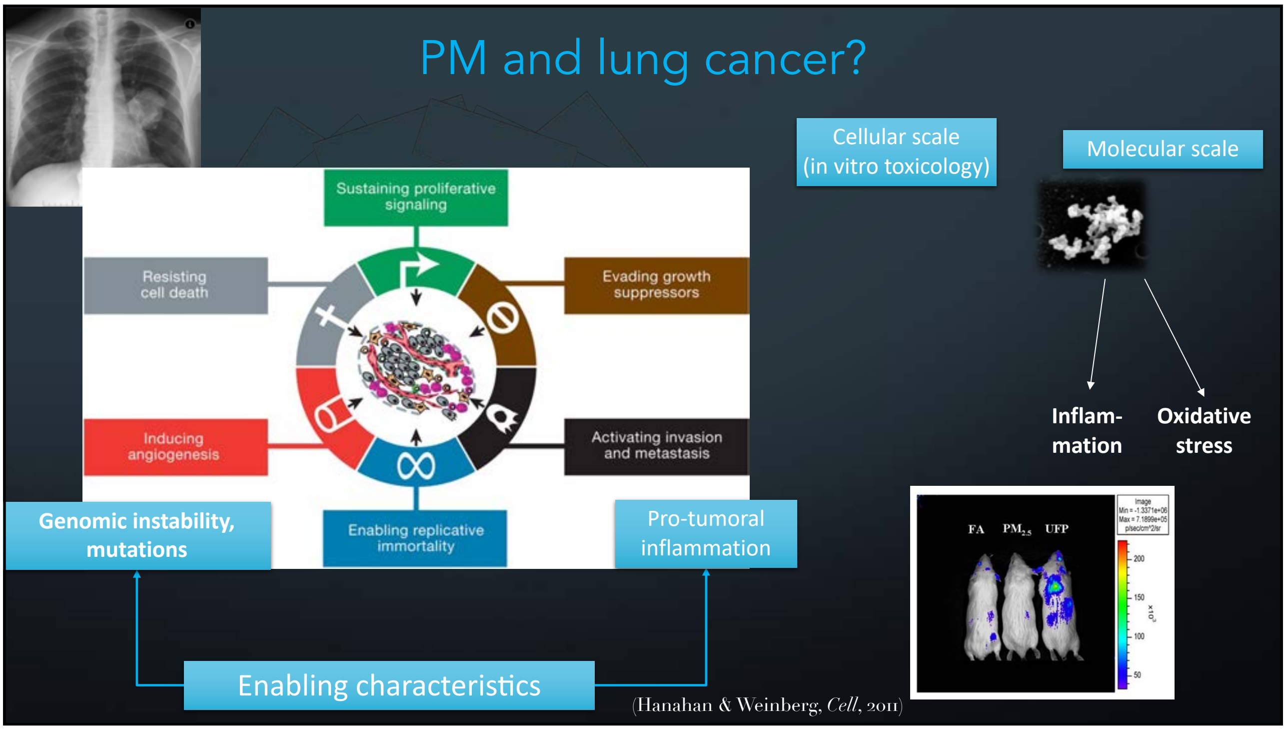
Autonomic nervous system imbalance

Inflam-mation

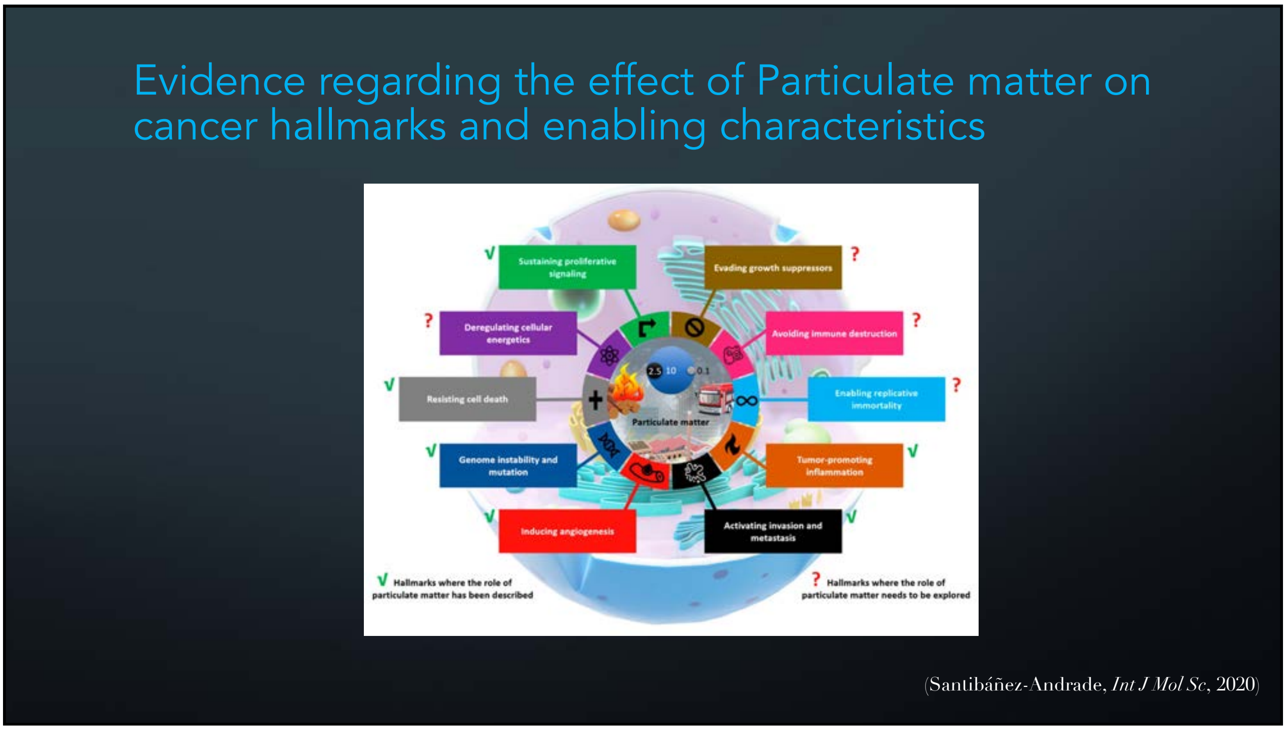
Oxidative stress



66


PM and lung cancer?
Cellular scale
(in vitro toxicology)
Molecular scale
Sustaining proliferative signaling
Resisting cell death
Evading growth suppressors
Inducing angiogenesis
Activating invasion and metastasis
Enabling replicative immortality
Genomic instability, mutations
Pro-tumoral inflammation
Enabling characteristics
Inflam-
mation
Oxidative stress
FA
PM2.5
UFP
(Hanahan & Weinberg, Cell, 2011)

68


Evidence regarding the effect of Particulate matter on cancer hallmarks and enabling characteristics
Sustaining proliferative signaling
Evading growth suppressors
Deregulating cellular energetics
Avoiding immune destruction
Resisting cell death
Enabling replicative immortality
Genome instability and mutation
Tumor-promoting inflammation
Inducing angiogenesis
Activating invasion and metastasis
Particulate matter
Hallmarks where the role of particulate matter has been described
Hallmarks where the role of particulate matter needs to be explored
(Santibáñez-Andrade, Int J Mol Sc, 2020)

69

Evidence regarding the effect of Particulate matter on cancer-relevant endpoints

End-point	Humans	Experimental animals	Mammalian cells	Plants	Bacteria	Acellular
Mutations	(+)[a]	+	+	+	+	–[b]
Cytogenetic damage (CAs, MN, SCEs)	+	+	+	+	NA	NA
Stable DNA adducts	+	+	+	NE	NE	+
DNA strand breaks	+	+/–[c]	+	NE	NE	+
Oxidatively damaged DNA	+	+/–[d]	+	NE	NE	+
Oxidative stress and inflammation	+	+	+	NE	NE	+
Cell transformation	NA	NA	+	NA	NA	NA
Epigenetic changes	+	+	NE	NE	NE	NA

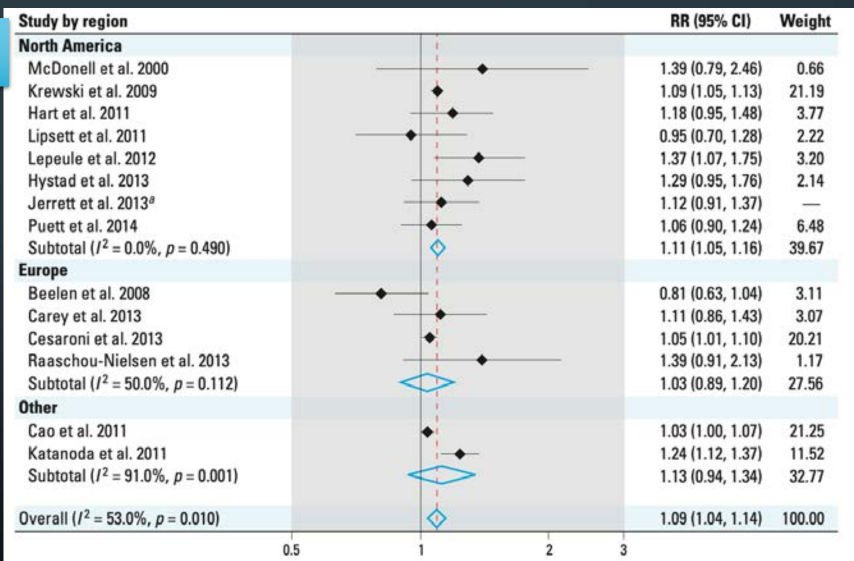
[a] Limited information available.
[b] Not applicable.
[c] Few studies, conflicting results. See Table 4.10, Section 4.2.3c.
[d] Few studies, conflicting results. See Supplemental Table S14 (available online), Section 4.2.3e.
+, positive; –, negative; CAs, chromosomal aberration; MN, micronuclei; NA, not available; NE, not evaluated; SCEs, sister chromatid exchanges.

(IARC; Loomis, *Lancet Oncol*, 2013)

70

$PM_{2.5}$ and lung cancer incidence – meta-analysis

Individual scale (cohorts)



(Hamra, *EHP*, 2014)

72

Sensitivity analyses

Exposure	RR (95% CI)	I^2 (p-value)	Homogeneity test[a]	Studies included (by ID)[b]
$PM_{2.5}$				
Full meta-estimate	1.09 (1.04, 1.14)	56.4% (0.007)		All
Continent				
North America	1.11 (1.05, 1.16)	6.5% (0.378)		2, 4, 6, 7, 8, 9, 10
Europe	1.03 (0.89, 1.20)	50.0% (0.112)		11, 12, 13, 15
Others	1.13 (0.94, 1.34)	91.0% (0.001)	$p = 0.656$	16, 17
Exposure assessment method				
Fixed site monitor	1.12 (1.04, 1.21)	77.1% (0.002)		2, 4, 8, 16, 17
Other	1.06 (1.00, 1.13)	16.2% (0.298)	$p = 0.268$	5, 6, 7, 9, 10, 11, 12, 13, 15
Smoking status				
Never	1.18 (1.00, 1.39)	0.0% (0.928)		3, 7, 8, 9, 10, 15
Former	1.44 (1.04, 2.01)	66.3% (0.031)		3, 8, 9, 15
Current	1.06 (0.97, 1.15)	0.0% (0.544)	$p = 0.197$	3, 8, 9, 15
Confounder adjustment				
Smoking status	1.10 (1.04, 1.17)	61.4% (0.004)		2, 4, 7, 8, 9, 10, 11, 12, 15, 16, 17
SES/income	1.04 (0.96, 1.12)	24.2% (0.252)		5, 7, 10, 11, 13, 15
Education	1.07 (1.03, 1.11)	37.7% (0.117)		4, 8, 9, 10, 12, 13, 15, 16,
Occupation	1.08 (1.05, 1.11)	0.4% (0.420)		4, 6, 7, 9, 10, 13, 15

(Hamra, *EHP*, 2014)

73

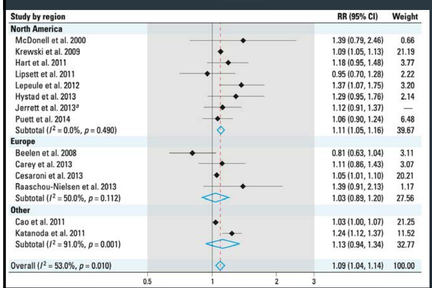
PM and lung cancer:
Body of evidence from populations to particles

Individual scale (cohorts)

Individual scale (in vivo toxicology)

Cellular scale (in vitro toxicology)

Molecular scale



(Hamra, *EHP*, 2014)

(Santibáñez-Andrade, *Int J Mol Sc*, 2020)

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Oxidatively damaged DNA	+	+/–[d]	+	NE	NE	+
Oxidative stress and inflammation	+	+	+	NE	NE	+
Cell transformation	NA	NA	+	NA	NA	NA
Epigenetic changes	+	+	NE	NE	NE	NA

[a] Limited information available.
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+, positive; –, negative; CAs, chromosomal aberration; MN, micronuclei; NA, not available; NE, not evaluated; SCEs, sister chromatid exchanges.

Atmospheric pollution and fine particulate matter are classified as certain carcinogens by IARC
(Loomis, *Lancet Oncol*, 2013)

74

Atmospheric pollution and respiratory health - overview

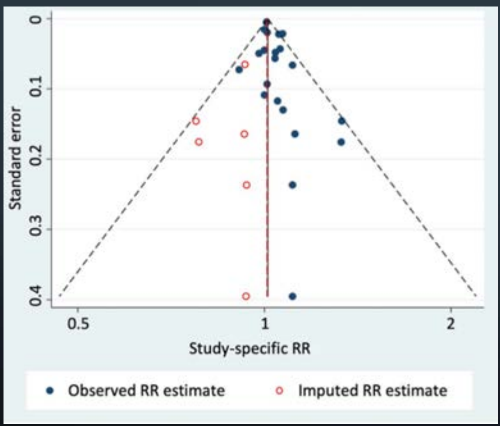
Endpoint	Population	Evidence	References
Lung cancer	Adults	Certain	(Loomis, *Lancet Oncol*, 2013)
Asthma incidence	Children	Very likely/certain	(Khreis, *Env Int*, 2017)
Asthma incidence	Adults	Likely	(Jacquemin, *EHP*, 2015)
Asthma attacks/symptoms	Children and adults	Certain	(Slaughter, *Ann Allerg Asthm Immun*, 2003)
COPD incidence	Adults	Likely	(Park, *Env Res*, 2021)
Lung function (FEV)	Children and adults	Very likely	(Gauderman, *NEJM*, 2004; Benmerad, *Eur Resp J*, 2017; Guo, *Lancet Plan Health*, 2018)
Hospitalization for acute bronchiolitis	Children <2 years	Likely	(Leung, *Thorax*, 2021)
Respiratory mortality	Adults	Certain	(WHO, 2014)

Various sources; thanks to Drs. V Siroux (Inserm) and I. Pin (CHU Grenoble)

76

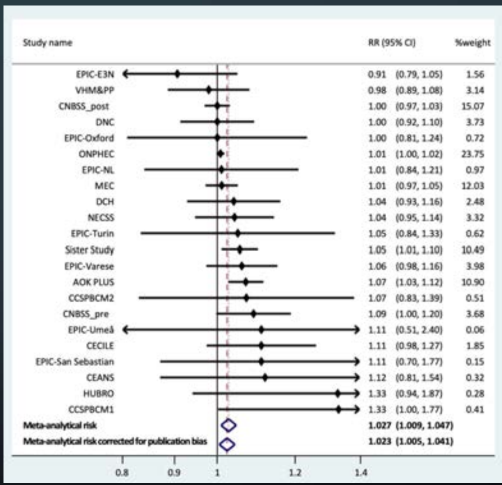
Atmospheric pollution and breast cancer

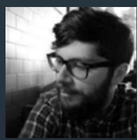
A meta-analysis



Trim-and-fill analysis (correction for possible publication bias)

Relative risk (RR) of breast cancer associated with a 10 µg/m^3 increase in NO_2 level





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Lille Univ.

(Gabet, *Env Health Perspect*, 2021)

77