The relations between human health and the environment in the Anthropocene

Course overview

COLLÈGE DE FRANCE 1530

#1 – 31 March 2022

Inaugural lecture: Causes and external conditions of diseases and health

#2 - 6 April 2022

Lead: the oldest enemy of human health

Seminar: **Lead, legal poison: uses and regulations of toxic in the nineteenth century**
Pr. Judith Rainhorn, Université Paris-1 Panthéon-Sorbonne (Paris)

#3 - 13 April 2022

Fine particulate matter: effects on mortality and cardiovascular and respiratory morbidity

Seminar: Air pollution effects on the central nervous system
Pr. Marc Weisskopf, Cecil K. and Philip Drinker Professor of Environmental Epidemiology and Physiology, Harvard TH Chan School of Public Health (Boston)

#4 - 20 April 2022

Fine particulate matter: new metrics, recently identified targets

Seminar: The Human Sensor – Toxicology in Real People in the Real World
Pr. Ian Mudway, Imperial College London, MRC for Environment and Health (London)

#5 - 11 May 2022

'Legacy' endocrine disruptors: the convergence between basic biology, (eco)toxicology, clinical research and epidemiology

Seminar: Endocrine disruption and nuclear receptors: mechanisms and impact on health
Dr. William Bourget, Centre de Biologie Structurale, Univ Montpellier, CNRS, Inserm (Montpellier)

#6 - 18 May 2022

Contemporary endocrine disruptors: assessing the health effects of non-persistent compounds

Seminar: Bad cocktails – the evaluation of combined exposures
Pr. Andreas Kortenkamp, Brunell University (London)

#7 - 25 May 2022

The Exposome: Promises and Challenges of a New Concept

Seminar: On the Regulation of Chemicals

#8 – 1 June 2022

A Global Vision: The Burden of Disease Attributable to the Environment

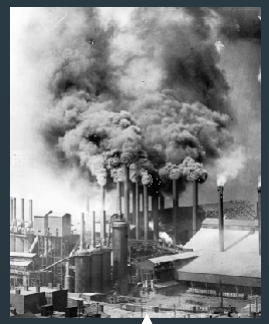
Seminar: Causality in public health research
Pr. Federica Russo, Philosophe des Sciences, Techniques, et Information, Université d'Amsterdam

#9 - 8 June 2022

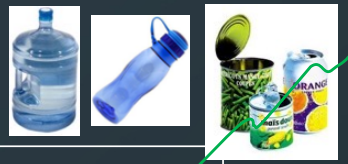
Climate change and human health

Seminar: on the Anthropocene concept
Dr. **Jean-Baptiste Fressoz**, CNRS et EHESS

The Anthropocene seen from the perspective of environmental pollution



Energy revolution
(1750-)



Chemical revolution
(1930s-)

Emissions or environmental level* *(arbitrary scales)*

DEHP (phthalate)

Organochlorine pesticides
(DDT…), PCB

Lead, other metals

Particulate Matter

Sulfur dioxide (SO_2)

CO_2

Organophosphate pesticides

Bisphenol A

Bisphenols S,F

DINCH…

1800 **1900** **1930** **1950** **1970** **2020**

Year

*Mostly rough qualitative estimates

(Slama, *CR Biol*, 2017)

Lead: the oldest enemy of human health

Le plomb : le plus vieil ennemi de la santé humaine

Rémy Slama

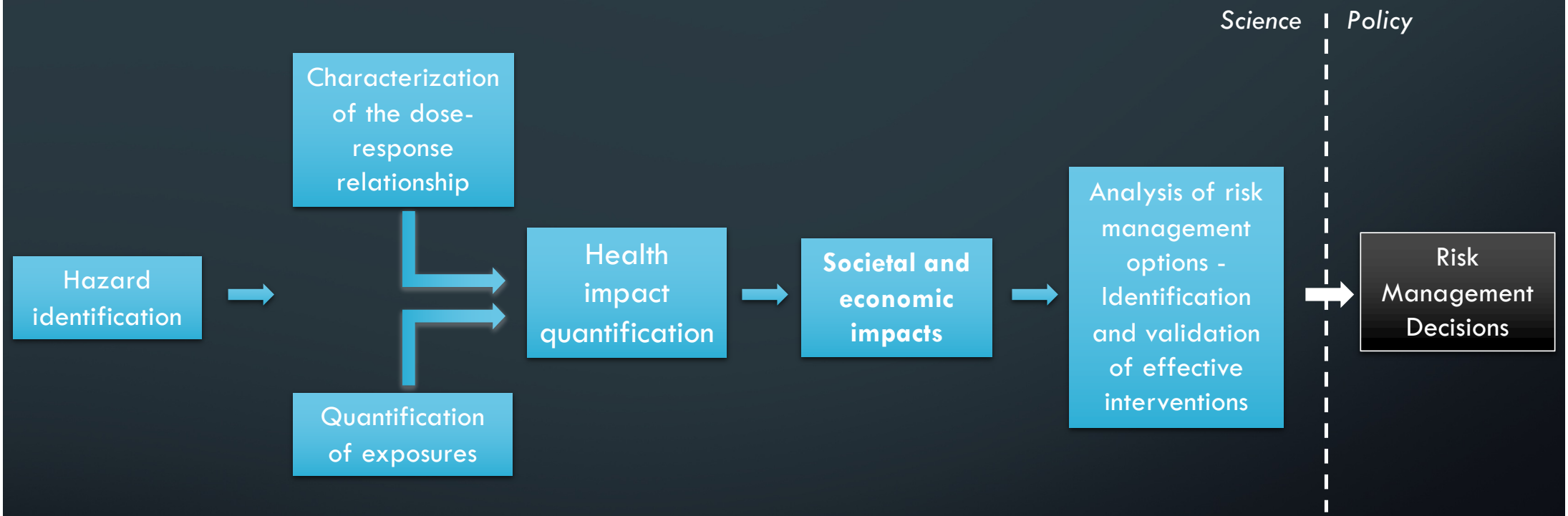
Collège de France & Inserm

The relations between human health and the environment in the Anthropocene

Lecture #2 – 6 April 2022

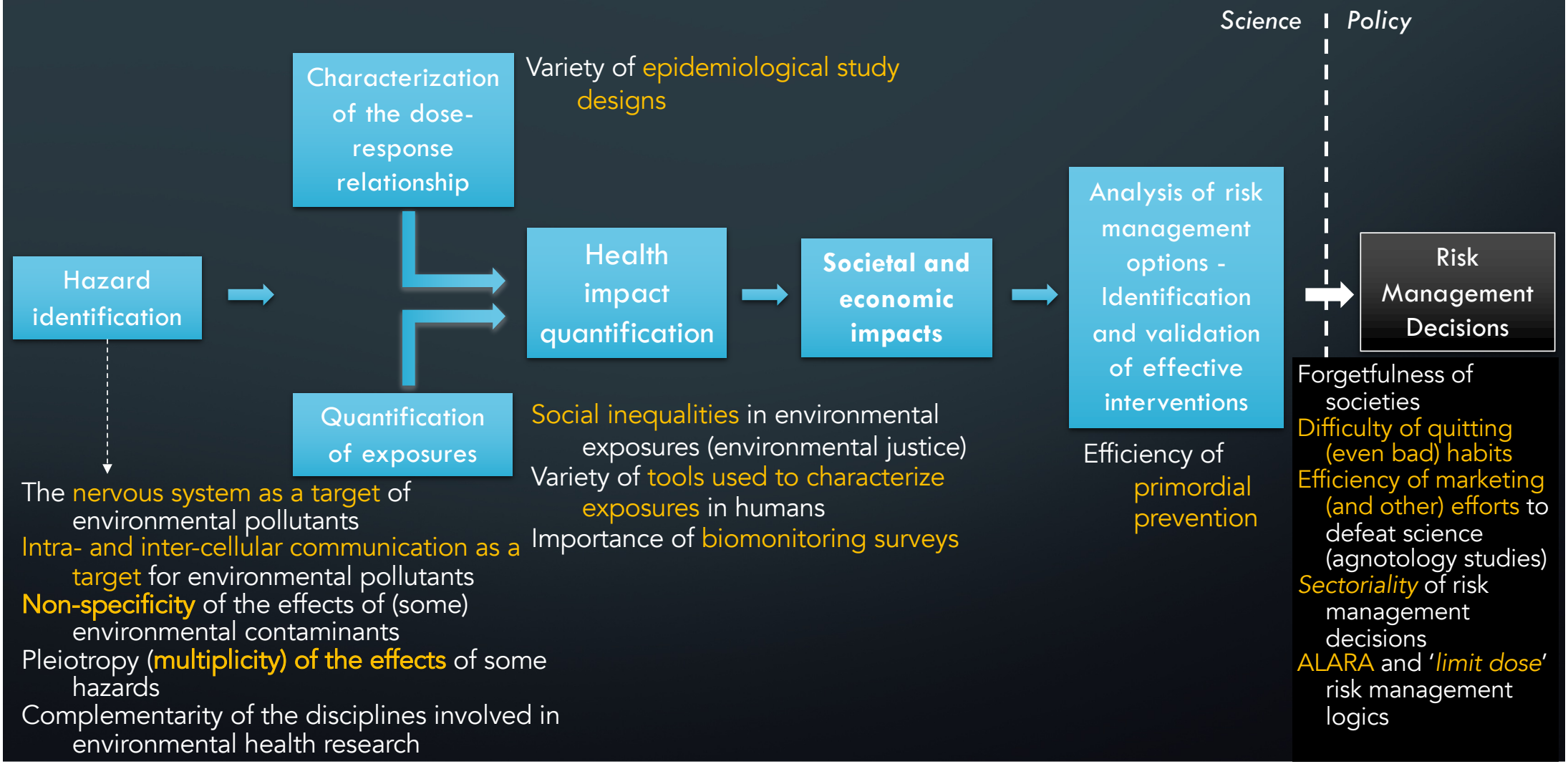
COLLÈGE DE FRANCE 1530

Environmental health research in support of public decision-making



Adapted from (Slama, *EHP*, 2016) and strongly adapted from the NTP Redbook (1983)

Some environmental health issues illustrated by **the case of lead**



Purpose of environmental health research

To characterize the health effects, positive and negative, of factors of external origin with respect to the body,

> whether physical, chemical, biological (including infectious), social or psychosocial in nature;

to identify the (biological, psychosocial, etc.) mechanisms underlying these effects;

to assess the corresponding societal impact,

and to identify interventions of all types allowing to alleviate these impacts and preserve or improve the health of current and future generations.

Lecture overview

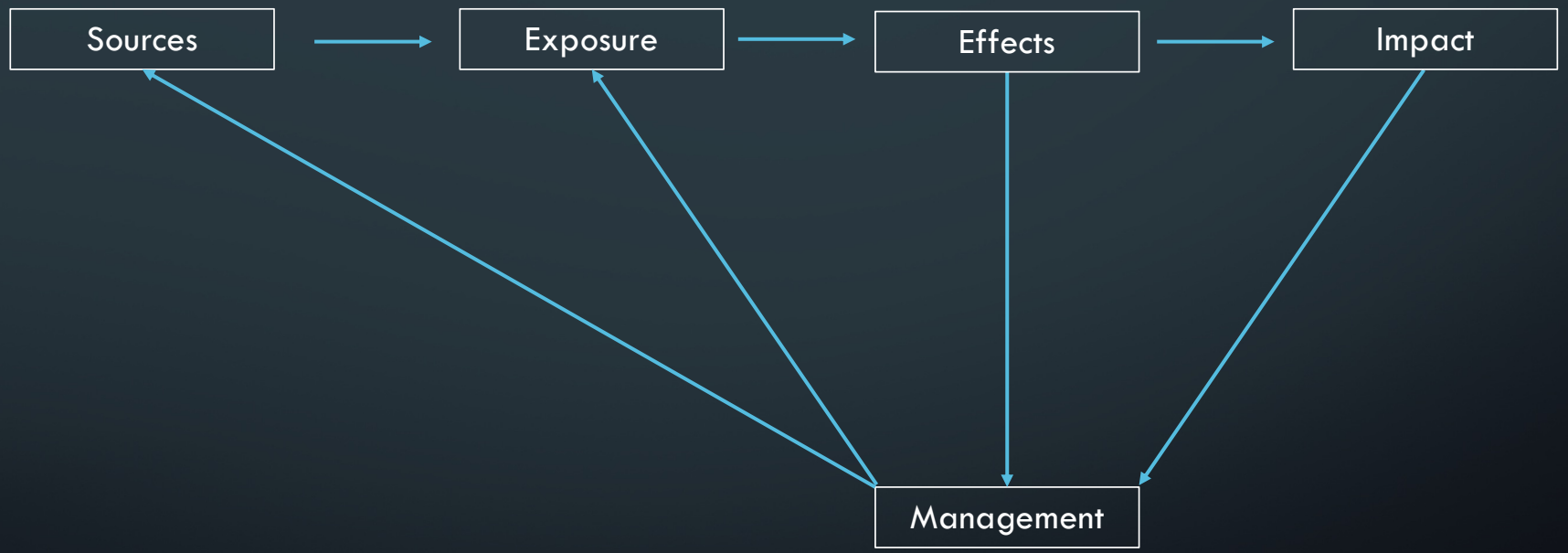
A. Nature and uses of various forms of lead — Sources

B. Human exposure to lead — Exposure

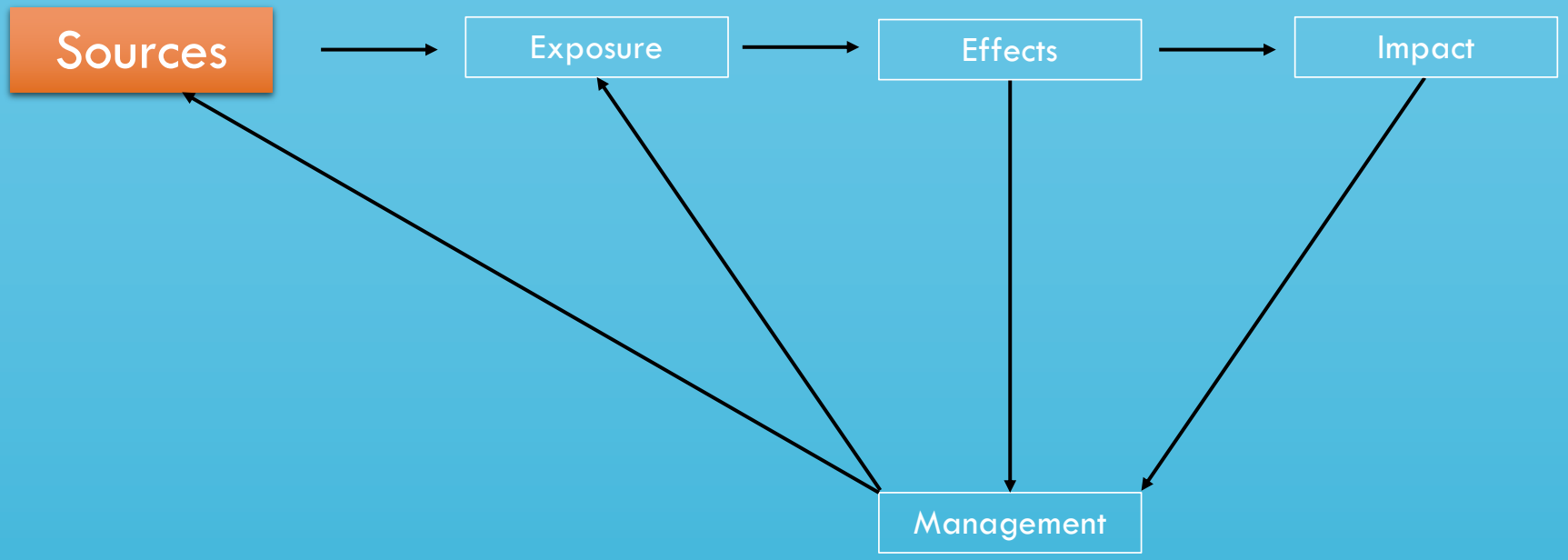
C. Some health effects of lead — Effects

D. The health and societal impact of lead today — Impact

E. Management of lead risk — Management


Sources
Exposure
Effects
Impact
Management

A. Nature and uses of various forms of lead



Physico-chemical properties of the metal lead

- Probably used for 40,000 years, certainly for 5500 years
- Low melting point (327°C)
- Malleability
- Ease of extraction
- Often present at the same time as silver (silver lead) and gold
- These can be separated by cupellation

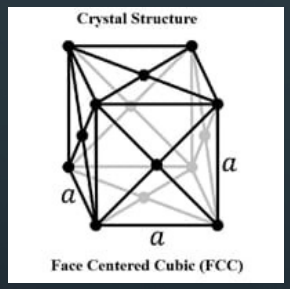
http://www.agab.be/orpaillage/extractionor/extraction.html

Some uses of lead throughout history

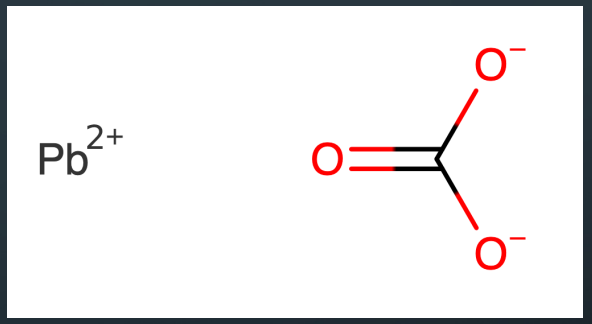
Musée des Confluences, Lyon Venenum exhibition (2017-2018)

Various forms of lead

Metallic form



Inorganic lead



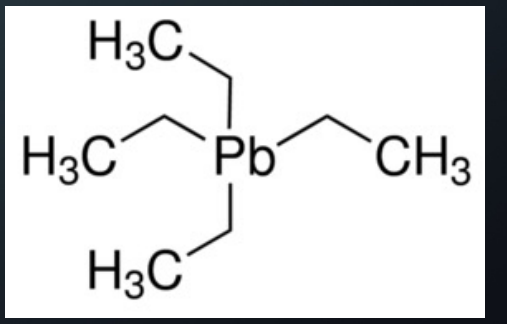
Lead carbonate (céruse): Pb CO_3

Lead bromide (II): $PbBr_2$

Lead acetate: $Pb(CH_3CO_2)_2$

Lead oxides: PbO (litharge), Pb_3O_4, PbO_2…

Organic lead



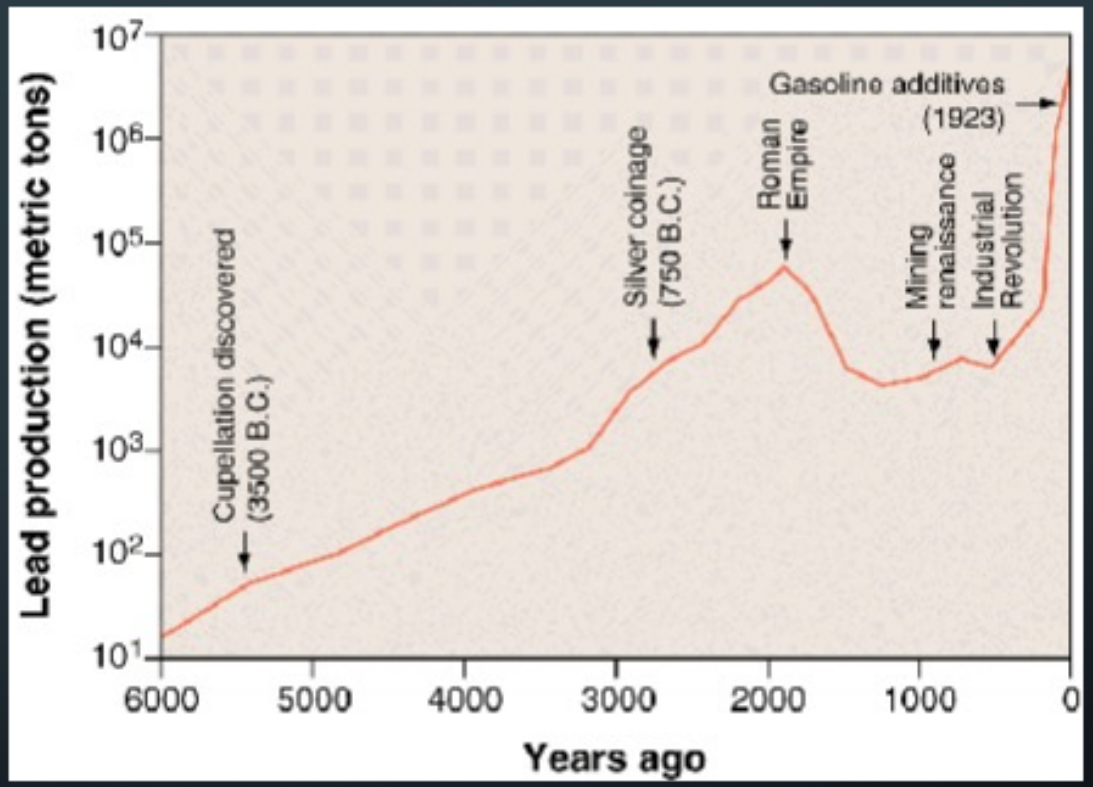
Tetraethyl lead $Pb(C_2H_5)_4$

Tetramethyl lead $Pb(CH_3)_4$

Some uses of lead throughout history

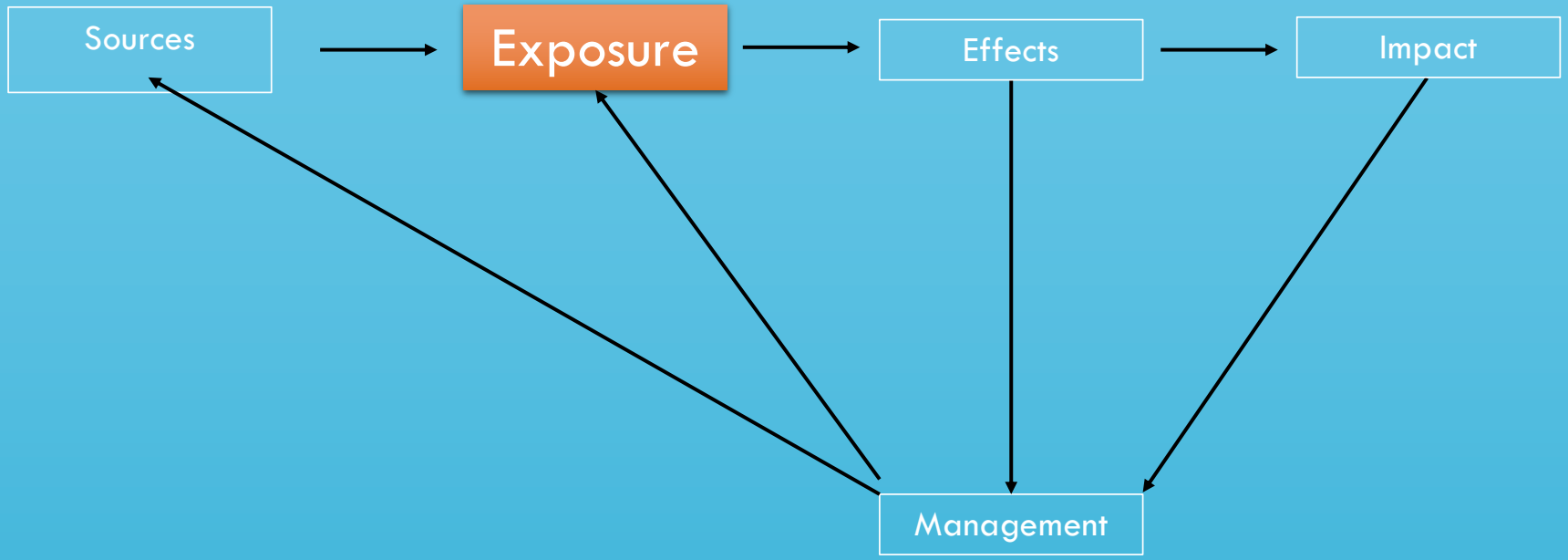
Period	Lead compound	Use/source
-3000 – 1900s	Metallic lead	Gold and silver mining
-2018 (USA, hair dyes)	Lead (di)acetate [$Pb(CH_3CO_2)_2$]	Wine additive/contaminant, sapa, sweetener, hair dye
-1000 – 1950?	Native lead	Tableware, consumer products, games
Antiquity-1900s	Lead carbonate (*ceruse*) [$(PbCO_3)_2 \cdot Pb(OH)_2$]	Cosmetics
0-1960 (France)	Native lead	Water pipes
1500-1950?	Native lead	Printing (characters)
1750-2019 (EU)	Lead carbonate (*ceruse*), lead oxide (*minium*, Pb_3O_4), lead chromate…	Paint
1923-2000 (EU)	Tetraethyl lead [$Pb(C_2H_5)_4$]	Additif dans l'essence
1859-today	Lead monoxide (PbO)	Batteries, enamel/glazing of ceramics
1898-1971	Lead arsenate: $Pb_3(AsO_4)_2$ $PbHAsO_4$	Insecticide
-2000 -…	Native lead	Weapons (arrows, ammunition…)
1900-today	Lead sulphide (galena): PbS	Semiconductor; infrared detectors

Lead production throughout history



Source: see (Hong,*Science*, 1994)

B. Human exposure to lead



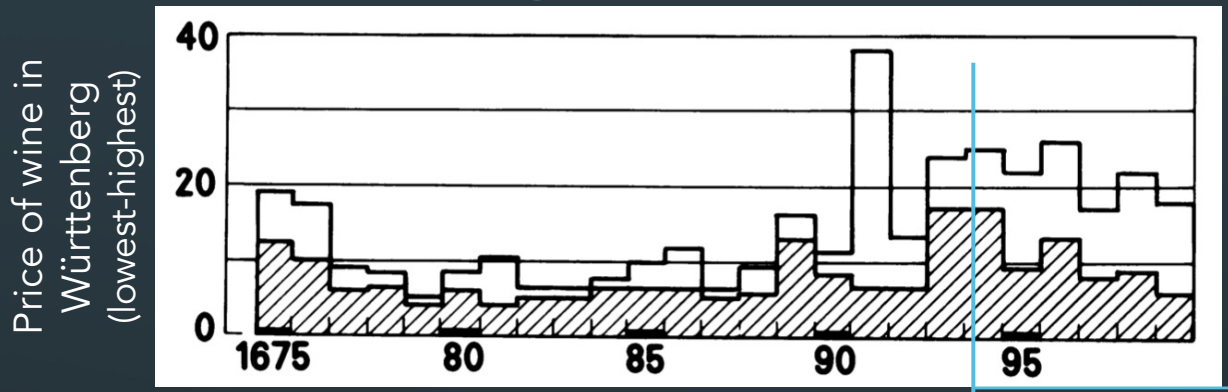
Main sources of exposure to lead in Antiquity

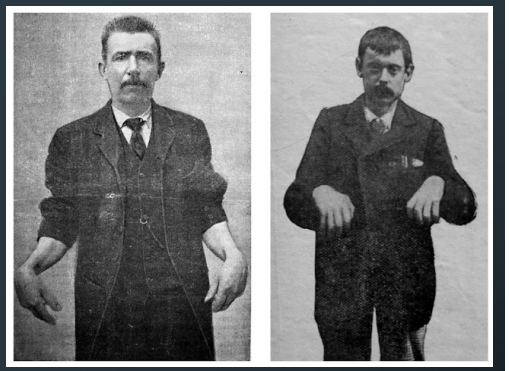
Lead (metal):
Water pipes
Gold, silver production

Ceruse (lead carbonate):
Cosmetics (pallor as a marker of social status)

Lead acetate:
Sweetener
Grape juice boiled in lead container: *defrutum*, *Sapa*

Lead use in wine and *colica Pictonum*: a connection through climatic conditions?





(Rainhorn, 2019)

Figure from (Eisinger, *Med Hist*, 1982)

Descriptions by Paul of Aegina (7th Century) and Citois (1639)

Other names: Devonshire colic, bilious colic, paralytic colic, saturnine colic, Grimmen (German), "dry belly-ache"

Symptoms of colica Pictonum: "violent gripes which declining takes away the use of the limbs. Their fingers stand stiffly bent, the hands of some hang…" (description from 1684, quoted by Childs, *Bull Hist Med*, 1970).

Eberhard Gockel, a Dr. from Ulm made the connection between lead addition and colica Pictonum in 1696 (Eisinger, *Med His*, 1982)

Ulm: a central trading place for wines from the Neckar valley.

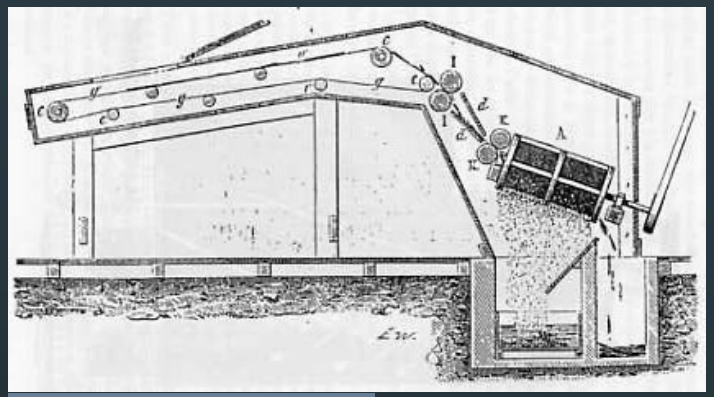
1694-96: epidemics of *colica Pictonum* in Ulm

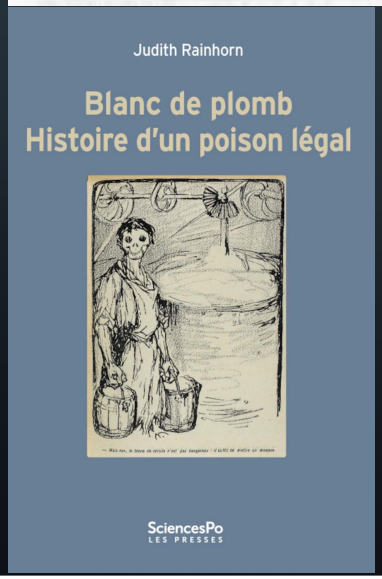
1694-96 corresponds to a very cold period with bad harvest, as seen from its increased price.

The habit to "correct" wine with lead to sweeten it may be particularly important when wines are acid, e.g. in case of a bad summer.

Rembrandt (1606-1669)

Main sources of lead exposure in the 19th century

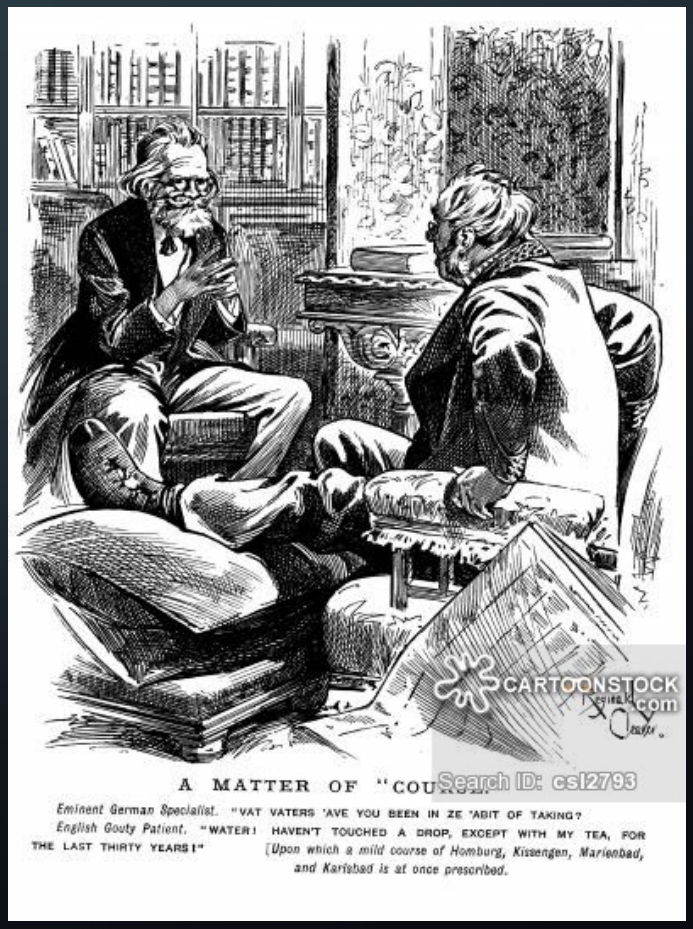




Lead acetate:
Still present in some alcohols (cooked wine)

Lead (metal):
Pipes

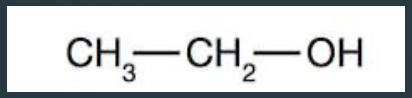
Ceruse (lead carbonate):
Occupational exposure
(Lestel L, 2002; Rainhorn J, 2019), as well as an invisible source of exposure in the general population



Leaded gasoline (1921-2021)

Ford Model T (1908-1927)

Which gasoline additives can improve the performance of engines?



Alcohol (ethanol)

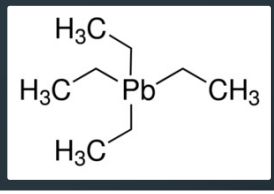
Effectiveness proven since 1920

Extremely simple and inexpensive to synthesize, produced from biomass

Combustion only releases water and CO_2

Can also also be used in high concentrations, as a fuel

Not patentable



Tetraethyl lead (TEL)

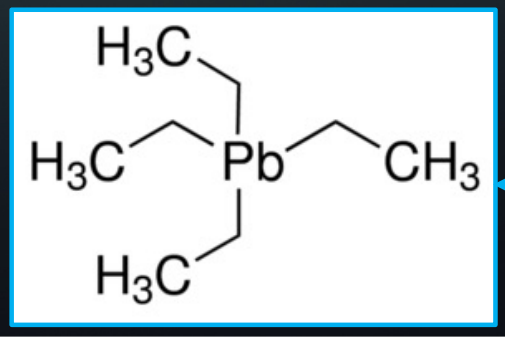
Difficult/dangerous to synthesize

Clogs the engine

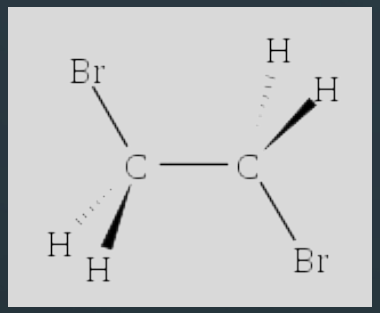
Concerns about the health effects of lead (ban on white lead paint by the International Labour Organization in 1921)

Patentable

Ford Model T (1908-1927)



What additive to improve the performance of gasoline engines?



Requires to add a scrubber: ethylene dibromide ($BrCH_2$-CH_2Br,)

Later used as a pesticide
Carcinogenic

Generates methane bromide (CH_3Br) in exhaust gases (Thomas VM, Geoph Res Lett, 1997) (toxic; destroys the ozone layer; powerful greenhouse gas)

Tetraethyl lead (TEL)

Difficult/dangerous to synthesize

Clogs the engine

Concerns about the health effects of lead (ban on lead white paint by the International Labour Organization in 1921)

Patentable

1920: Discovered a fuel with added ethanol
1921: Discovers that tetraethyl lead reduces the rattling of heat engines
1923: Made a cure in Florida after being intoxicated by lead

Late 1920s: Contributed to the synthesis of Freon, the first chlorofluorocarbon (CFC) and its use in refrigerators. CFCs have been shown to destroy the ozone layer (Molina & Rowland, Nature, 1974)
1944: Elected President of the American Chemical Society

Midgley is considered to have "had more impact on the atmosphere than any other single organism in Earth's history" (McNeill, 2001)

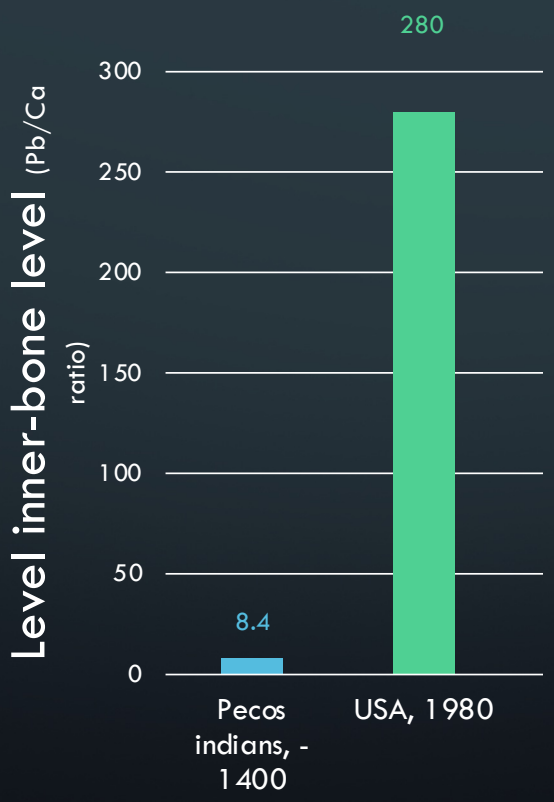
Thomas Midgley Jr (1889-1944)

Perhaps if leaded gasoline kills enough people soon enough to impress the public, we may get from Congress a much-needed law and appropriation for the control of harmful substances other than foods. But it seems more likely that the conditions will grow worse so gradually and the development of lead poisoning will come on so insidiously (for this is the nature of the disease) that leaded gasoline will be in nearly universal use and large numbers of cars will have been sold that can run only on that fuel before the public and the Government awaken to the situation….

This is probably the greatest single question in the field of public health that has ever faced the American public (…)

Pr. Yandell Henderson (Univ. Yale), quoted by Kitman, 2005
See https://www.thenation.com/article/archive/secret-history-lead/

Making lead contamination visible



In the mid-20th Century, lead contamination was already widespread.
Claims from the toxicologist working for the leaded gasoline industry was that this corresponded to "natural contamination"

Comparisons with levels in lead level the inner bone of Peruvian bodys from -1400 allowed to demonstrate that levels had strongly increased since this time.

(Ericson, *N Engl J Med*, 1972; Ericson, *EHP*, 1991)

Main sources of lead exposure in the 20th century

Lead (metal):
Pipes

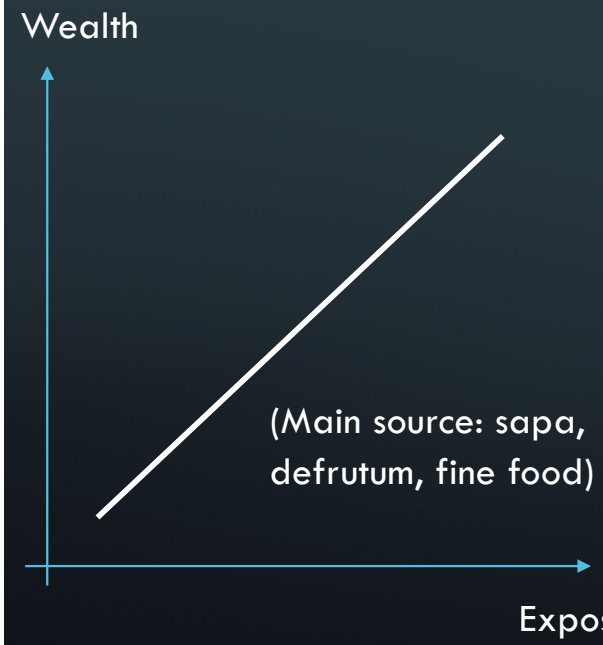
Leaded paints:
Progressively banned during the 20th Century

Leaded gasoline (1923-2021)

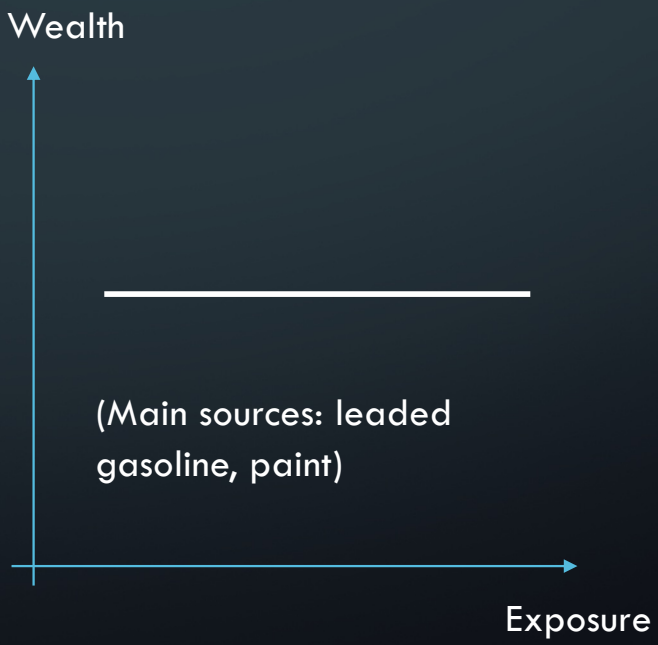
Lead batteries

Social inequalities in lead exposure

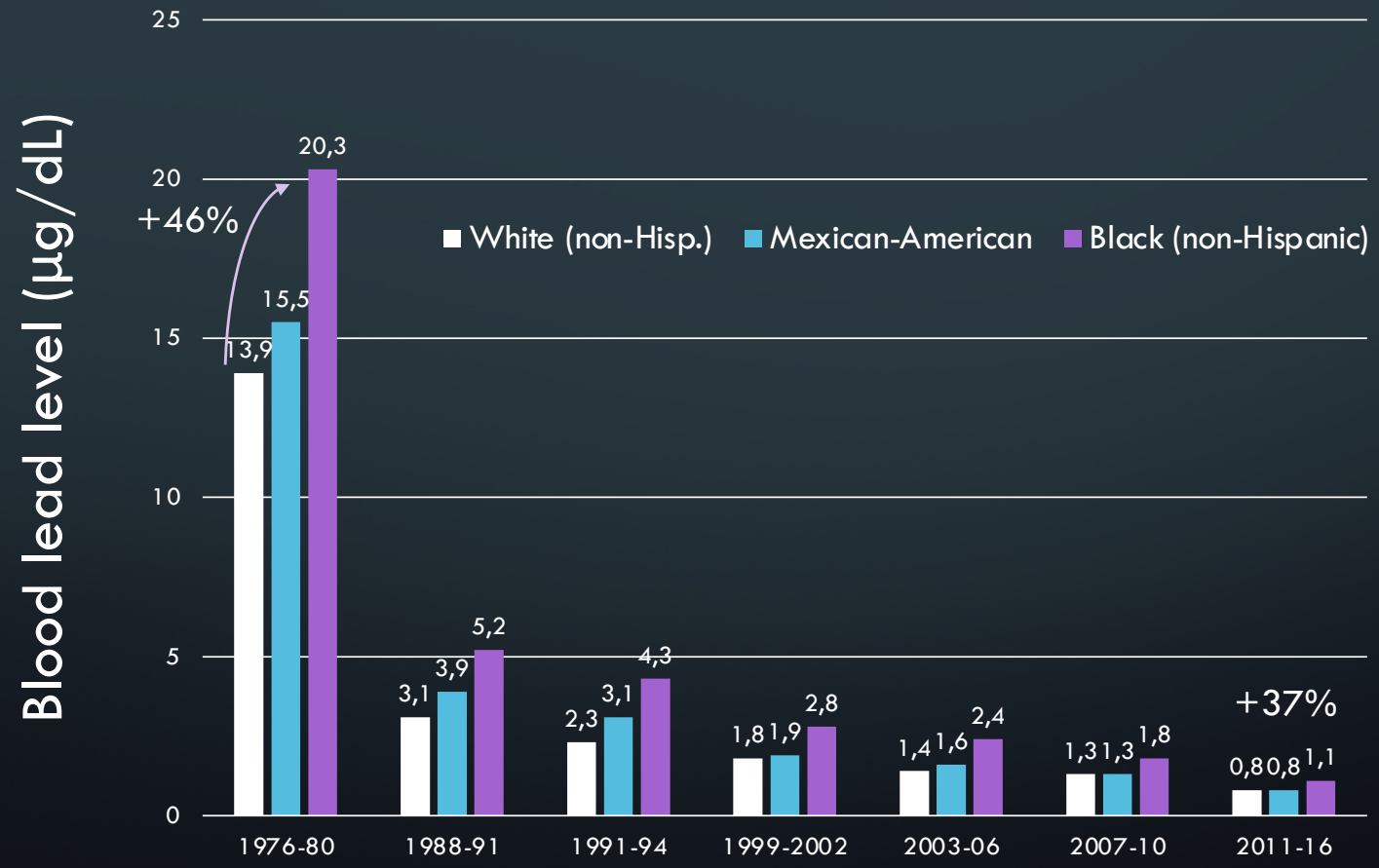
0 (ROMAINS)



1950



Socio-ethnic disparities in blood lead levels
(USA, children aged 1 to 5 years, 1976-2016)

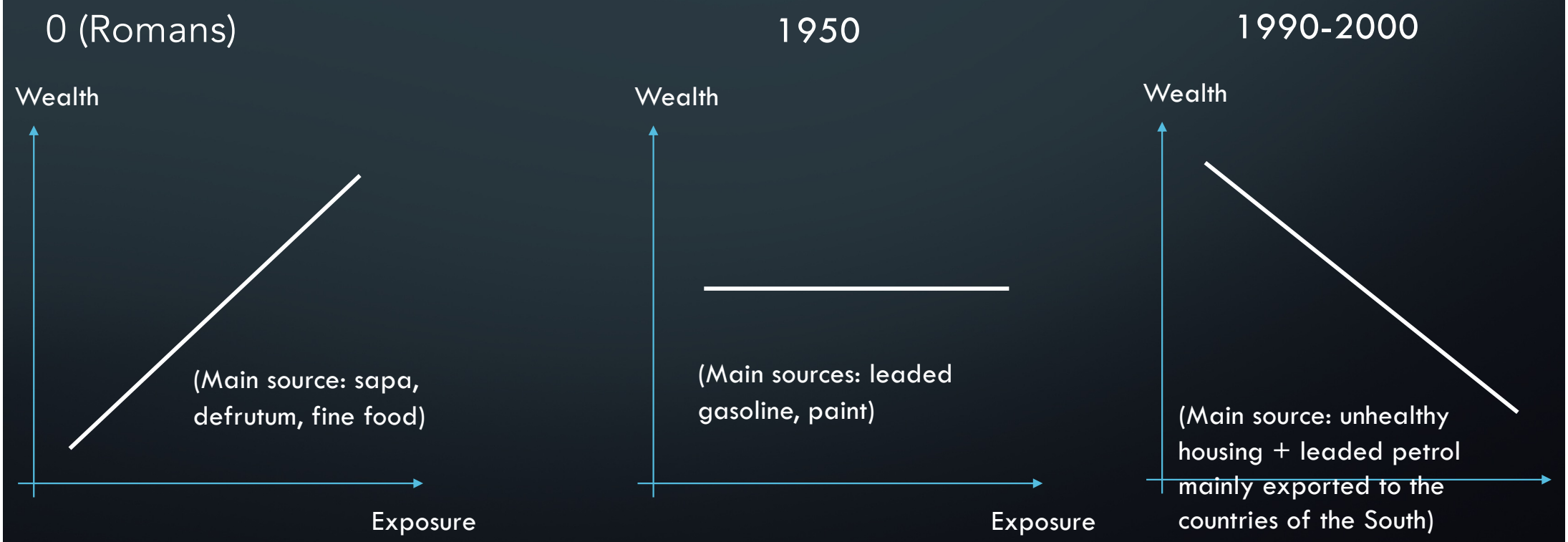


General downward trend (19-fold division of blood lead levels in 35 years)

Gradients between ethnic groups that do not completely disappear on a multiplicative scale (but strongly attenuated on an additive scale).

(Adapted from Egan, *EHP*, 2021)

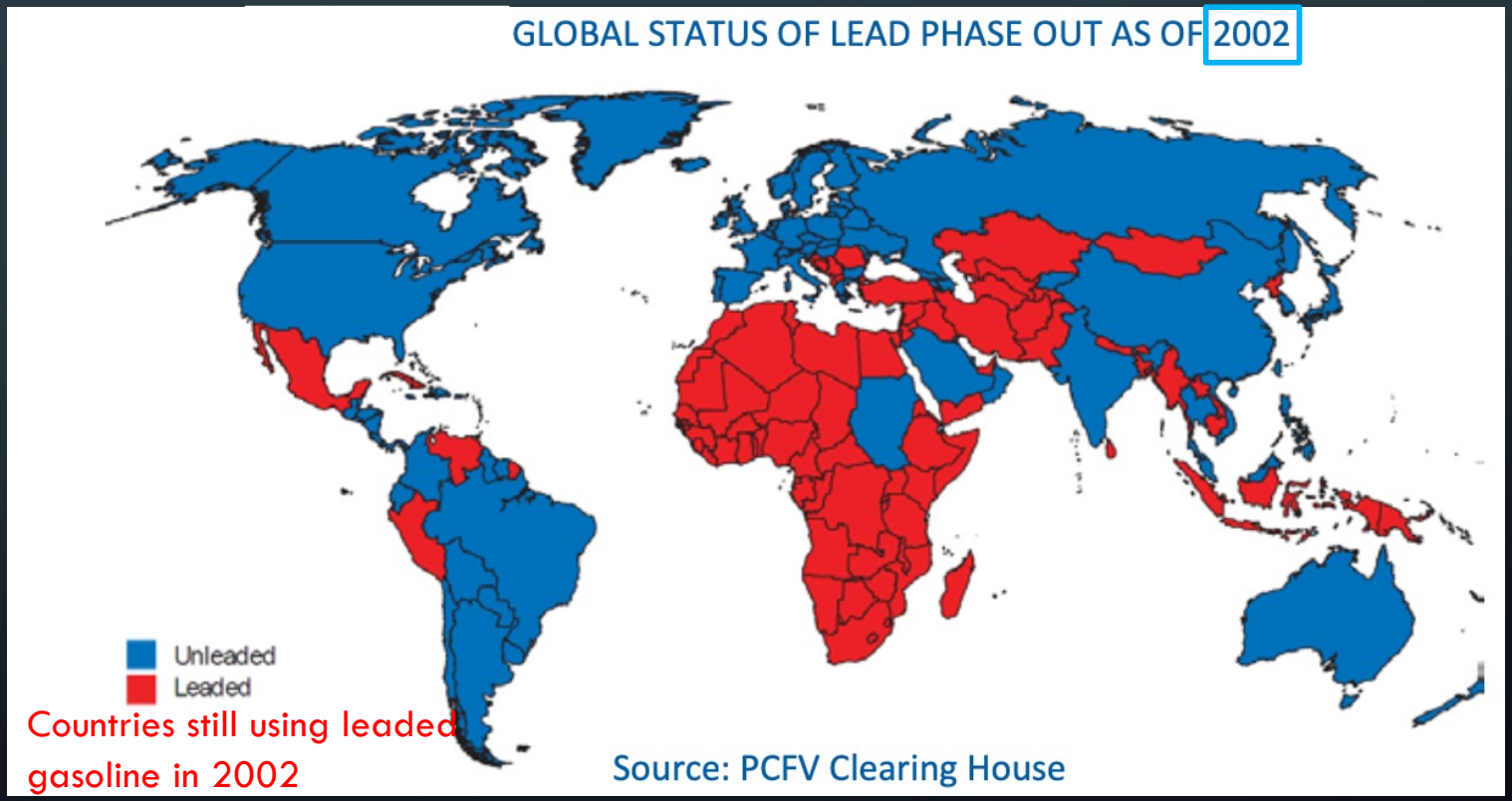
Social inequalities in lead exposure



Reversal of the social gradient in exposure throughout history

After its ban in rich countries, leaded gasoline continued to be used in many less wealthy countries.

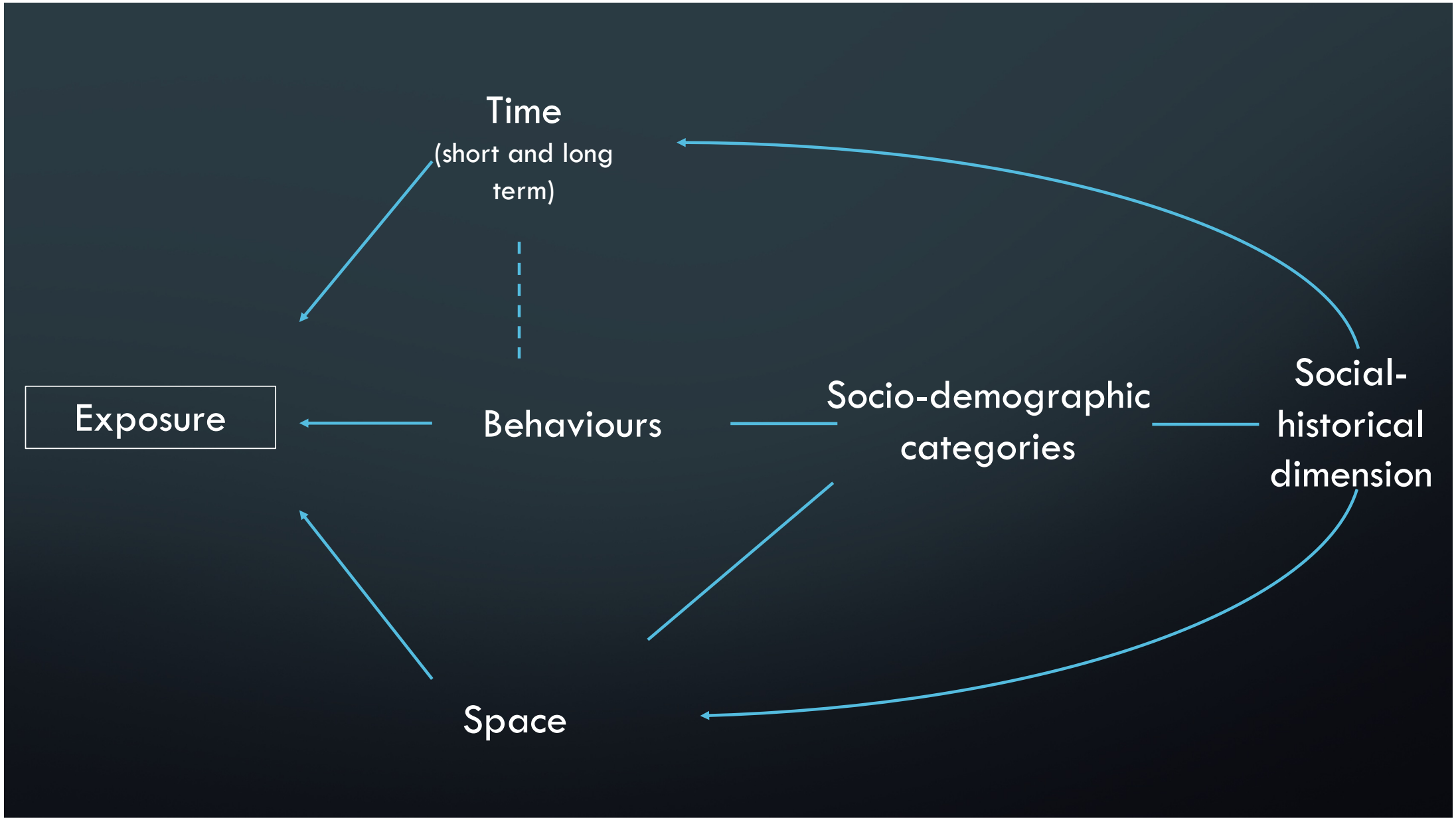
Between-country exposure gradients related to wealth tend to parallel those observed within countries



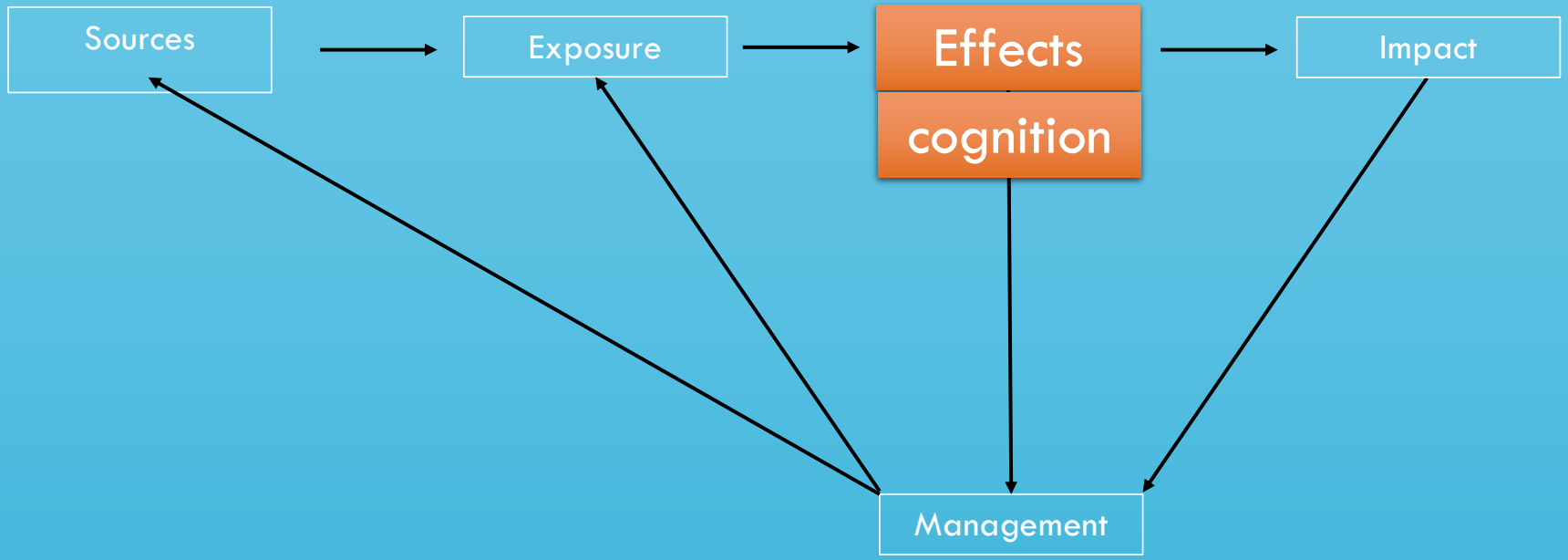
2011

2021

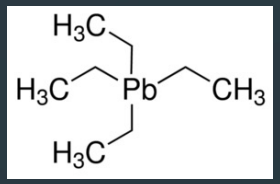
Worldwide ban
(in theory at least)


Time
(short and long term)
Exposure
Behaviours
Socio-demographic categories
Social-historical dimension
Space

C.1. Some health effects of lead exposure



Absorption, Distribution, Metabolism and Excretion (ADME)



ABSORPTION

Lung

Digestive tract

DISTRIBUTION and METABOLISM

Red blood cells
Plasma
Half-life: 1 month

Liver
Metabolism of organic lead

Bones
Cortical bones
Half-life: 30 years

Nervous system

Placenta
Foetal brain

Other organs

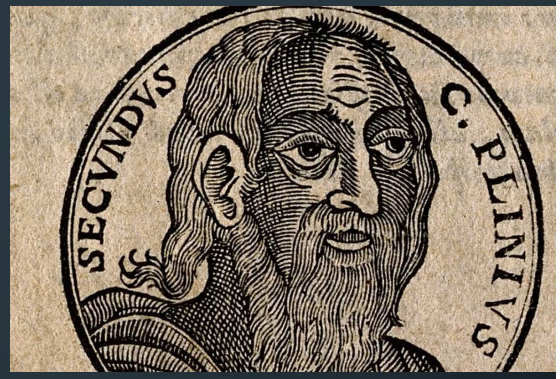
Kidneys

EXCRETION

Urine

Faeces

Health effects historically attributed to lead



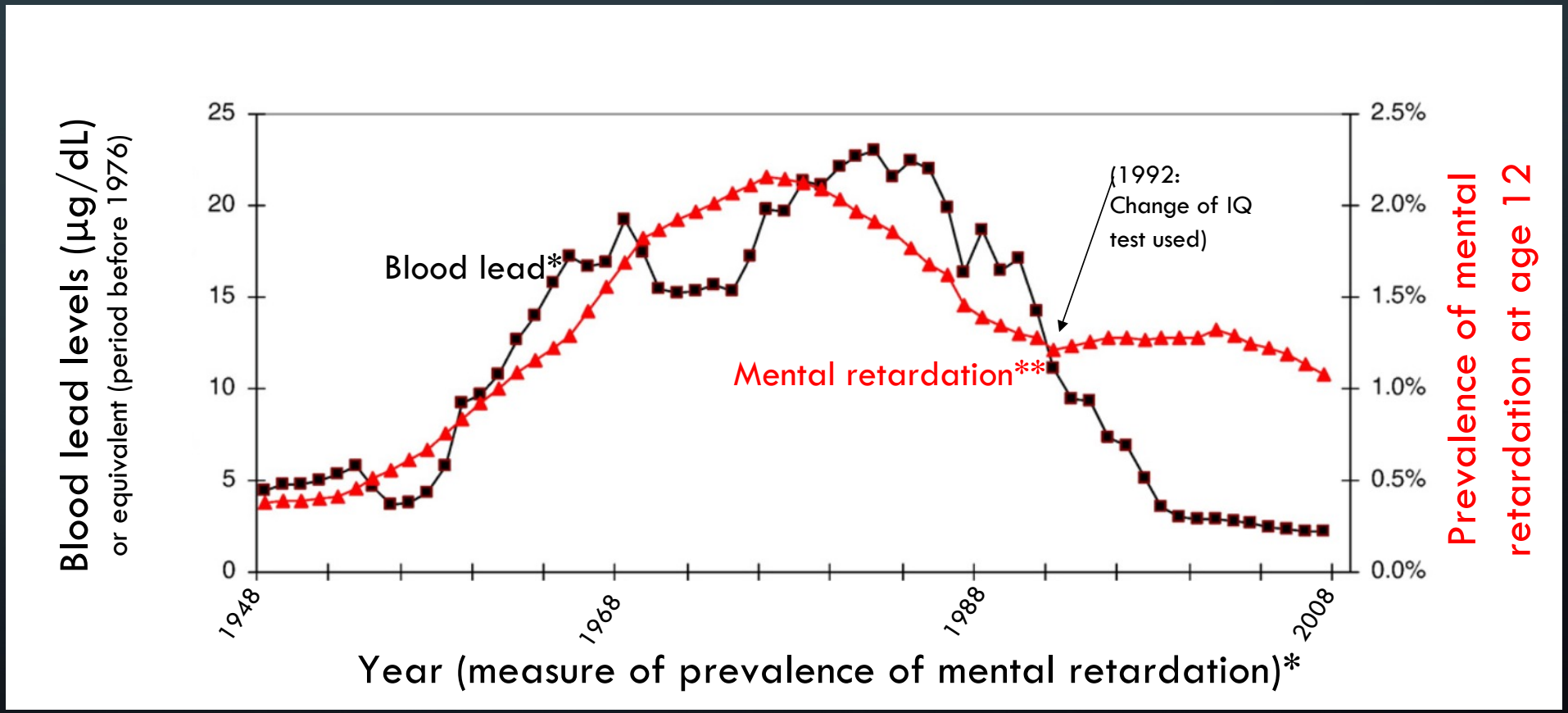
Gastrointestinal effects (colic, constipation)

Pliny the Elder (ca. 77), Galen (129-210), Citois (1616, Poitou), B. Ramazzini (1700), Baker (1767, Devonshire)

Central neurological disorders (hallucinations) or peripheral disorders (paralysis of peripheral limbs…)

Paul of Aegina (7th Century)

Blood lead and frequency of mental retardation 12 years Later: an ecological study



*Blood lead levels were measured 12 years prior to the indicated year

** Proportion of children requiring special education for mental retardation

(Carpenter & Nevin, *Phys & Behav*, 2010)

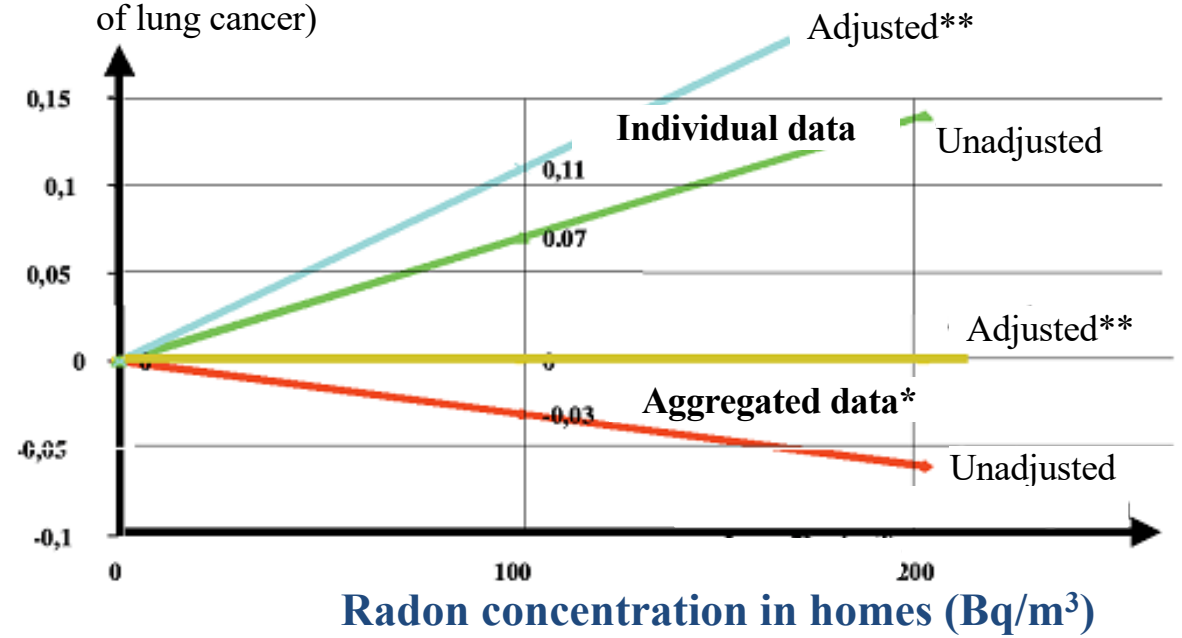
Methodological issue

Why long-term temporal ecological studies are not considered to bring a high level of evidence

- Ecological studies can rely on spatial contrasts (e.g., between-city or country comparison) or temporal contrasts (short- or long-term comparisons: from hours to decades)
- In ecological studies, exposure and/or health data are aggregated at the population level (and not available for each individual)
- Consequently, the efficiency of control for confounders is much more limited than in studies with individual data ("ecological fallacy")(Greenland, *Am J Epid*, 1994)
- Spatial ecological studies and long-term ecological studies are particularly prone to confounding and ecological fallacy and are therefore considered to provide a lower level of evidence than other epidemiological designs
  - Note that short-term temporal ecological studies do not fall in this category, as will be illustrated in a future lecture

Methodological issue

Illustration of the aggregation of exposure data on dose-response functions (radon and lung cancer)



*Data were aggregated at the county level

**Adjusted for tobacco smoking, occupation, urbanisation.

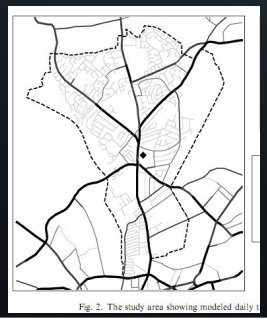
(Lagarde, *AJE*, 1999)

Methodological issue: Assessment of environmental exposures in human studies

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

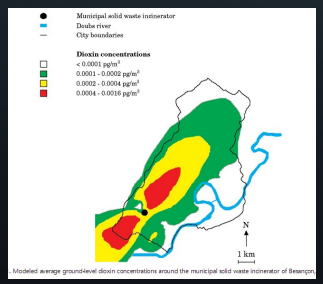
Data on sources (e.g. localisation of factories, roads -when leaded gasoline was used)

Emission cadastres

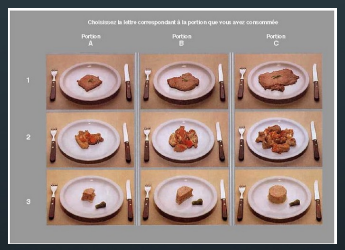


Dosimeter

Environmental model or measurements



Questionnaire X Environmental model or data



Dosimeter

Job-exposure matrix (occupational setting)

Exposure biomarker (biospecimen + biochemical assay)

Exposure (bio)marker X TD-TK modelling

Characterization of lead exposure in humans: Which metric?

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

Overall lead production or use at a given time

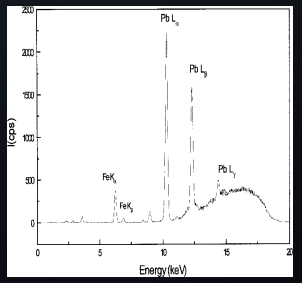
Atmospheric concentration (Short term; ignores sources of exposure other than inhalation)

Occupational data, questionnaires

Blood lead levels (half-life: 30 days)

Tooth lead levels

Bone lead levels (X-ray fluorescence; Hu H, EHP, 1991)

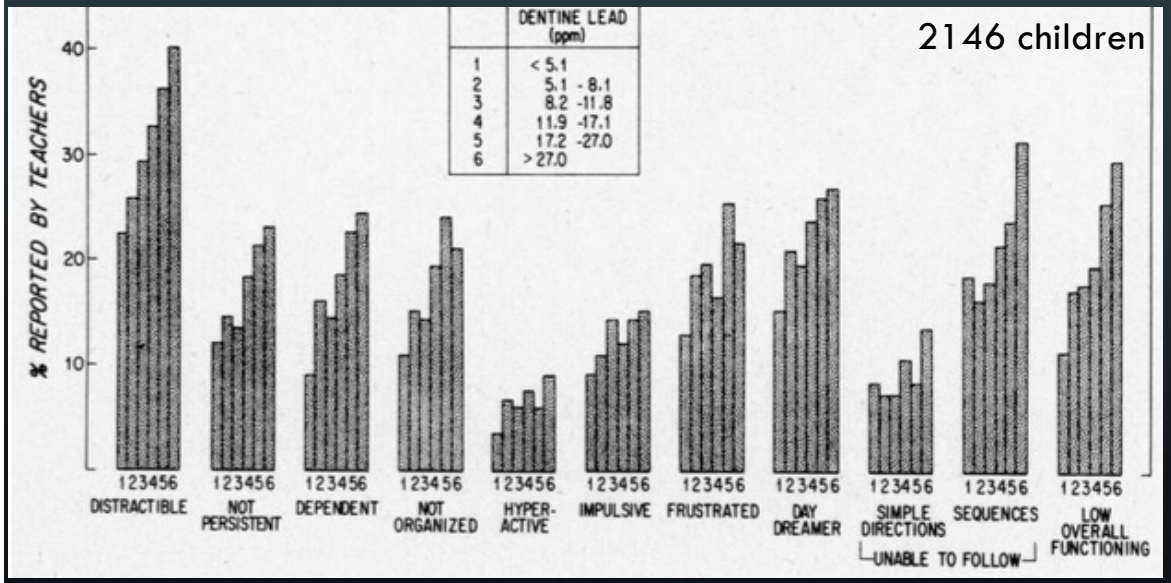


Half-life: 8-20 years (patella) to 50 years (cortical bone, e.g. tibia)

Blood lead: link to neurobehavioural function and academic success

Individual scale (cohorts)

1975-78: Recruitment of 7-year-olds following the first classes of elementary school in Chelsea and Somerville (suburb of Boston).
Collection of fallen milk teeth, determination of lead in enamel (n=2335).
Teacher questionnaire (2146) and detailed neurological examination of 158 children at the 2 extremes of lead (tooth) exposure



(Needleman, *NEJM*, 1979)

In children most exposed to lead:
- Lower overall IQ*
- Lower verbal IQ and more limited vocabulary*
- Ability to repeat a more limited sentence as well as to maintain attention*

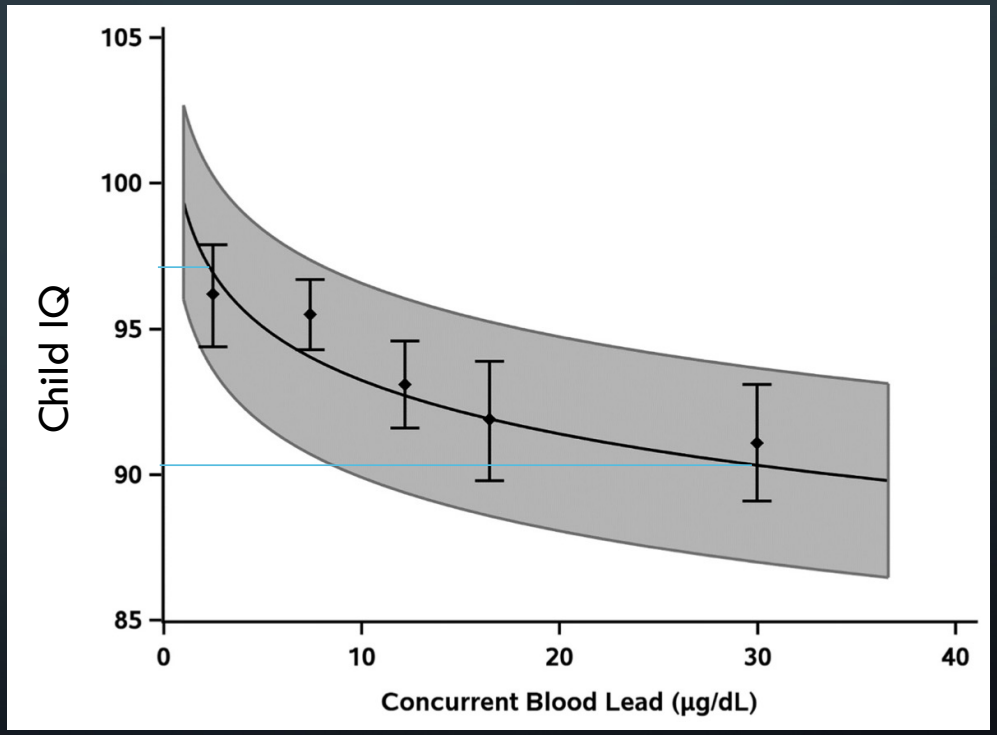
*After adjusting for parents' level of education and age, IQ, number of children at home
(Needleman, *Science*, 1985)

Follow-up in adulthood (Needleman, *NEJM*, 1990)
In children most exposed to lead:
- Lower grade at school leaving*
- More limited reading level and vocabulary
- More frequent school absenteeism
- Poorer hand-eye coordination
- Increased reaction time

*After adjustment for the level of education and age of the parents, their IQ, the number of children at home, the sex of the subject...

Blood Lead and Intelligence Quotient (IQ)

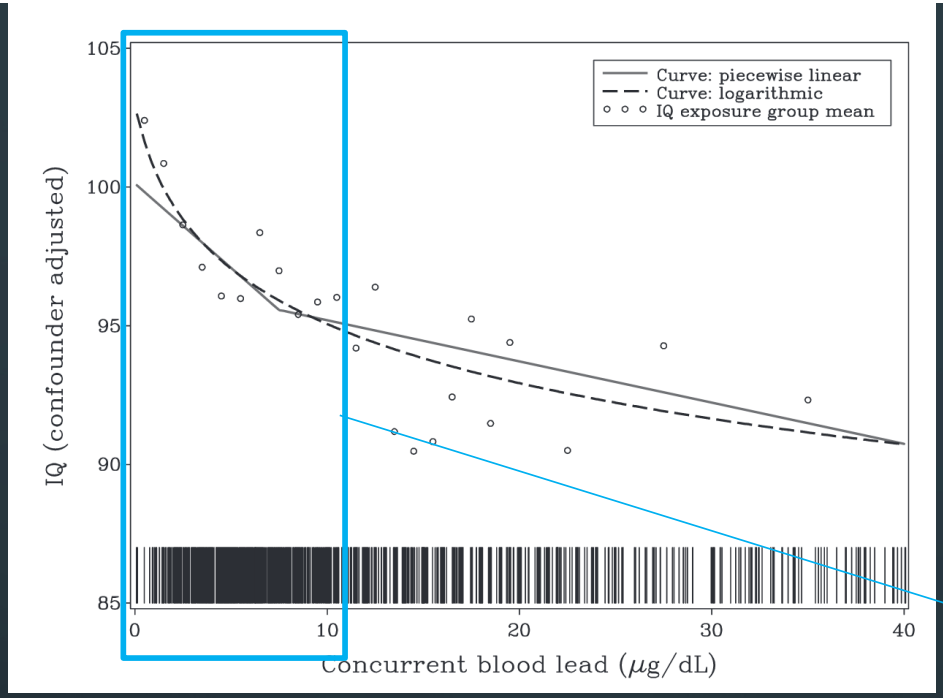
7 cohorts, 1033 children. Model adjusted on maternal education and IQ, birth weight, and HOME score

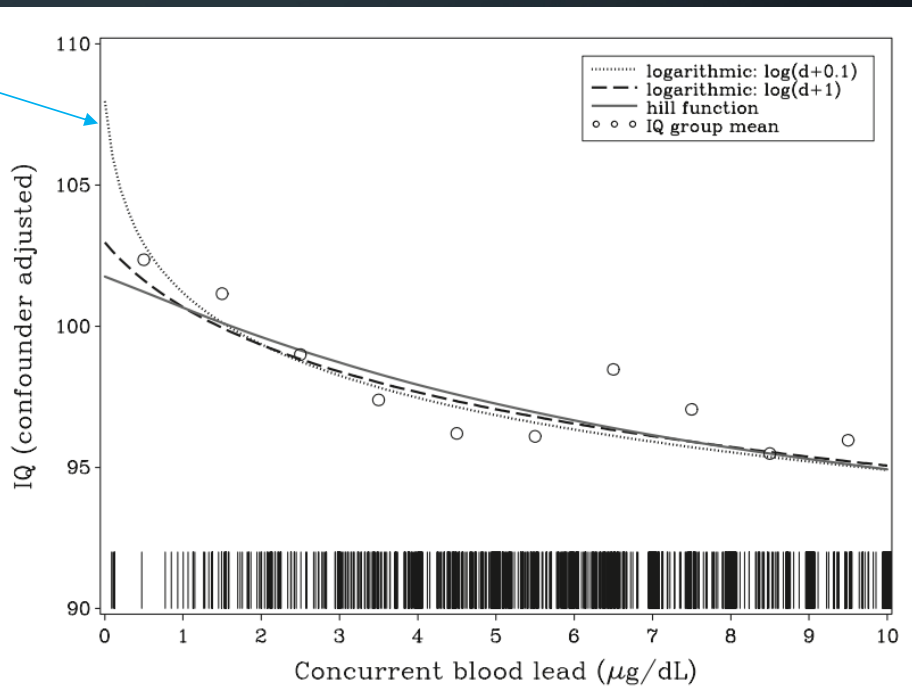


6.7 IQ points decrease when blood lead decreased from 2.4 to 30 µg/dL (95% CI: -9.3; -4.1)

(Broadly similar association when blood lead level in early life is used instead of concurrent blood lead)

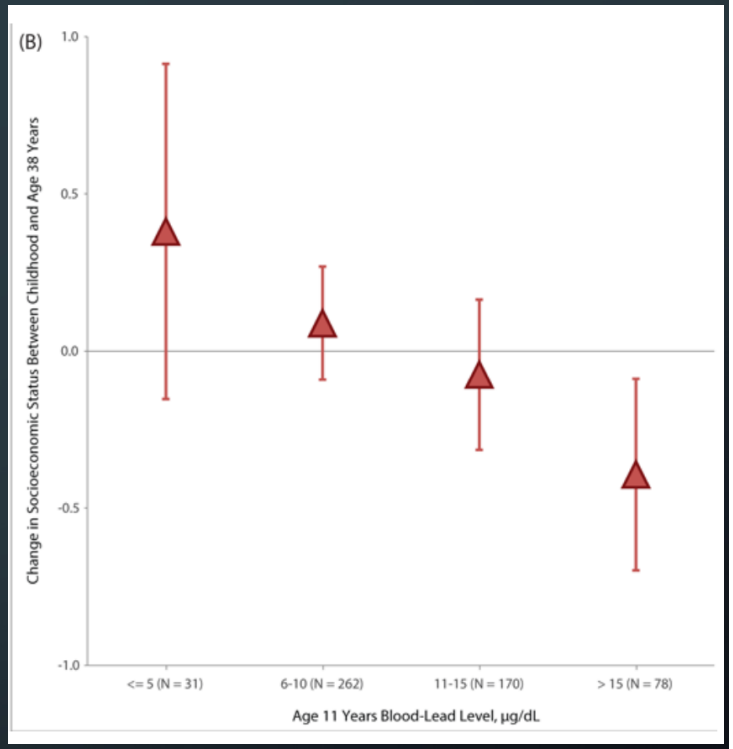
(Lanphear, *EHP*, 2019)





(Budtz-Jorgensen, *Risk Anal*, 2012)

Lead, social categories and IQ: beyond confounding – a more complex causal model



Socio-economic status (parents)

Lead in childhood → IQ In childhood → IQ In adulthood → Economic status (adulthood)

(Reuben et coll., *JAMA*, 2017)

Lead and cognition: animal models

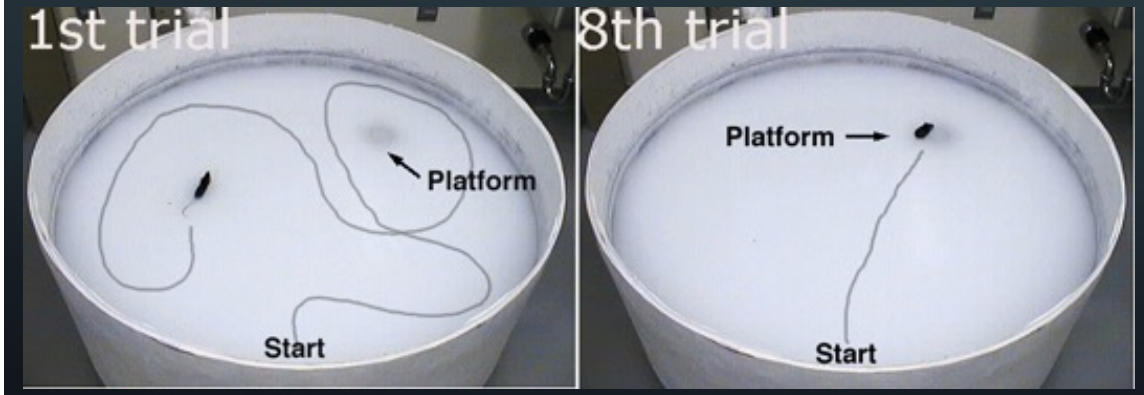
Population scale (ecological studies)

Individual scale (cohorts)

Individual scale (in vivo toxicology)

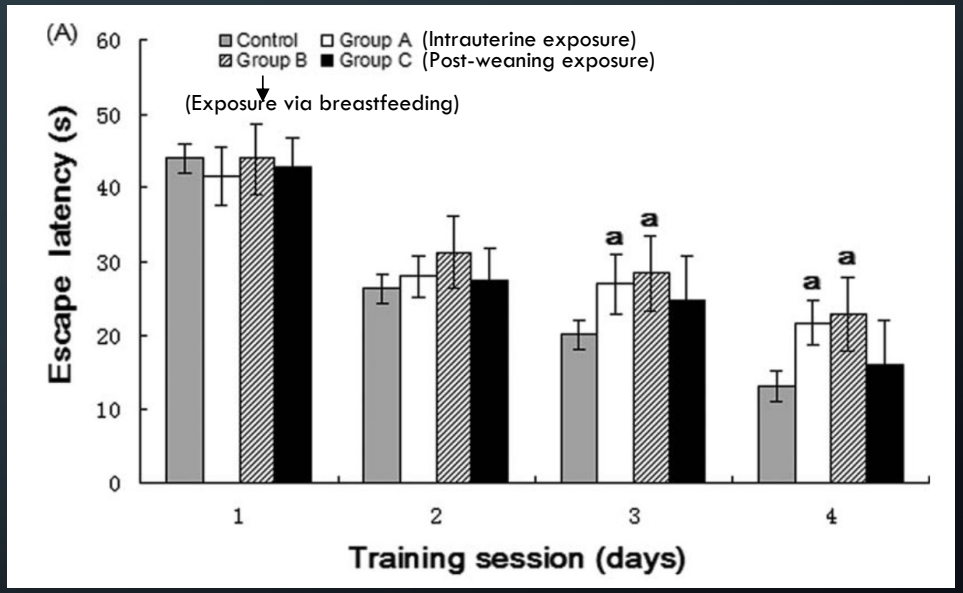
Exposure to water/milk with 0.2% lead acetate at different stages of development (A: Pregnancy; B: Lactation; C: post-weaning).
Increased levels of lead in the blood or hippocampus.

Morris water maze at the age of 64 days



(Wang XM, *Tox Ind Health*, 2012)

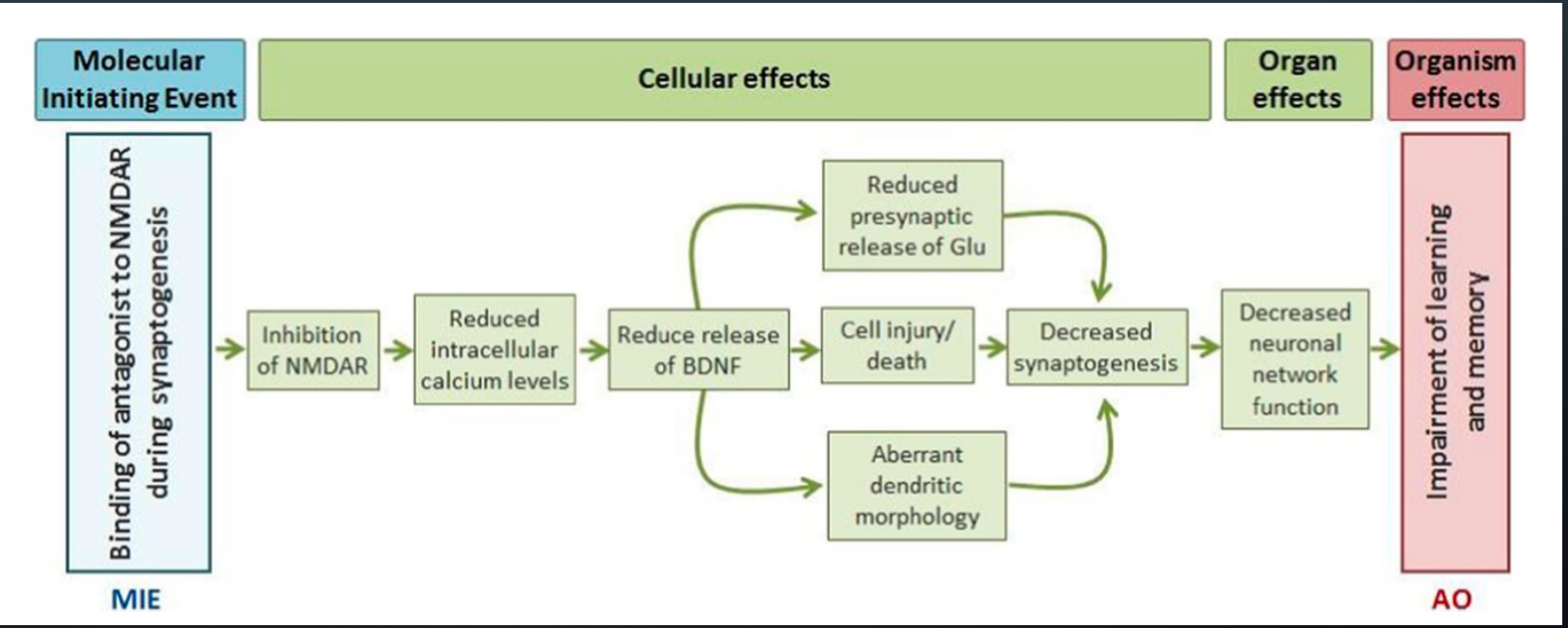
*NMDA: N-methyl-D-aspartate



No difference in time to reach the platform in the first sessions.
After training, rats exposed in-utero or before weaning take longer than others to escape.
Cognitive effects (memory, learning)
Alteration of mRNA expression encoding NMDA*

NMDA* receptor is involved in an *adverse outcome pathway* (AOP) that can lead to impaired learning

Pb^{2+} →



AO: Adverse Outcome. BNDF: Brain-derived Neurotrophic Factor.
MIE: Molecular Initiating Event. NMDA: N-methyl-D-aspartate.

(Sachana et al., *Tox Appl Pharm*, 2018)

Pb^{2+}

Astrocytes

Mitochondria

Calmodulin (CaM)

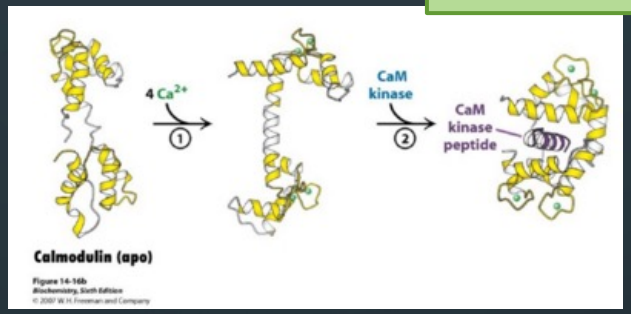
(Shirran, *J Am Soc Mass Spec*, 2009)

Inhibition of NDMA receptor

(Wang XM, *Tox Ind Health*, 2012)

Protéine kinase C

Neurogenesis, neurotransmission, apoptosis...



Cellular calcium levels

Permeability of the blood-brain barrier

Sensitivity to other neurotoxicants

Adverse outcome

Calcium signal transduction, neuronal plasticity

Impaired learning and memory

Growth, differentiation, learning, memory...

For a review, see e.g., (Rocha, *Neurotox*, 2019)

Population scale (ecological studies)

Individual scale (cohorts)

Individual scale (in vivo toxicology)

Cellular scale (in vitro toxicology)

Adverse outcome

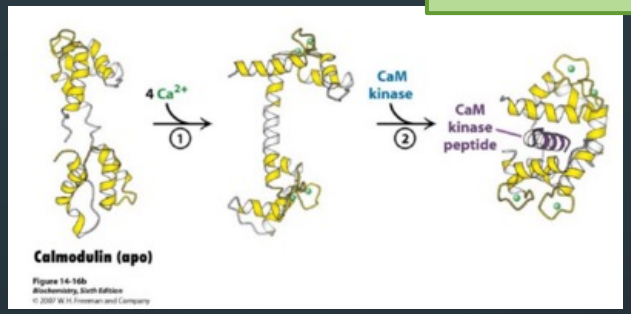
Pb^{2+}

Astrocytes

Mitochondria

Calmodulin (CaM)

(Shirran, *J Am Soc Mass Spec*, 2009)



Neurogenesis, neurotransmission, apoptosis...

Calcium signal transduction, neuronal plasticity

Inhibition of NDMA receptor

(Wang XM, *Tox Ind Health*, 2012)

Cellular calcium levels

Impaired learning and memory

Protéine kinase C

Permeability of the blood-brain barrier

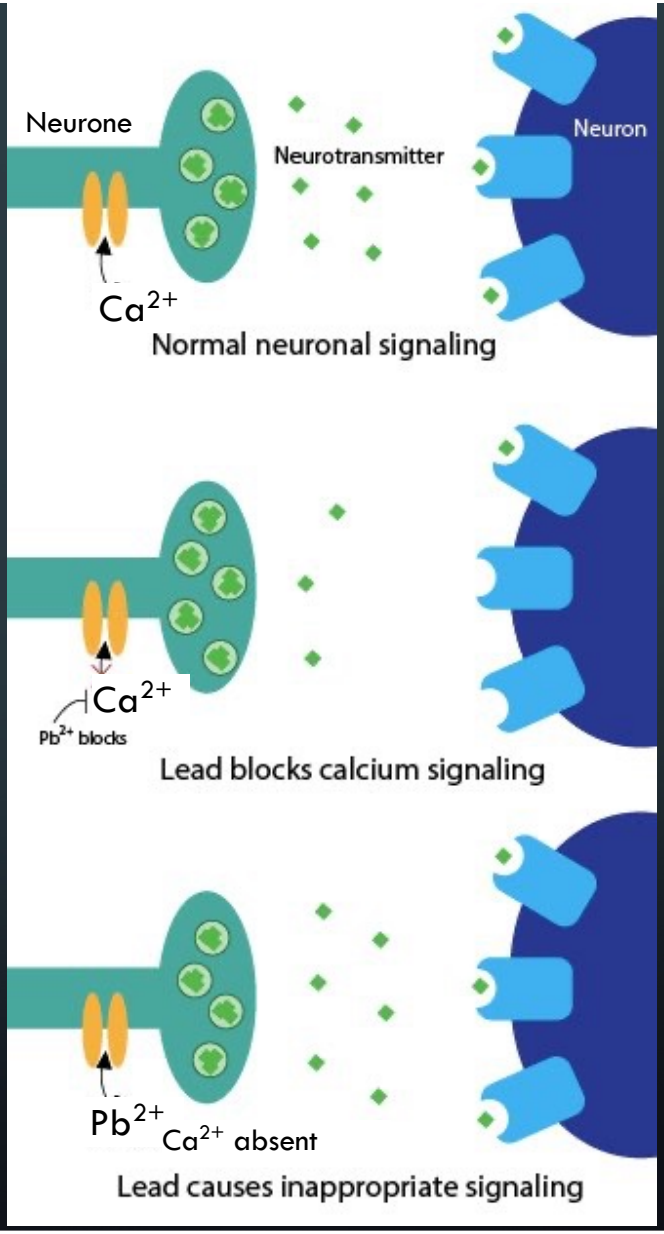
Sensitivity to other neurotoxicants

Growth, differentiation, learning, memory...

For a review, see e.g., (Rocha, *Neurotox*, 2019)

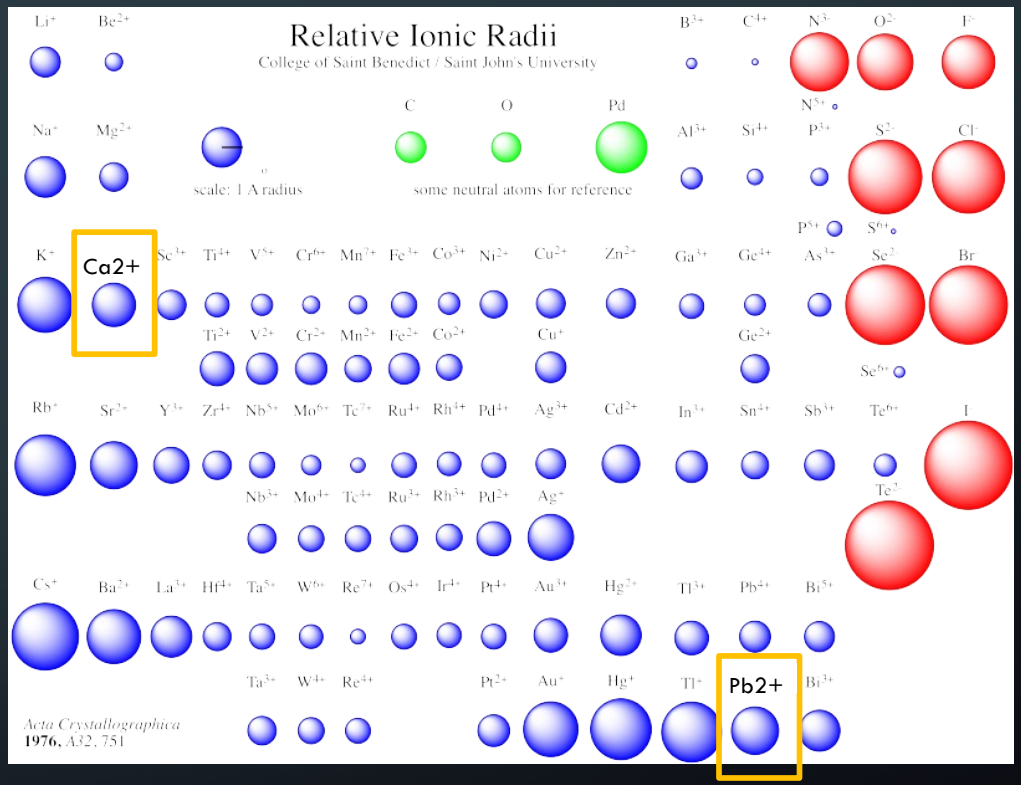
Lead as a disruptor of a "second messenger" (or intercellular signaling disruptor)

$Pb^{2+} \leftrightarrow Ca^{2+}$



Disruption of neurotransmission

Population scale (ecological studies) | Individual scale (cohorts) | Individual scale (in vivo toxicology) | Cellular scale (in vitro toxicology) | Molecular/atomic scale



$Pb^{2+} \leftrightarrow Ca^{2+}$

Similar ionic radius (1 to 1.3 Å)
Same number of coordination (8)
Some similarity in external electron orbitals
Differences in internal electron orbitals that makes Pb^{2+} more apt at creating strong (covalent) bonds with molecules in the body

Neurological effects of lead: from populations to ions

Population scale (ecological studies)

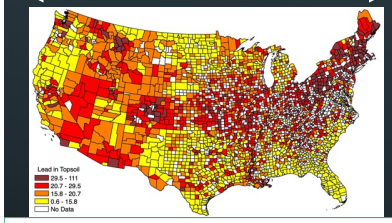
Individual scale (cohorts)

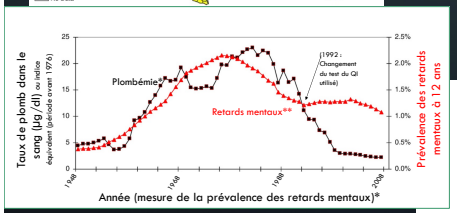
Individual scale (in vivo toxicology)

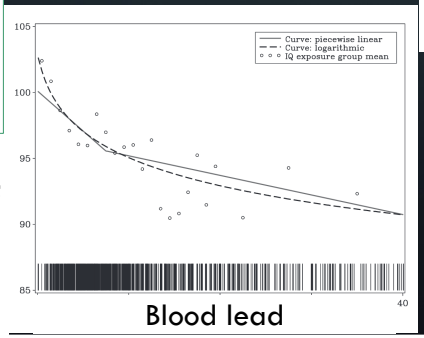
Cellular scale (in vitro toxicology)

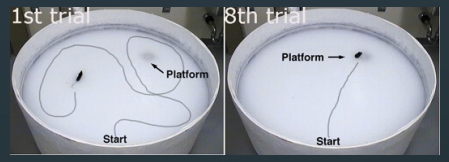
Molecular/atomic scale

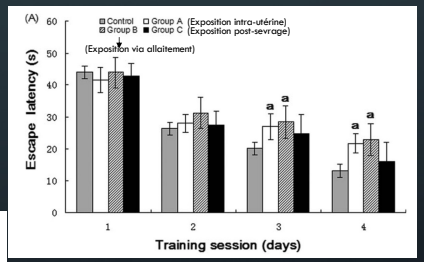
5,000 km





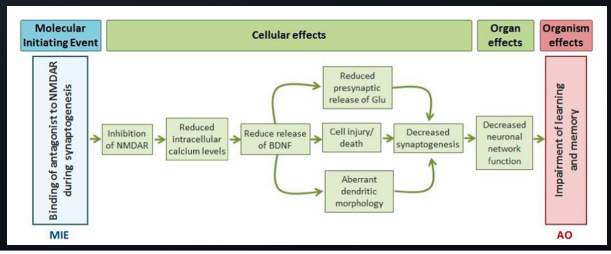




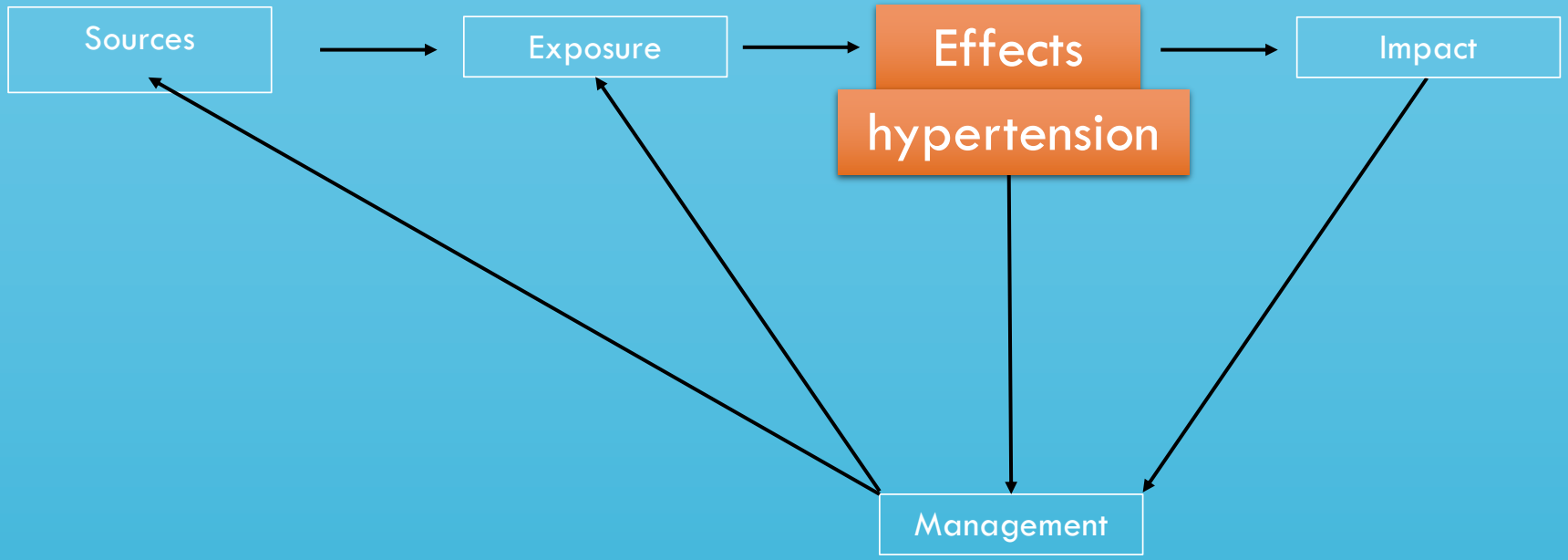


1 Å

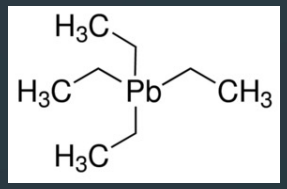
$Pb^{2+} \leftrightarrow Ca^{2+}$



C.2. Some health effects of lead exposure



Absorption, Distribution, Metabolism and Excretion (ADME)



ABSORPTION

Lung

Digestive tract

DISTRIBUTION and METABOLISM

Red blood cells
Plasma
Half-life: 1 month

Liver
Metabolism of organic lead

Bones
Cortical bones
Half-life: 30 years

Nervous system

Placenta
Foetal brain

Other organs

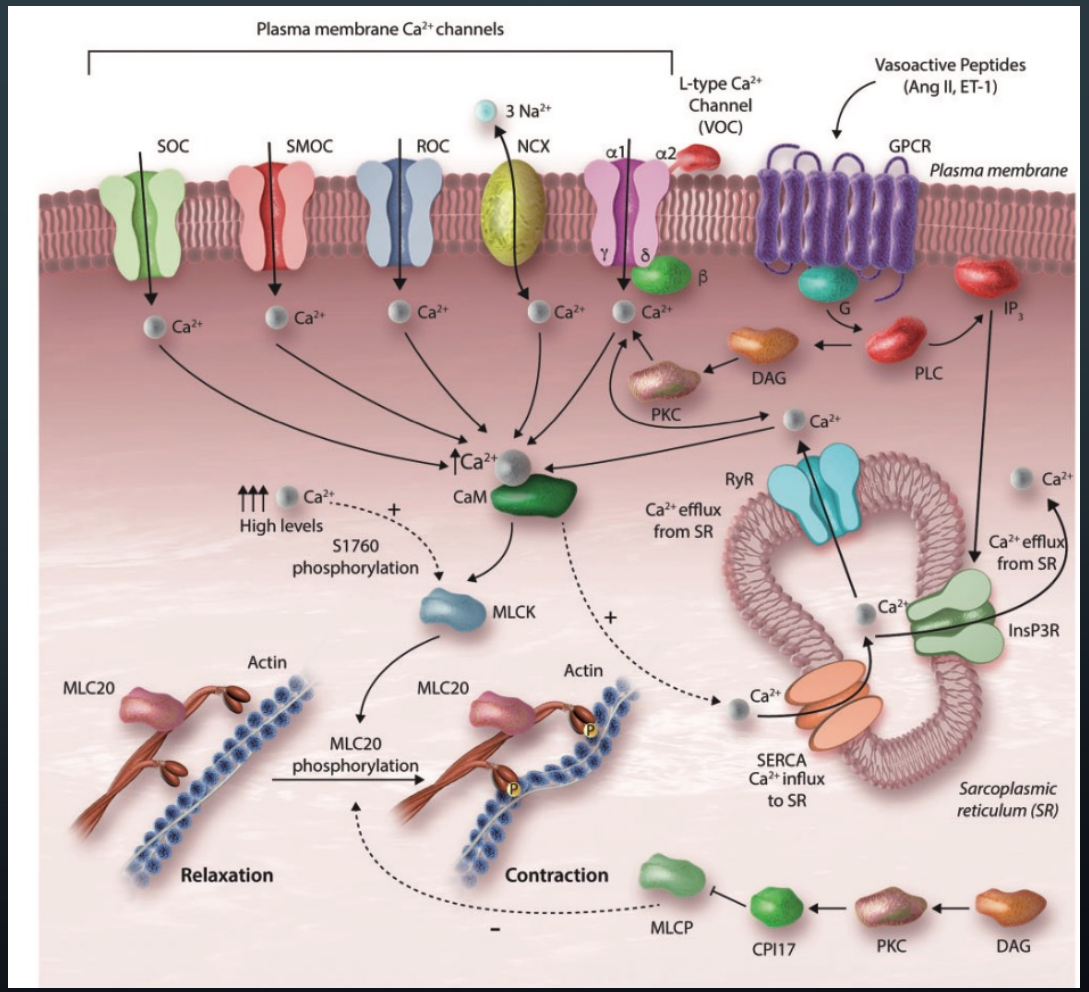
Kidneys

EXCRETION

Urine

Faeces

Ca^{2+} signaling of vascular smooth muscle contraction

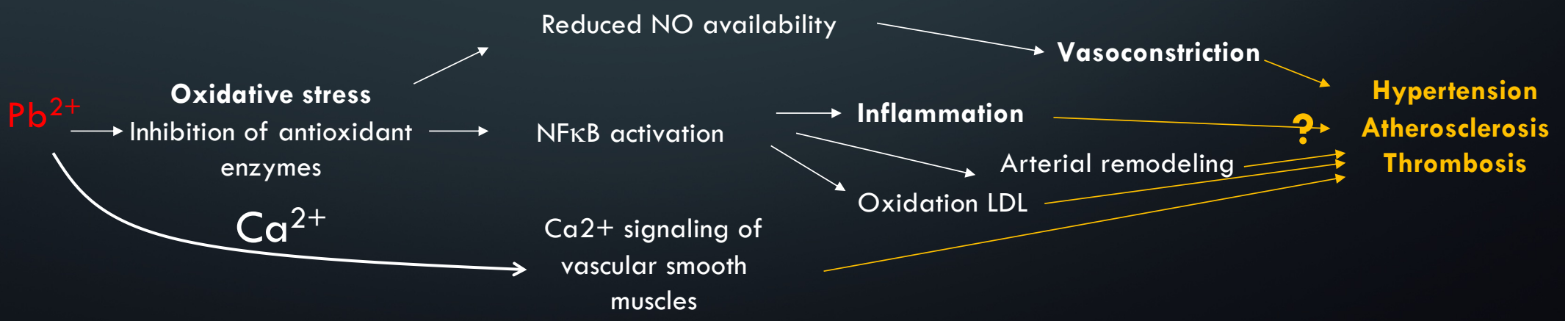


(Touyz, *Cardiov Res*, 2018

Lead and high blood pressure

Cellular scale (in vitro toxicology)

Molecular/atomic scale



(Adapted from Vaziri, *Am J Phys Hear Circ Physiol*, 2008; Touyz, *Cardiov Res*, 2018)

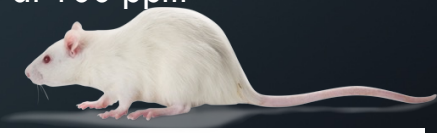
Effects on blood pressure and hypertension in animal models

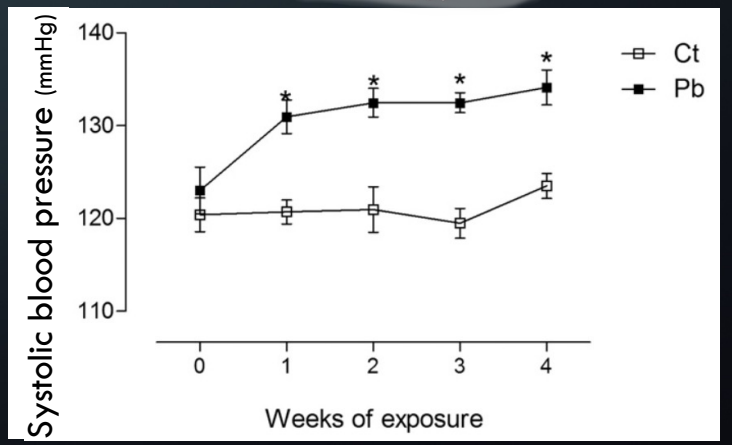
Individual scale (in vivo toxicology)

Cellular scale (in vitro toxicology)

Molecular/atomic scale

Ingestion (30 days) of water additioned with lead acetate at 100 ppm





(Toscano, *Life Sci*, 2017)

Effects on blood pressure and hypertension in humans

Individual scale (cohorts)

Normative Aging Study (475 with hypertension)

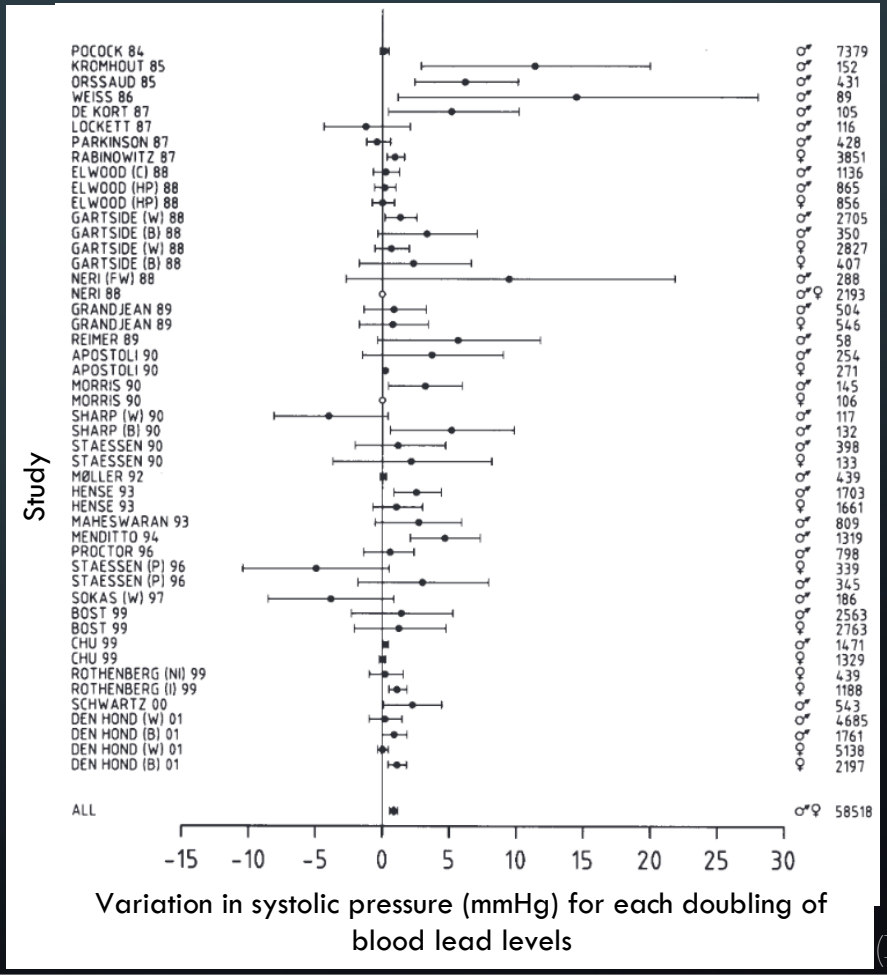
Matrix*	RR** (95% IC)
Tibia	1.19 (1.01-1.41)
Patella	1.10 (0.92-1.31)
Blood	1.11 (0.88-1.40)

*In which lead is quantified.

Relative risk of **treatment-resistant hypertension for an interquartile increase in lead concentration (15.5 µg/g for tibia, 4.6 µg/l for blood).

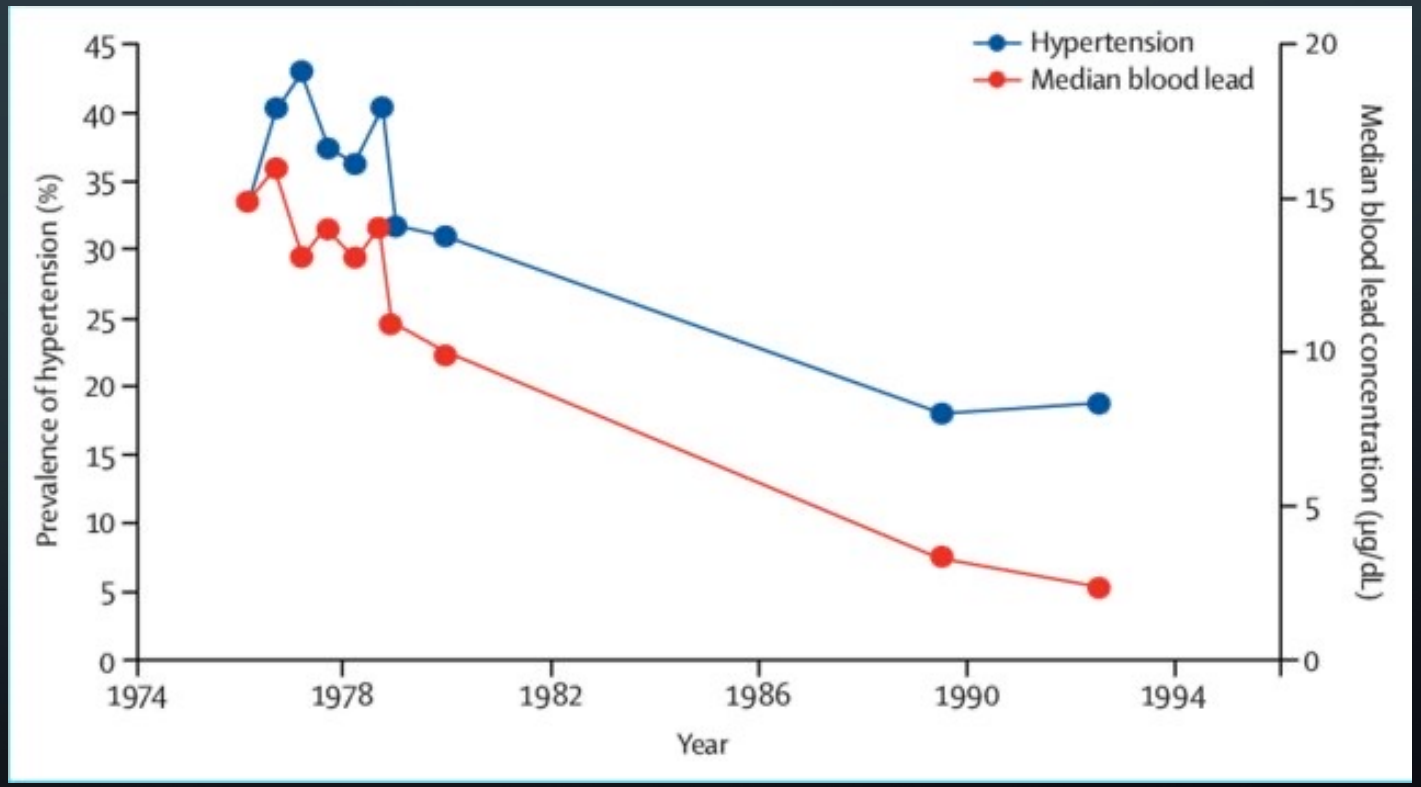
Adjusted for BMI, age, tobacco, income, education level, ethnicity, family history of hypertension.

(Zheutlin, *J Am Hear Ass*, 2018)



(Nawrot, *J Hum Hyp*, 2002)

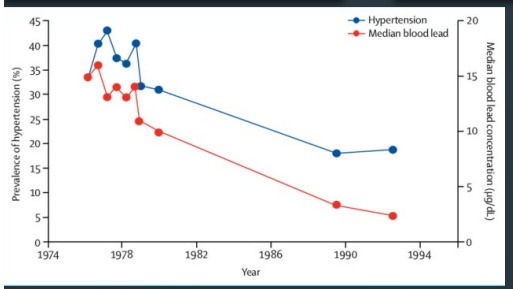
Population scale
(ecological studies)



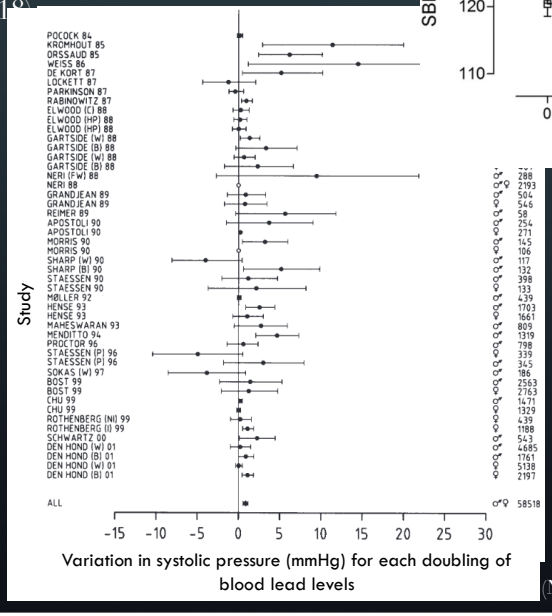
(Lanphear, *Lanc Pub Health*, 2018)

Lead and blood pressure:
Body of evidence from populations to ions

Population scale (ecological studies)	Individual scale (cohorts)	Individual scale (in vivo toxicology)	Cellular scale (in vitro toxicology)	Molecular/atomic scale

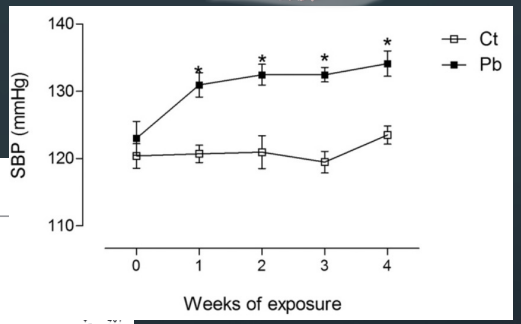


(Lanphear, *Lanc Pub Health*, 2018)

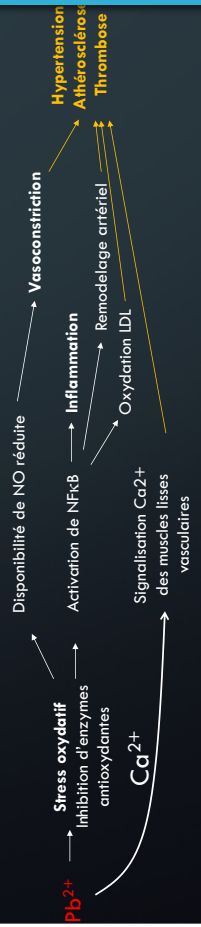


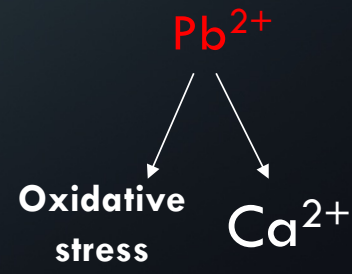
(Nawrot, *J Hum Hyp*, 2002)

Ingestion (30 days) of water additioned with lead acetate at 100 ppm

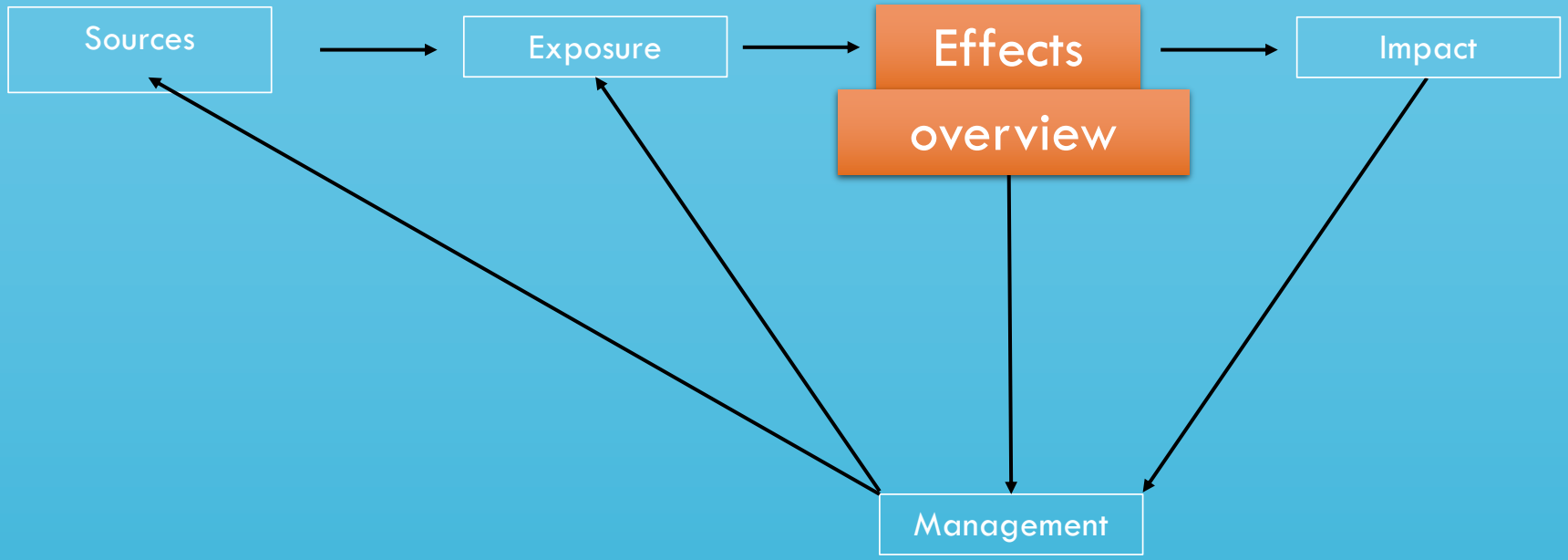


(Toscano, *Life Sci*, 2017)





C.3. Some health effects of lead exposure



Lead and anemia

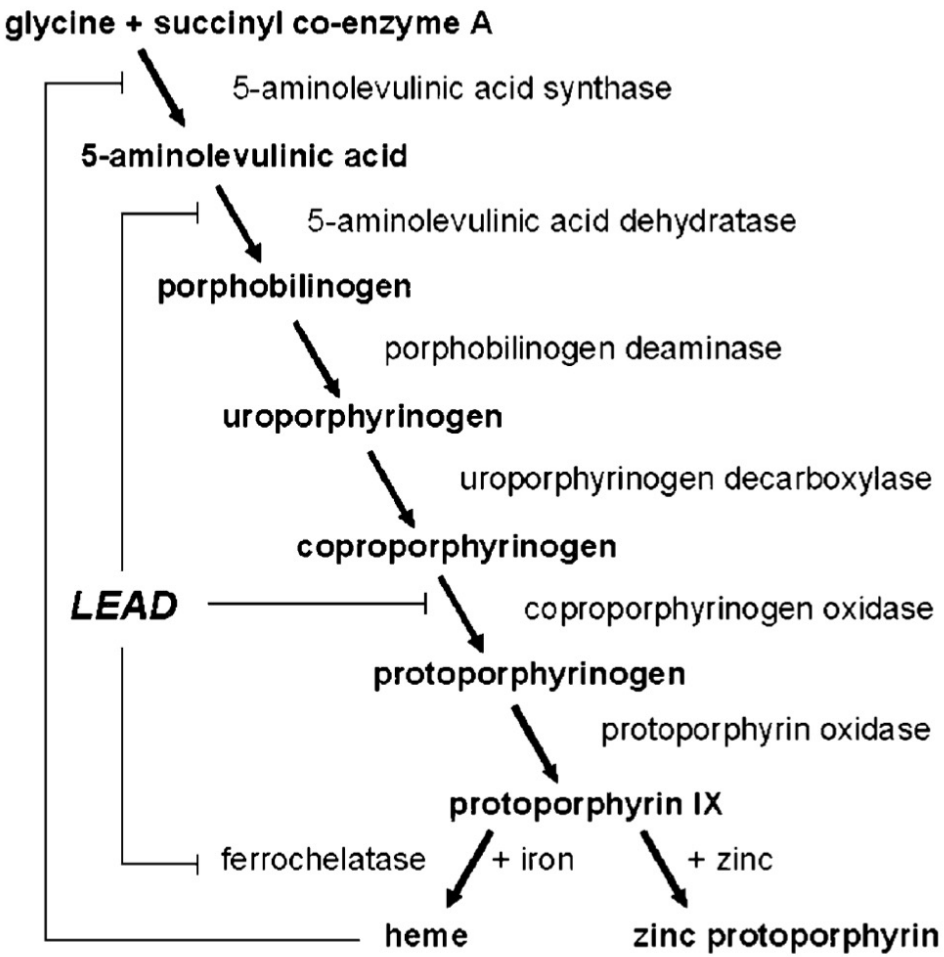
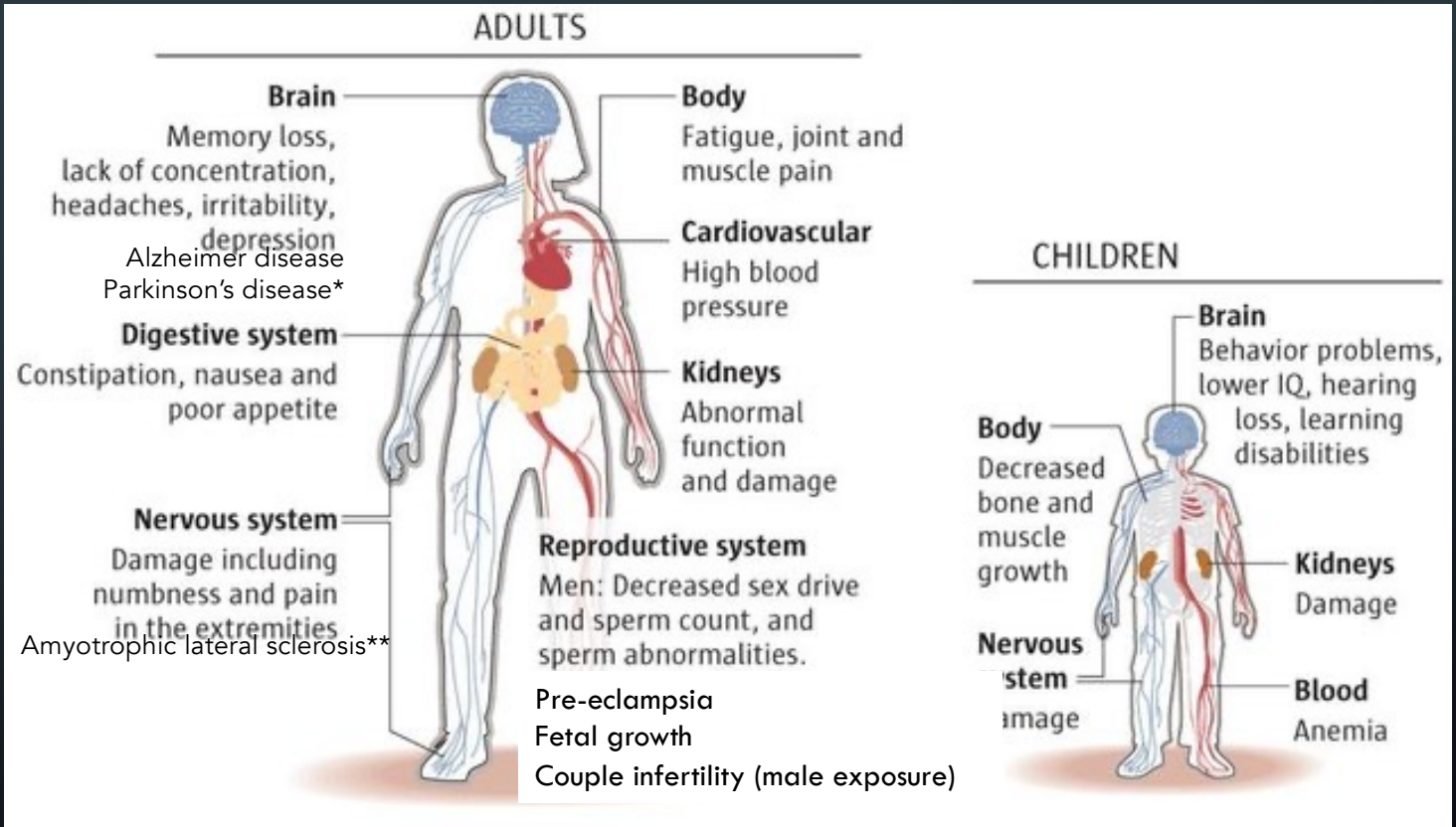


Figure 1. Effect of lead on heme synthesis. Lead inhibits (⊣) 5-aminolevulic acid dehydratase, coproporphyrinogen oxidase, and ferrochelatase. Inhibition of ferrochelatase increases free protophorphyrin IX which chelates with zinc and forms zinc protoporphyrin within the erythroctes, a marker of lead exposure within the past 3 months.

Lead and health: overview

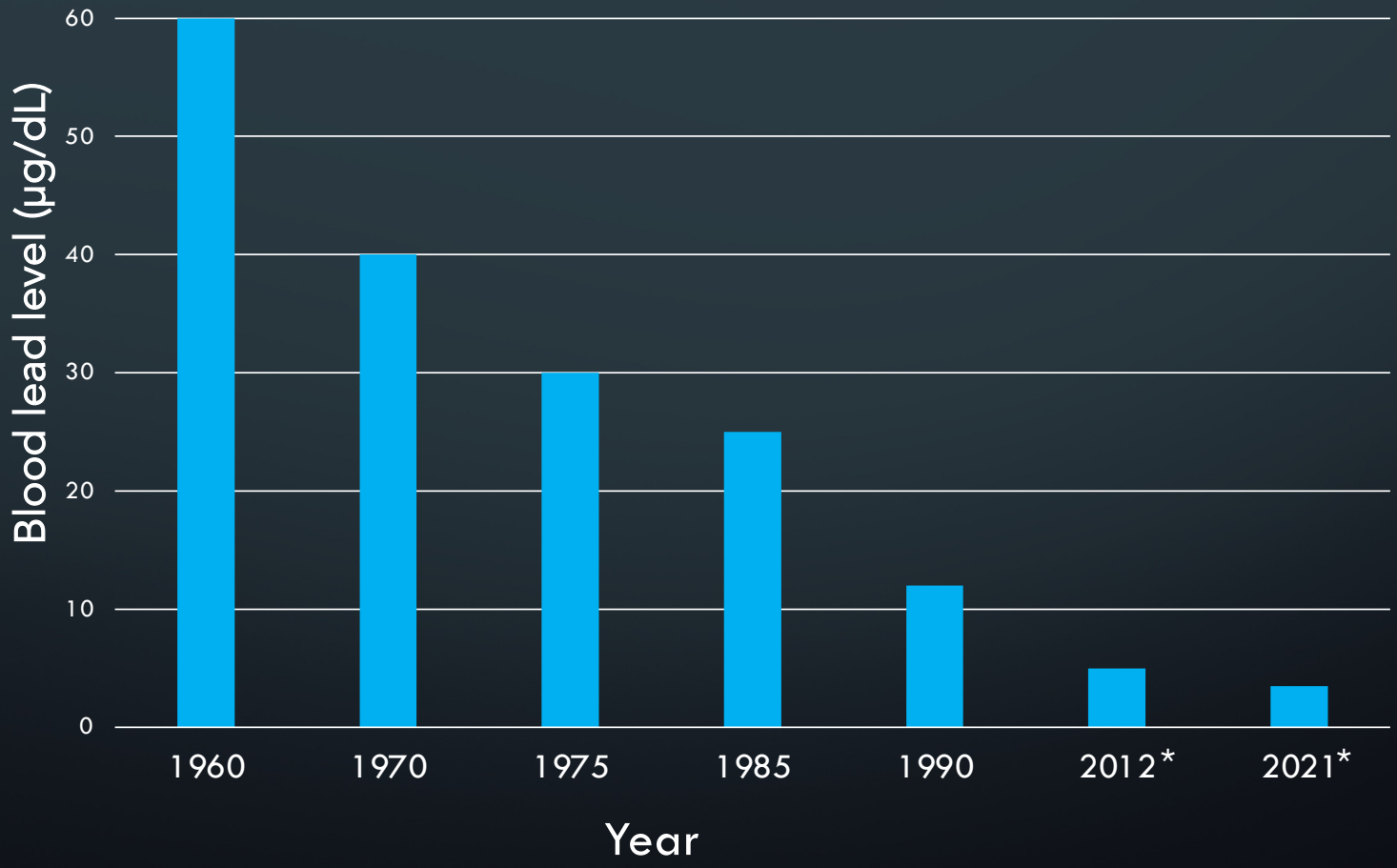


*Weisskopf, *EHP*, 2010

**Wang M, *J Occ Env Med*, 2014

Carcinogenicity: probably carcinogenic to humans (IARC group 2A)
(See also ATSDR, 2012)

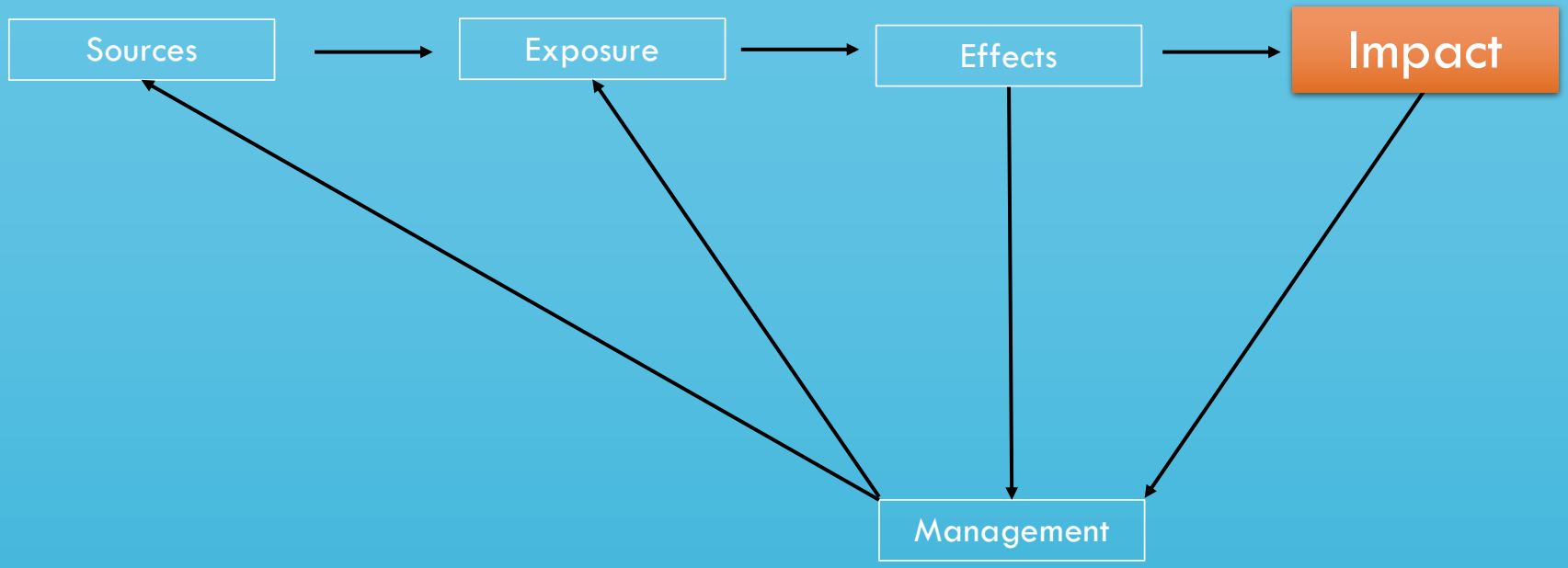
Evolution of blood levels of lead identified as being of concern* for health (CDC, USA)



(*from 2012, the concept of "reference level" was used instead of level of concern)

(Sources: ATSDR and CDC)

D. Population impact of lead exposure

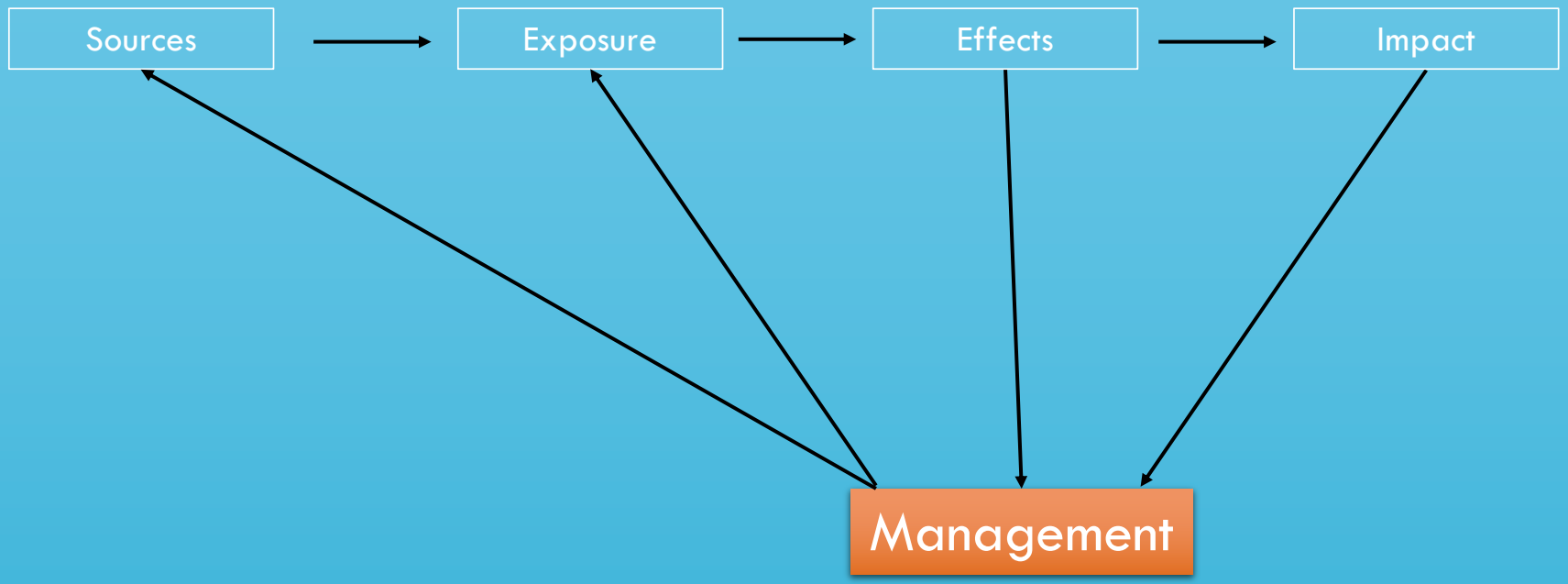


Deaths due to several environmental factors (in million/year; world, 2015)

	GBD study best estimate (95% CI)
Air (total)	6·5 (5·7–7·3)
Household air	2·9 (2·2–3·6)
Ambient particulate	4·2 (3·7–4·8)
Ambient ozone	0·3 (0·1–0·4)
Water (total)	1·8 (1·4–2·2)
Unsafe sanitation	0·8 (0·7–0·9)
Unsafe source	1·3 (1·0–1·4)
Occupational	0·8 (0·8–0·9)
Carcinogens	0·5 (0·5–0·5)
Particulates	0·4 (0·3–0·4)
Soil, heavy metals, and chemicals	0·5 (0·2–0·8)
Lead	0·5 (0·2–0·8)
Total	9·0

(Landrigan, *Lancet*, 2018,)

E. Management of health risks induced by lead



Limiting production and/or use

Detoxification (chelation)
(Gracia, Am J Health Syst Pharm, 2007)
Housing improvement
Workers' protection
Controlled use

Therapy

Non-lead specific
Not very effective for many of the induced pathologies (ALS, IQ alteration...)
Low cost-effectiveness

Risk management

Lead and wine: an early regulation

Dr. Eberhard Gockel, (1636-1703)


Eberhard Ludwig, Earl of Württemberg (1676-1733)

- *Colica Pictonum* (colique du Poitou) was known (under various names) since the Roman times
  - Descriptions by Paul of Aegina (7th Century) and Citois (1639)
  - Other names: Devonshire colic, bilious colic, paralytic colic, saturnine colic, Grimmen (German), "dry belly-ache" (America)
- However, it seems that it was only in 1696 that the disease was identified as being due to lead, that was used to "correct" wine or other alcohols
- Underlying toxicological mechanism: ability of Pb2+ to bind the the sulphydryl (S-H) residues of proteins, including enzymes
- This induces a variety of symptoms, including in the nervous system (paralysis of the peristaltic movement of the gut)
- 1645-1715: unusual quiescence of the sun ("Maunder Minimum), leading to poor wine quality
- Attempts to improve the taste by adding litharge (PbO)
- Eberhard Gockel, a physician living in Ulm, demonstrated that this could transform very sour wines into "the best and loveliest wine" in a few minutes. He developed an assay to detect contaminated wine
- Following this, the Earl of Württemberg banned the use of lead in wine, with penalties as stiff as death in 1696.

(Eisinger, *Med Hist*, 1982)

Management of lead health risks: some historical landmarks

- 1696: Ban of the addition of lead (litharge, PbO) in wine in Württemberg (Ulm)

- 1909: Ban of the use of leaded paints **by professionals** in buildings (France). Application decree published in…**1949**
- 1919: Saturnism recognized as an occupational disease in painters (France)
- 1977: Ban of lead paint in residential properties and public buildings (USA)
- 1992: Official ban of (most) leaded paints (EU). Importation and sale of (most) leaded paints banned in 1993.
- 2019: Ban of lead chromate in paint pigments by the EU court of justice

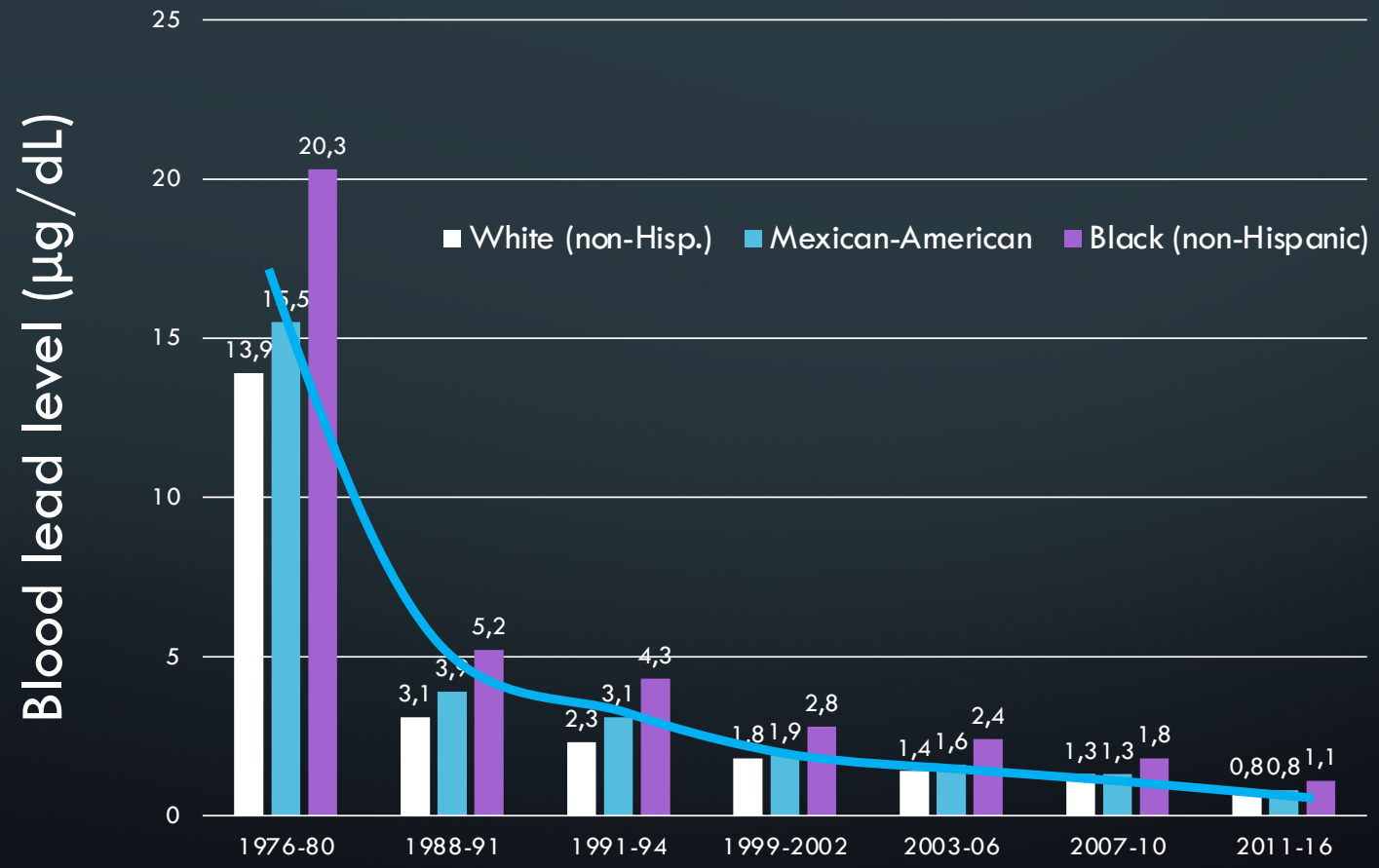
- Mid 1970s: Start of the ban of leaded gasoline (USA)
- 2000: Leaded gasoline banned in France and China
- 2021: Last country to officially ban leaded gasoline

Substitution of harmful compounds: 2 case studies implying lead

Use	Paint	Gasoline additives
Leaded compound	Lead white	Tetraethyl lead (TEL)
Substitute	Zinc white	Ethanol
Discovery of substitute	1845*	1920 (before the invention of TEL)
End of use of leaded compound	1993 (EU)	2000 (EU)

*Patent by Jean Leclaire. See (Rainhorn, 2019)

Changes in blood lead levels (children 1-5 years) as a result of ban of leaded gasoline (USA)

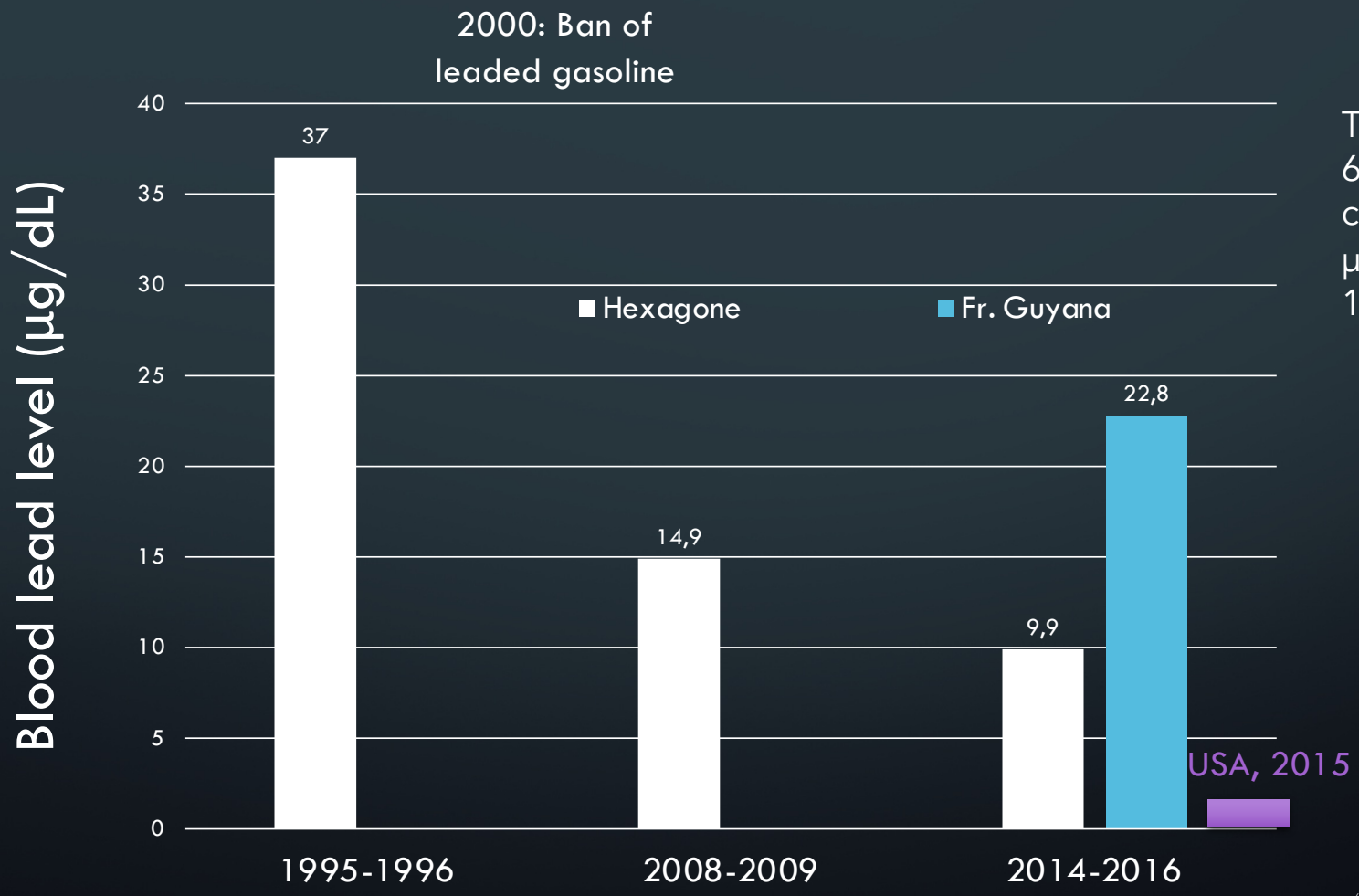


94% decrease in mean blood lead concentration in the population of the USA aged 1-74 years between 1976 and 2016.

The ban on lead in gasoline as one of the great public health successes to improve air quality in the 20th century.

(Adapted from Egan, EHP, 2021)

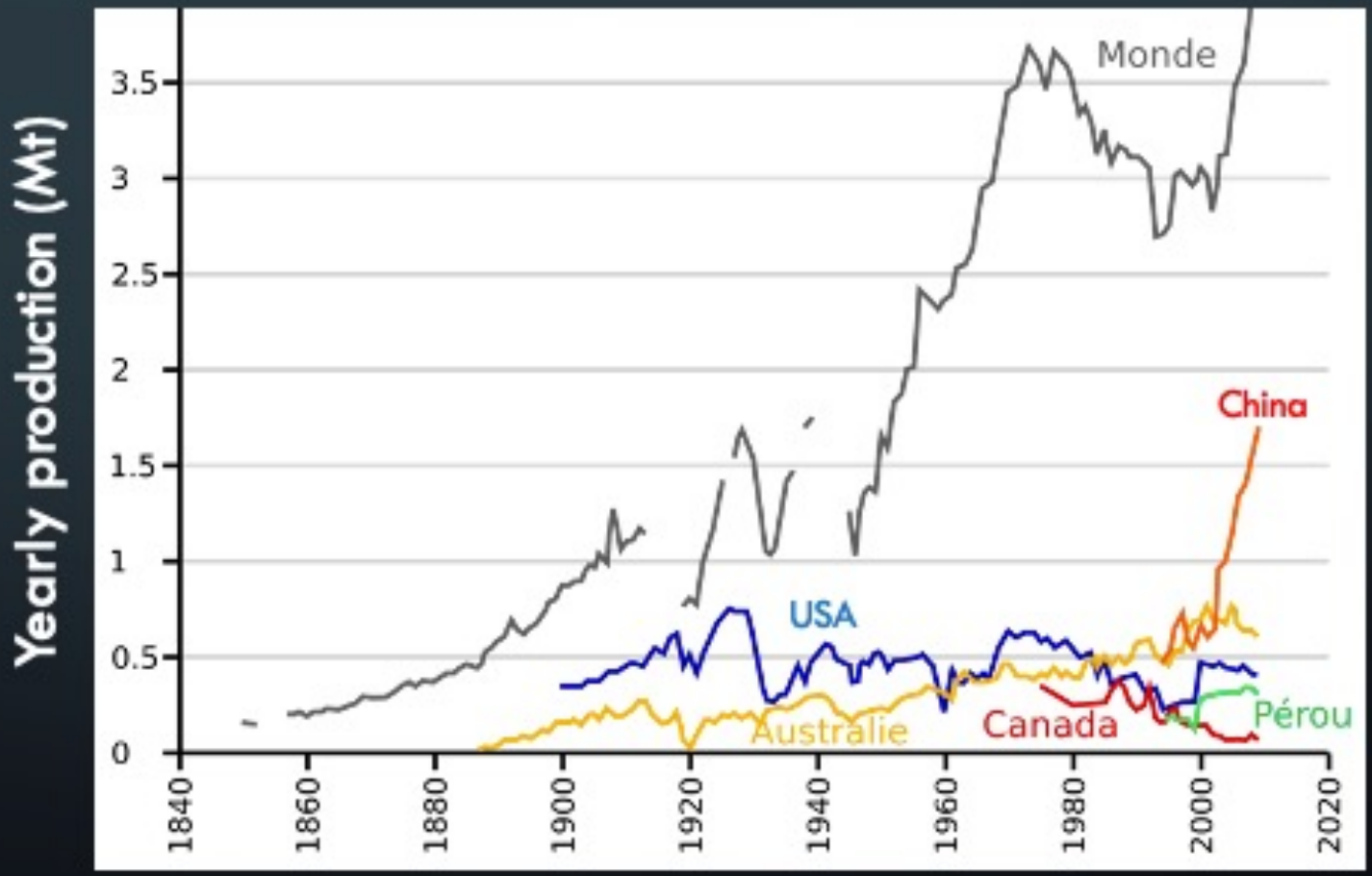
Blood lead levels (**France**, children aged 1 to 6 years, 1995-2016)



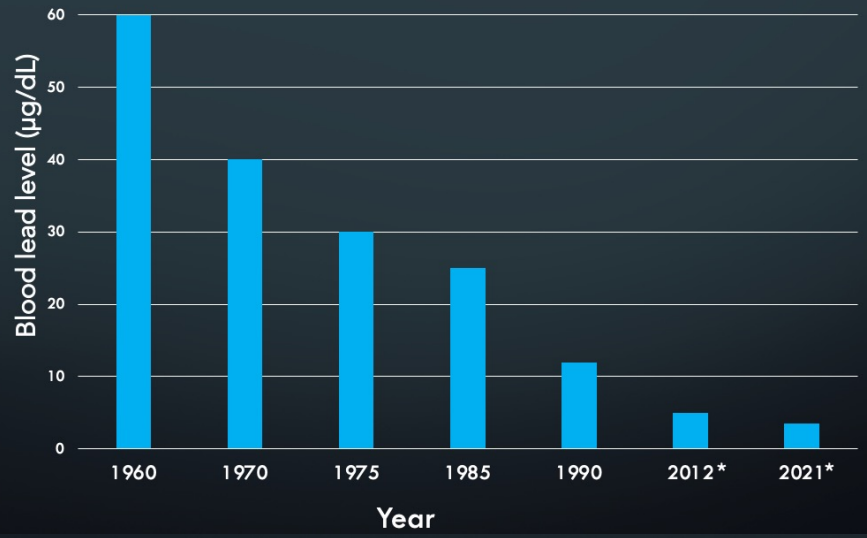
The number of children aged 1 to 6 years with a blood lead concentration greater than 100 µg/L was divided by 20 between 1995-1996 and 2008-2009

(Data from Santé publique France, 2020)

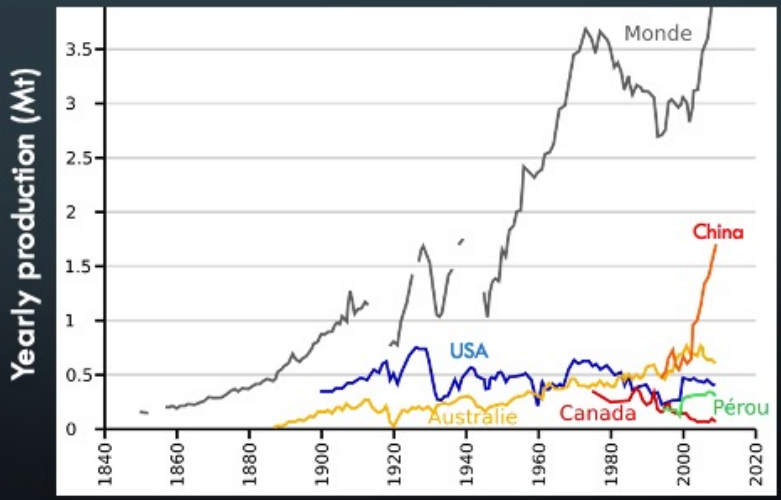
Lead production is still increasing worldwide



Evolution of blood levels of lead identified as being of concern* for health (CDC, USA)



Lead production is still increasing worldwide

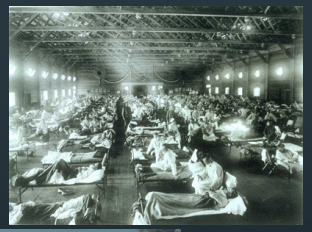


Lead, health and societies: *a provisory conclusion*

- Lead has multiple uses, multiple chemical forms and a variety of biological targets and clinical effects
- For several clinical effects (e.g., on mental retardation/cognition, hypertension), there is consistency between biological knowledge at all scales, from molecules to populations
  - Illustration of the multidisciplinary nature of environmental health research
- These effects prompted risk management decisions
  - These were generally *sectorial* and limited in each sector
  - The slow reaction of decision makers to limit what can be seen as a mass poisoning was made possible by relying on a variety of approaches to generate doubts and obfuscating knowledge in decision-makers and society (e.g., through conflict of interests, marketing techniques…)
- Banning lead from gasoline has had a huge impact in terms of decrease in the health burden due to environmental factors worldwide and in environmental health inequalities
- Lead production is still on the rise. Although increased production does not equate increased exposure (at least on the short term), lead exposure is still a health concern today, in particular in the EU, Asia and many other areas of the world

Is *lead* really the oldest enemy of human health?
Some possible competitors

- Other metals
  - Mercury
  - Arsenic
- Infectious agents
  - *Yersinia pestis*
  - Influenza viruses
- Other animals
  - Tyrannosaurus rex
- Ethanol
- Man



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