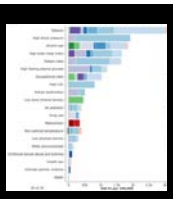


A global vision: The burden of disease attributable to the environment

Le fardeau sanitaire dû à l'environnement

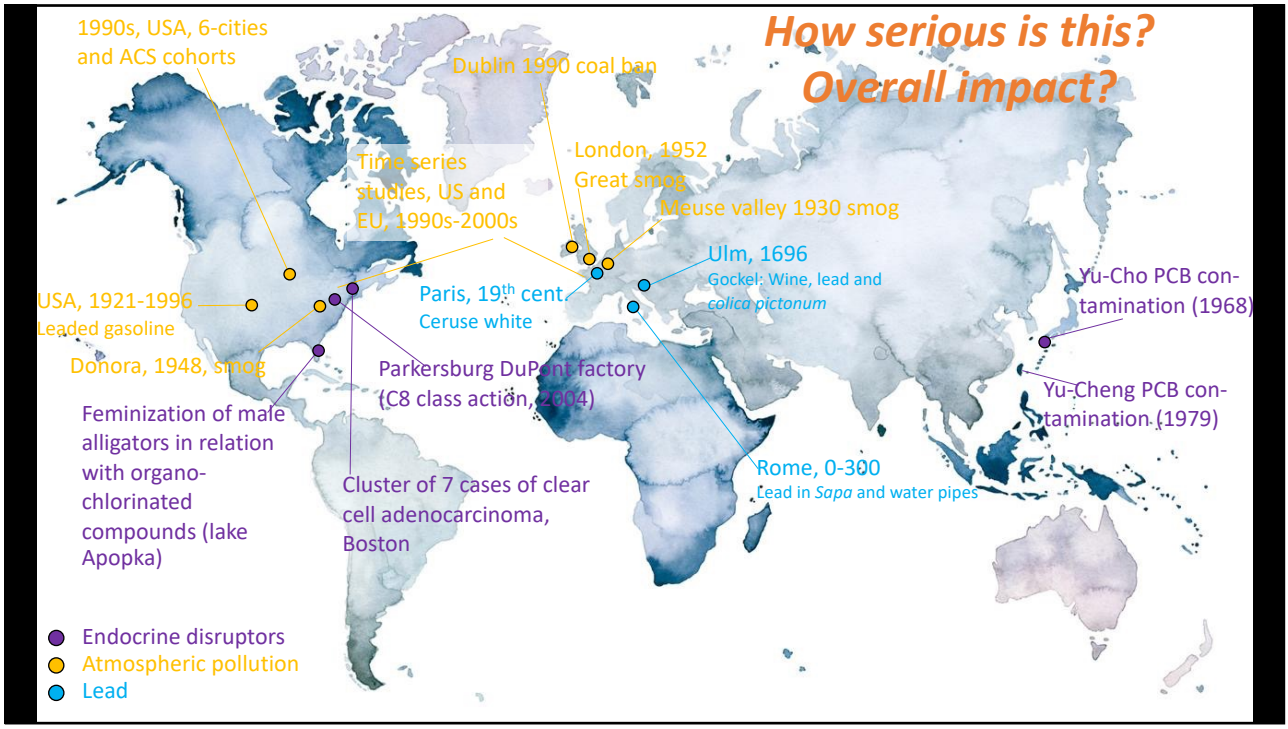
Rémy Slama
Collège de France & Inserm

The relations between human health and the environment in the Anthropocene

Lecture #8 – 1 June 2022

COLLÈGE DE FRANCE 1530

1



2

3 types of measures in environmental epidemiology

Frequency
of disease, exposure…

Count
Incidence
Prevalence
Other rates
Durations
Amount
Level
(*Standardized* or not)
…

Association
between exposure and disease

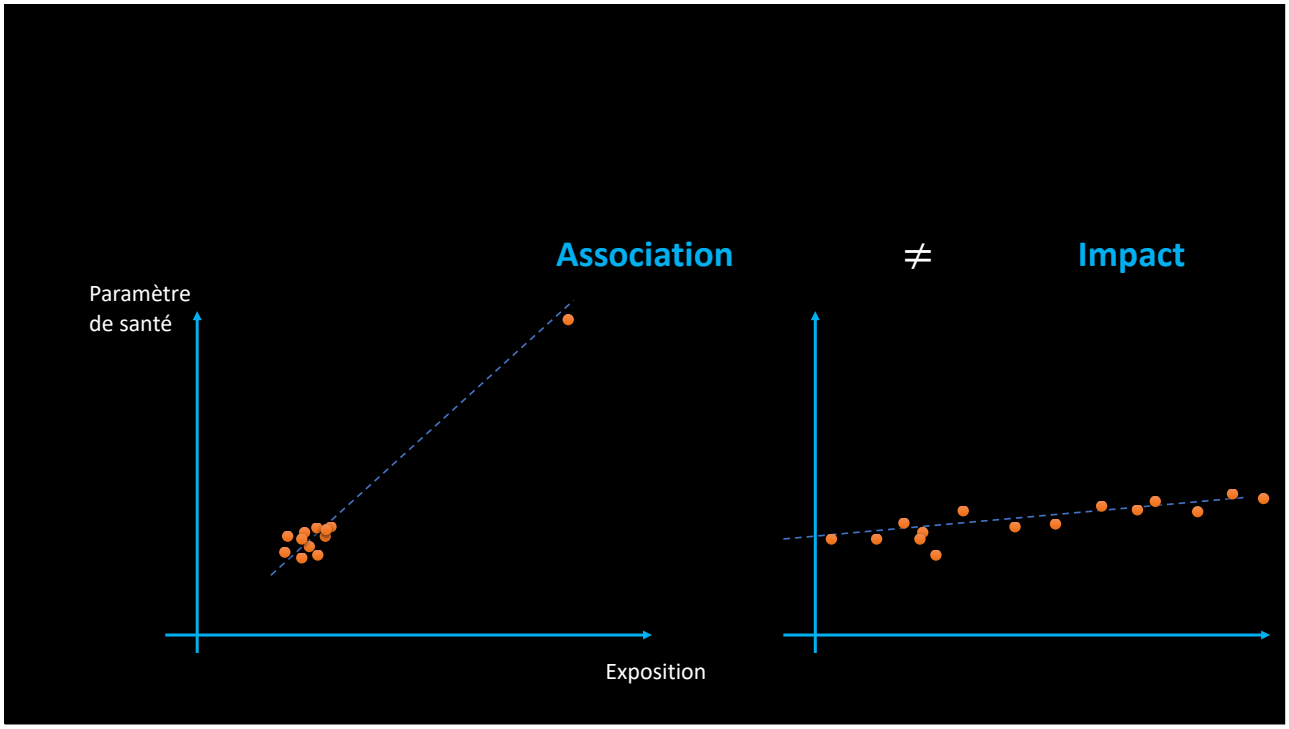
Coefficient of correlation
(standardized) incidence ratio (SIR)
Relative risk (RR)
Odds-ratio (OR)
Hazard rate (HR)
Regression parameters
(p-value)
…

Impact
of exposure on society

Number of attributable cases
…of healthy life years lost
Attributable fraction
"Risk"
Share of variance explained
Predictive power
…

These can all be accompanied by *qualifying measures*:
Indicators of accuracy, uncertainty, robustness, level of evidence…

3



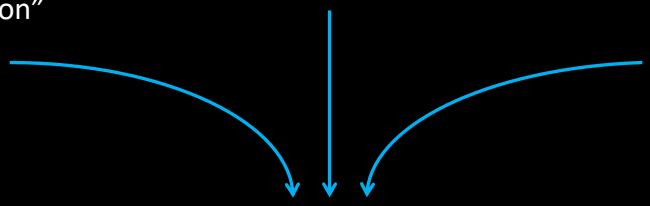
4

Origins of a concept

Health impact assessment,
Regulatory impact assessment
(law, EU, international agencies…)

"Attributable risk fraction"
(epidemiology)
(Poole, *Ann Epid*, 2015)

"Risk assessment"
(regulatory toxicology)



Environmental health burden

5

Lecture overview

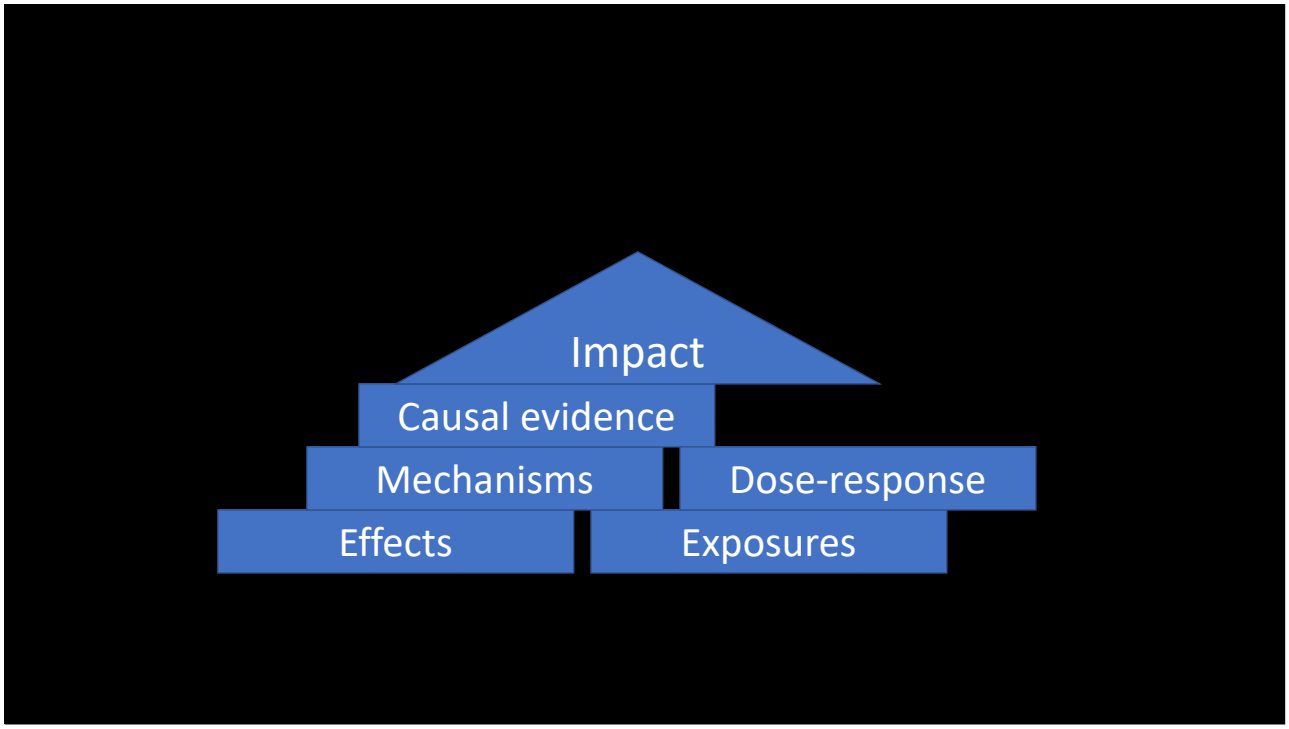
A. Introduction to risk assessment: motivation and challenges
B. The toxicological view to environmental risk assessment
C. The epidemiological view to environmental risk assessment (1): Single exposure view
D. The epidemiological view to environmental risk assessment (2): Integration of multiple exposures
E. Perspectives

Causal pluralism and public health *(seminar of Pr. Federica Russo)*

6

A. Introduction

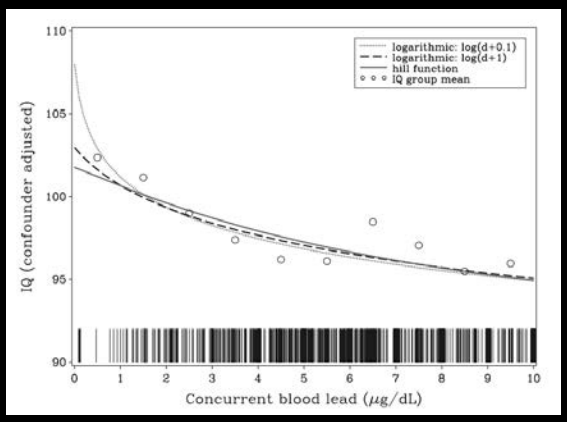
7



8

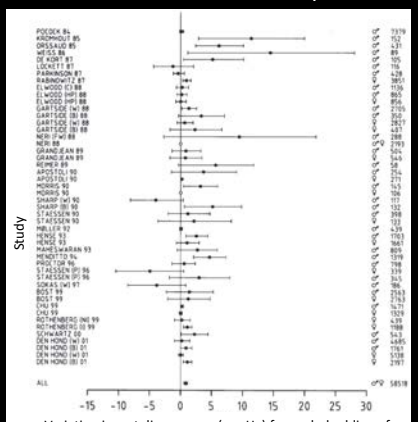
Dose-response functions are somewhat abstract entities in terms of public health…(1)

Lead blood level and Intelligence Quotient



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

Lead blood level and blood pressure

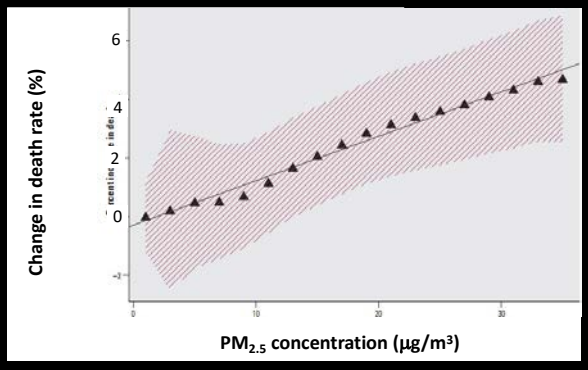


(Nawrot, *J Hum Hyp*, 2002)

9

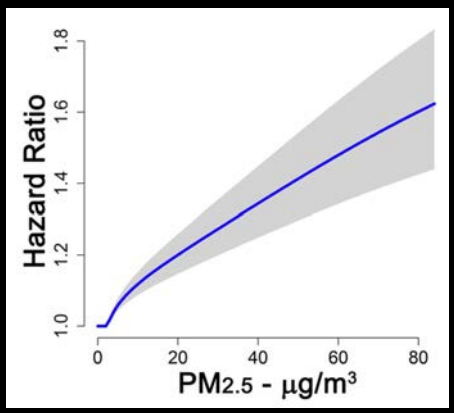
Dose-response functions are somewhat abstract entities in terms of public health…(2)

Fine particulate matter *daily* airborne concentration and mortality (time-series analysis)



(Schwartz, *EHP*, 2002)

Fine particulate matter *long-term* airborne concentration and mortality (cohort analyses)



(Burnett, *PNAS* 2018)

10

London (Dec. 1952) smog episode

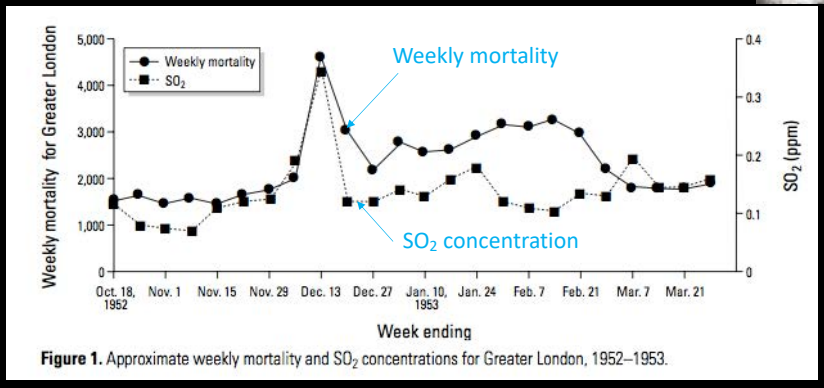


Figure 1. Approximate weekly mortality and SO_2 concentrations for Greater London, 1952–1953.

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)

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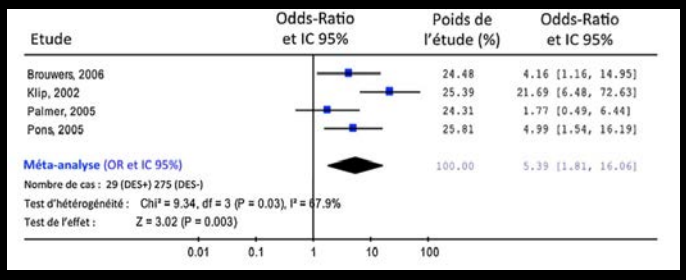
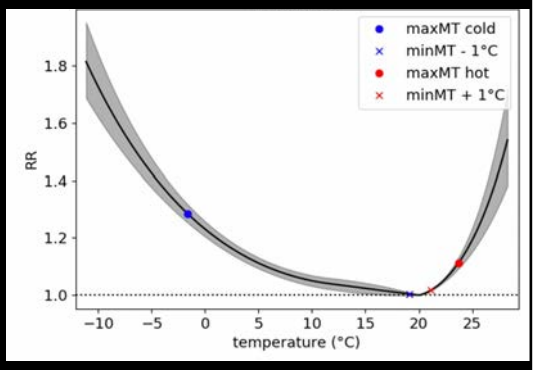
Dose-response functions are somewhat abstract entities in terms of public health…(3)

Diethylstilbestrol use during pregnancy and risk of male genitalia malformation (hypospadias) in the grand-son



(Slama, *J Gyn Obs*, 2013)

Daily temperature and mortality



Time-series analysis

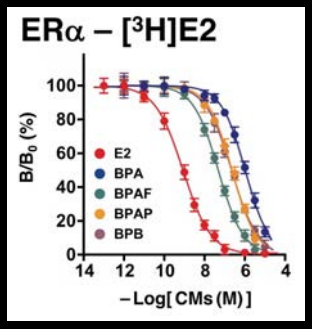
CépiDc (Inserm), France, 1968-2016

(Lehmann, *Am J Epid*, in press)

12

Dose-response functions are somewhat abstract entities in terms of public health…(3)

Bisphenol A (BPA) binding to Estrogen nuclear receptor (ERα)
(Dose response relation from in-vitro assay)



(Liu, *Tox Appl Pharmacol*, 2017)

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Relevance of environmental health impact assessment

- (Generally) provides a quantitative answer on a scale relevant for public health
  - Typically a number of cases in a specific population
  - More easy to interpret than a dose-response function or a relative risk or an odds-ratio
  - Provides a bridge between science and decision-making
- (Deceivingly) easy to interpret
- Provides an integrated view (across all effects of an exposure, within a population, possibly across exposures)
  - allowing comparisons (across exposures, regions, periods?)
- Can serve as a basis for *cost-benefit* assessments and hence be used to compare various risk management options

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Some *issues* of environmental health impact assessment

- Adding cases due to various causes / conceptual issues related to the multifactorial nature of human diseases
- Many hidden hypotheses. Conceptually more subtle than it may seem.
- As an end-of-chain product, health impact assessments potentially suffer from the uncertainties along a long chain
- Terminology (undefined terms/different definitions in various areas)
- "Grouping" causes
- Defining "the environment"
- *Toxicology*-based and *epidemiology*-based approach to health impact assessment tend to widely differ
- Ethical issues (economic cost of human life; use of animal models for toxicological risk assessment)

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Examples of impact assessments

- World war I caused 15 to 24 million deaths
- The 1918 influenza killed 30 to 50 million people
- Covid-19 killed about 130,000 people in France in 2020-2021
- Road traffic kills 18,000 persons/year in France (1972)
  (corresponds to deaths within 30 days after the accident)
- Road traffic kills 3,000 persons/year in France (2020)
- Tobacco smoke kills 3 million persons worldwide
- Tobacco smoke costs €**120** Billion to the French society each year
- Outdoor air pollution kills 4 million persons worldwide
- 34 million people lost their job because of the 2008 economic crisis

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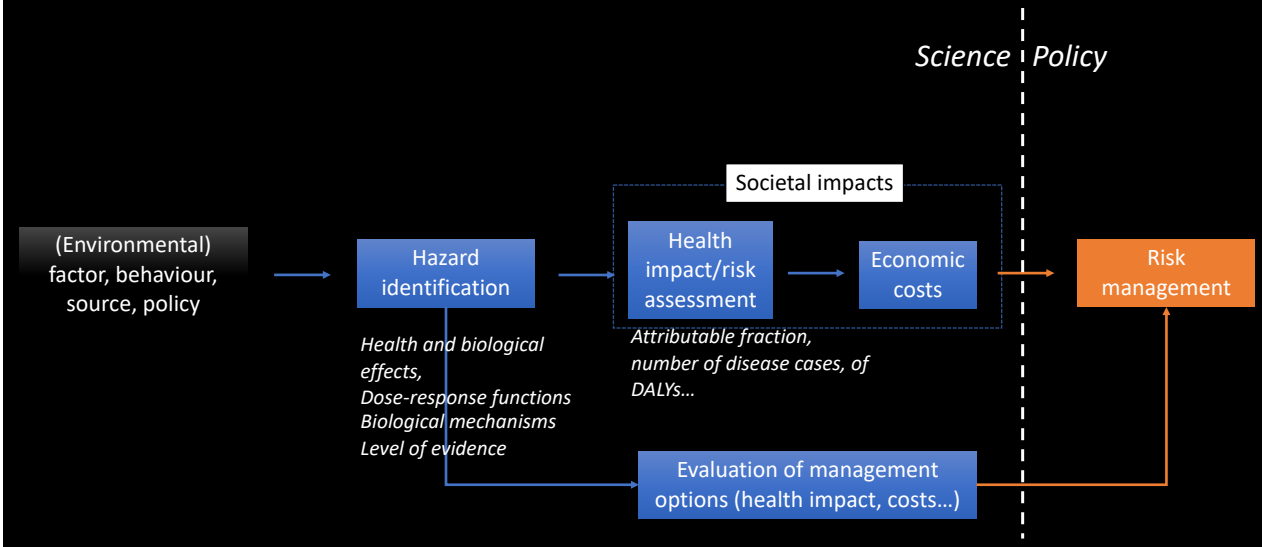
From hazard identification to risk management



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Terminology

Hazard

Something that can cause harm

Qualitative notion

List of biological hazards, of carcinogens, of endocrine disruptors…

Exposure

Contact with a hazard

Expressed as a frequency, amount, number of subjects, distribution

Risk (or impact)

The actualisation of the hazard, expressed in probability or number of cases

Quantitative notion

Risk =f(exposure)

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Heritability of some phenotypes and chronic diseases

Phenotype	Heritability (from familiy studies)
Type 1 diabetis	90 %
Eye colour	80 % *
Height	80 %
Autistic spectrum disorders	80 % ***
Schizophrenia	70-80 %
Crohn disease	60-80 %
Multiple sclerosis	30-80 %
Thyroid cancer	**53 % ** **
Cholesterol level (HDL)	50 %
Obesity (BMI)	40-60 %
Type 2 diabetis	30-60 %
Breast cancer	**25** - 30 %**
Testis cancer	25 % **
Central nervous system cancer	12 % **
Lung cancer	8 % **
Leukaemia	≈ 1 % **

From Visscher *et al.*, 2012, unless otherwise specified; * Bräuer et Chopra, 1978 ; ** Czene *et al.*, 2002 ; *** Sandin *et al.*, 2017.
See also Slama, Le Mal du Dehors, Quae, 2017.

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B. The toxicological approach to risk assessment

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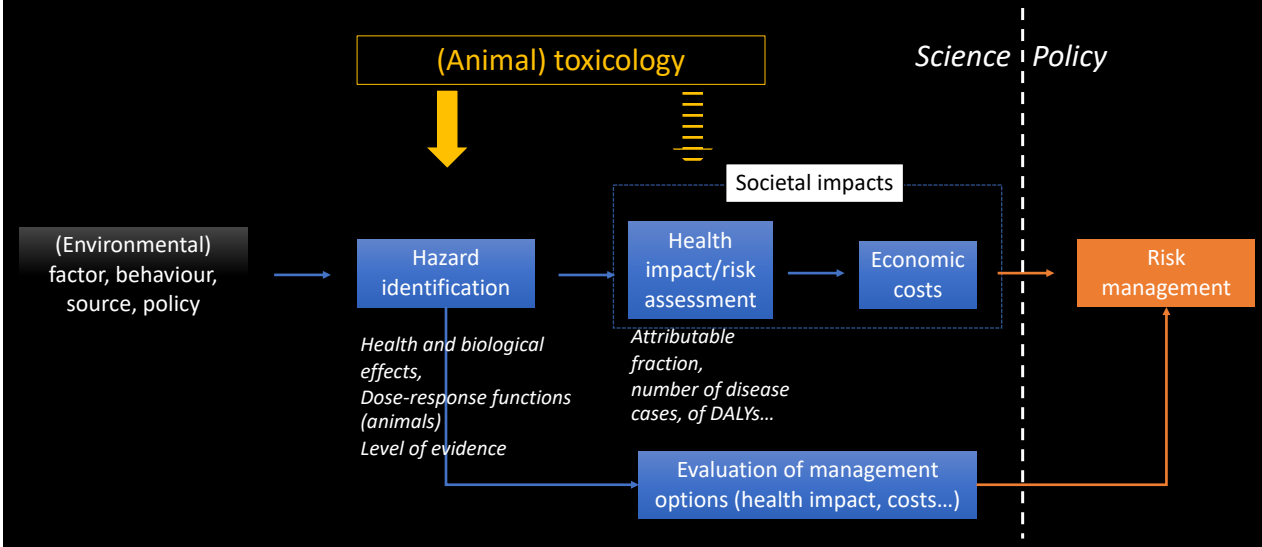
From hazard identification to risk management



Challenge: Is it possible to provide quantitative results in humans while working on another species? Issues related to between-species extrapolation (rather a qualitative exercise)

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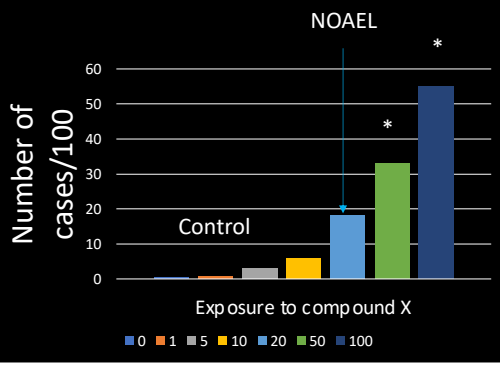
The **NOAEL** (no observed adverse effect level) approach: *Principle*

- Make random groups of equally-sized test animals (typically 10-20 per group) exposed at different levels to the compound
- Compare the frequency of the adverse outcome between each tested dose and the control group
- Identify the highest dose without 'significant difference' (i.e., generally for which p>0.05) in terms of adverse outcome frequency
- This is the NOAEL (no observed adverse effect level)
- Divide the NOAEL by an uncertainty factor (typically, 100-1000)
  - This is the tolerable intake (or daily tolerable intake, DTI)(or *acceptable* daily intake, for food additives)

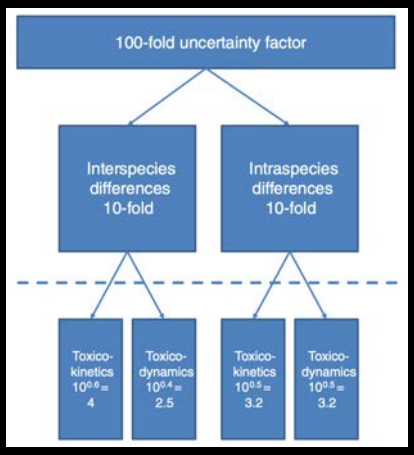
« A TDI is an estimate of the amount of a substance in air, food or drinking water that can be taken in daily over a lifetime without appreciable health risk. TDIs are calculated on the basis of laboratory toxicity data to which uncertainty factors are applied. »



22

The **uncertainty factor**, a (magic?) value to take into account between- and within-species variability in sensitivity…

DTI = NOAEL / UF



(Martin, *Env Health*, 2013)

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Safety versus *risk* assessment

- The Daily tolerable intake aims to indicate a "safe area":
  - If all members of a population are exposed below the DTI, then, assuming that all hypotheses of the DTI estimation are valid, there is no reason to believe that the exposure entails a risk for the general population
  - If all (or some) members of the population are exposed above the DTI, then the population cannot be said to be safe (which of course does not mean they can be said to be at risk)
  - There is no direct estimate of the health risk in humans (e.g., in terms of number of disease cases attributable to the exposure)

For this reason, this approach actually corresponds to "safety" assessment (rather than risk assessment strictly speaking)

From the DTI, one can estimate the ratio of the DTI to the estimated or observed actual exposure ("margin of exposure") (the higher the better)

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Illustration: Safety of the diet of children

Tableau 3 : Conclusions établies en fonction de la caractérisation du risque toxicologique

Résultats	Statut au regard du risque
Dépassement significatif de la VTR ou marge d'exposition faible	Situation jugée préoccupante
Dépassements non significatifs ou non robustes ou Dépassements significatifs et robustes de la VTR sous l'hypothèse haute (UB) seule, c'est-à-dire le scénario qui majore les teneurs et donc l'exposition ou Pas de dépassement avec une VTR robuste uniquement pour la population adulte mais exposition proche	Risque ne pouvant être exclu
Aucun dépassement de la VTR ou marge d'exposition suffisamment élevée (proposée pour chaque substance)	Risque jugé tolérable ou acceptable*
Conditions ne permettant pas de mener une ERS pertinente : par exemple, point de départ toxicologique non établi du fait de l'absence de données ou jugé pas assez robuste	Impossibilité de conclure quant au risque

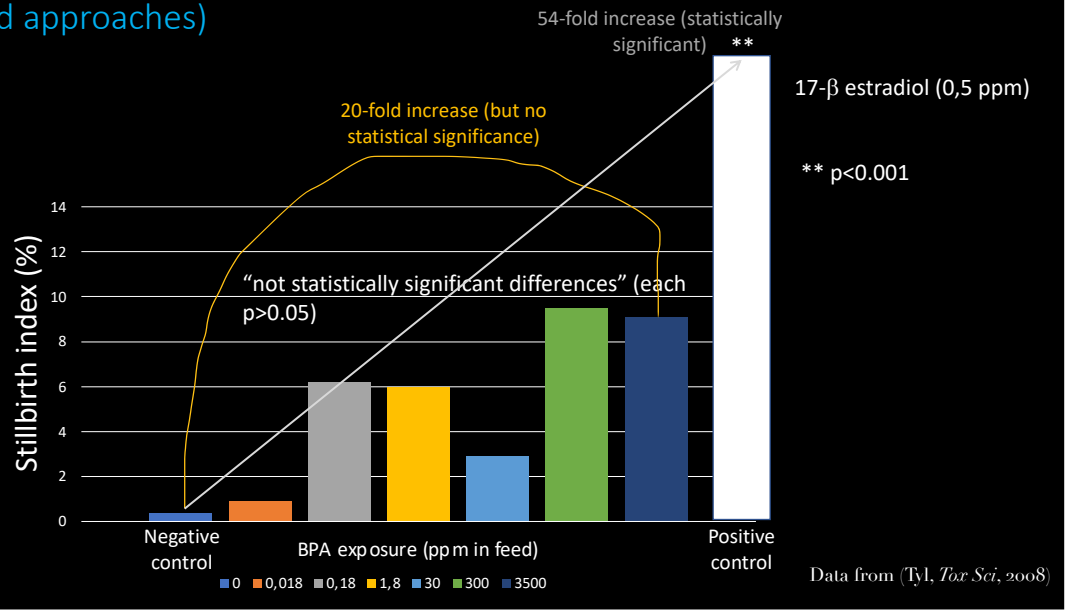
* Le terme « tolérable » est employé pour les substances présentes de façon non intentionnelle dans les aliments (par exemple, les polluants organiques persistants ou les mycotoxines). On utilise alors une VTR de type dose journalière/hebdomadaire/mensuelle tolérable (DJT, DHT, DMT, etc.). Le terme « acceptable » est utilisé pour caractériser le risque dans le cas de substances dont l'utilisation est soumise à une évaluation préalable (par exemple, les additifs ou résidus de pesticides). On utilise alors une VTR de type dose journalière admissible (DJA).

(Anses, rapport EATi, 2018)

	Situation jugée préoccupante	Risque ne pouvant être exclu	Risque jugé tolérable ou admissible	Impossibilité de conclure quant au risque
Eléments traces métalliques et minéraux	plomb**, arsenic inorganique**, nickel	aluminium, méthylmercure**, strontium, chrome VI, selenium (> 1 an), cobalt, baryum, cadmium**, cuivre (> 1 an)	chrome III, mercure inorganique, antimoine	Germanium, cuivre (< 1 an), sélénium (< 1 an), argent, arsenic organique, étain**, gallium, tellure, vanadium
Polluants organiques persistants	Dioxines et furanes**, polychlorobiphényles**		Polybromodiphényl éthers (7 congénères), PBDE-209, polybromobiphényls, hexabromocyclododécane, Acide perfluorooctanesulfonique, Acide perfluorooctanoïque, tétrabromobisphénol A	Acides perfluoroalkylés (autres que PFOS et PFOA)
Composés néoformés	Acrylamide, furane		Hydrocarbure aromatiques polycycliques**	
Mycotoxines	Toxines T2/HT2**, déoxynivalénol** et ses dérivés	Ochratoxine A**, aflatoxines**	Nivalénol, patuline**, fumonisines**, zéaralénone**	Toxines d'*Alternaria*
Substances issues de la migration de matériaux au contact des denrées alimentaires		Bisphénol A	Benzophénone, 4-méthylbenzophénone (4-MBP), nonylphénols, BADGE et produits d'hydrolyse, DEHP, DnBP, DiDP & DiNP, BBP	*4-tert*-octylphénol, 4-hydroxybenzophénone (4-HBP), 4-benzoylbiphényle (PBZ), 2-isopropylthioxanthone (ITX), Dérivés chlorhydrines du BADGE, DiBP, DEP, DCHP, DnOP
Phytoestrogènes et stéroïdes sexuels d'origine animale		Génistéine (chez les consommateurs de produits à base de soja)	Génistéine (chez les non consommateurs de produits à base de soja)	17β-testostérone & 5α-dihydro-testostérone, 17α et 17β-estradiol et estrone, progestérone, et autres stéroïdes

25

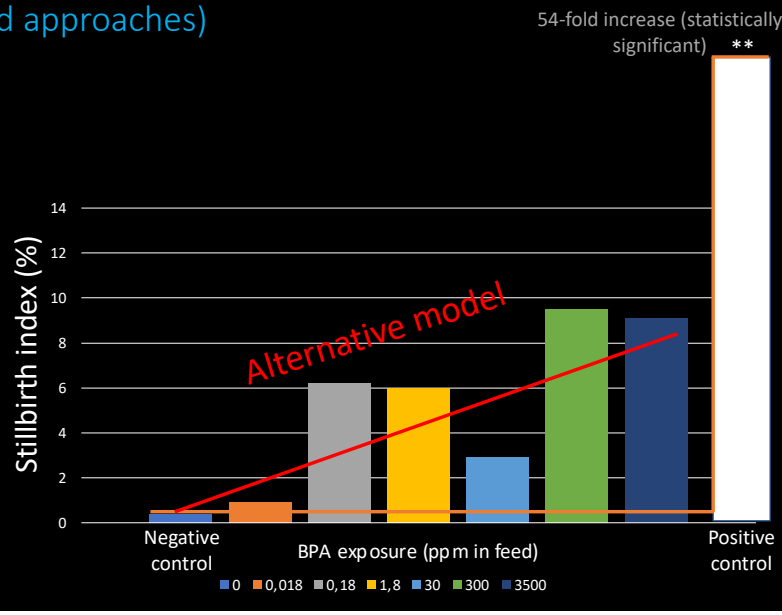
Past regulatory toxicology studies were often underpowered in design (in addition of being analysed by little-powered approaches)



Data from (Tyl, *Tox Sci*, 2008)

26

Past regulatory toxicology studies were often underpowered in design (in addition of being analysed by little-powered approaches)



17-β estradiol (0,5 ppm)

** p<0.001

Authors' conclusion (no expected effect of BPA on stillbirth risk until at least 3500 ppm)

Data from (Tyl, *Tox Sci*, 2008)

27

(Original publication)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0	0.018	0.18	1.8	30	300	3500	0.5
Still birth index (%)[a,b]								
F1	0.4 ± 0.4	0.9 ± 0.7	6.2 ± 3.9	6.0 ± 3.9	2.9 ± 2.6	9.5 ± 5.7	9.1 ± 4.5	21.5*** ± 8.1
							0.0 ± 0.0	5.8 ± 5.0

(Tyl, *Tox Sci*, 2008)

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Why comparing equal-sized groups and testing for pairwise differences with a control group is not an efficient way to identify thresholds…

- Interpreting a "non-significant" test (corresponding to a p-value above a threshold of usually 0.05) as *evidence of a lack of effect* (while it generally should only be seen as lack of evidence of an effect) is a statistical mistake
- Remember that the p-value of a test depends on the difference between the compared groups *and* the size (number of observations) of each group
  - The lower the expected risk difference, the higher the number of observations should be in each group to maintain a given statistical power
  - Comparing pairs of (small) groups limits power, compared to an approach that would simultaneously consider all observations
- There are more rigorous and powerful ways to statistically test for the existence of possible thresholds in a dose-response function (e.g. using piecewise linear models)

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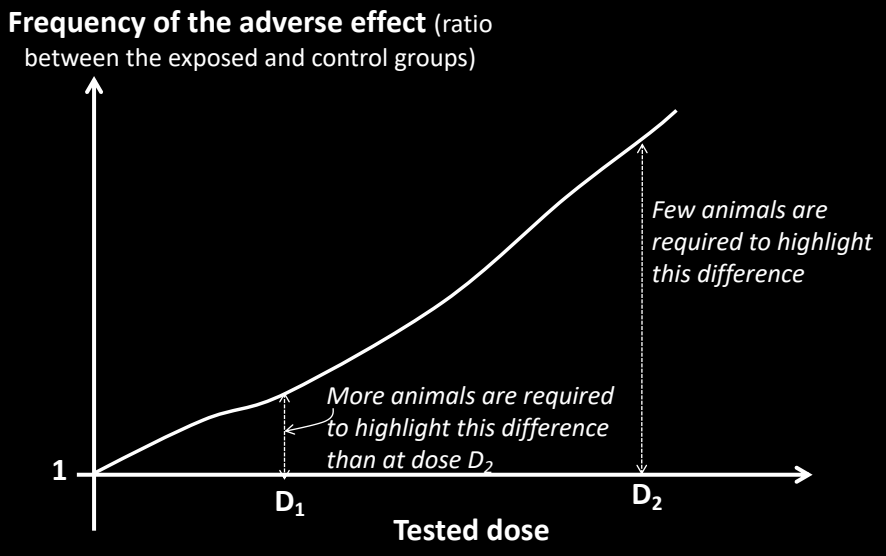
Why making tests relying on equal-sized groups is not a good approach



30

More conceptual issues with thresholds…

Metrological threshold ≠ Biological threshold ≠ Management threshold

- The experimental NOAEL/NOEC is not equivalent to the true biological threshold but rather reflects the limit of detection of the method for that endpoint,
- The sensitivity of the biological outcomes considered by the tests used in regulatory toxicology (in particular for endocrine disruptors, such as those validated by OECD guidelines) may be limited (e.g., organ weight…)
- Lack of consideration of mixtures/cumulative exposures

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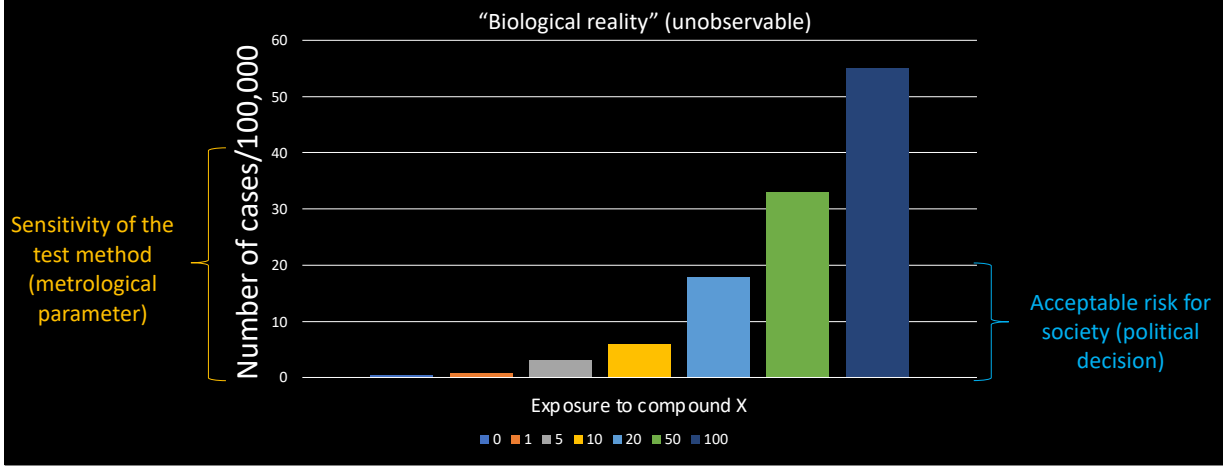
More conceptual issues with thresholds…

Test threshold ≠ Biological threshold ≠ Management threshold



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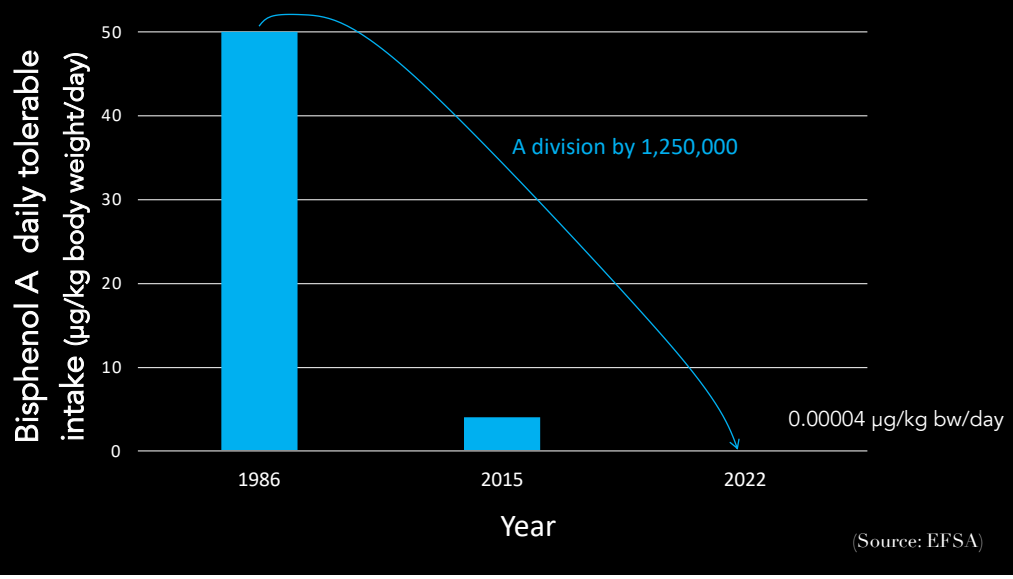
Remember that the estimation of NOAEL carries strong uncertainties…
Evolution of the bisphenol A Daily Tolerable Intake (EFSA, EU)



(Source: EFSA)

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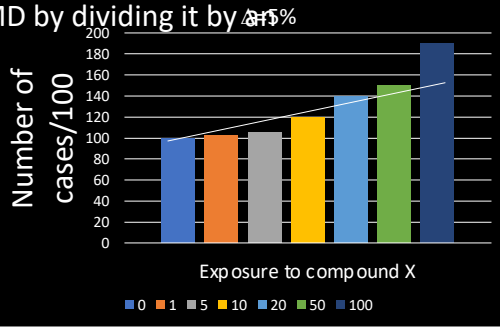
The benchmark dose (**BMD**) approach

- This time an overall fit is done on the data (instead of pairwise comparisons with the control group)
  - This allows to derive a dose-response function
  - No necessary "threshold" identification or assumption
- The *benchmark dose* is given as the dose eliciting a predefined change in the outcome (e.g., a 5% or 10% change)
- A daily tolerable intake can be provided from the BMD by dividing it by a 5% uncertainty factor



(Slob, *Crit Rev Toxicology*, 2014)

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Extending the toxicological approach to risk assessment to the context of mixtures

1. Hazard index (HI) method (Teuschler & Hertzberg, *Toxicology*, 1995)

2. Mixture assessment factor (MAF)

   Principle:
   Considering that populations may be exposed not to one but to several compounds that may contribute to a given toxic effect, the reference dose (e.g., NOAEL, DTI…) for each given compound could be divided by a « safety » factor (the MAF) allowing to consider that other chemicals contributing to the same effect will likely co-exist.
   The MAF may be estimated as the number of compounds that "dominate" the combined effect considered (not the total number of chemicals in the environment).(RIVM, 2016)
   Values of 10 to 100 have been suggested for the MAF

   DTI = NOAEL / (UF x MAF)

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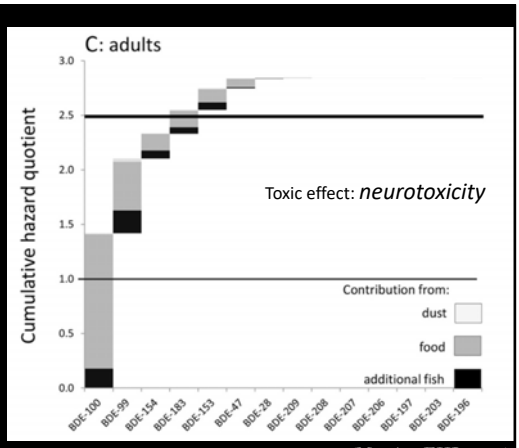
Hazard index (HI) method

For all compounds i=1…n contributing to a specific toxic effect, estimate

$$HI = \sum_{i=1}^{n} \frac{E_i}{RfD_i}$$

Where
E_i is the estimated intake (exposure) for compound i
RfD_i is the reference dose for this compound
-Possibly a Tolerable daily intake
-or preferably a benchmark dose corresponding to the toxic effect of interest, e.g., the ED_{10} for this effect



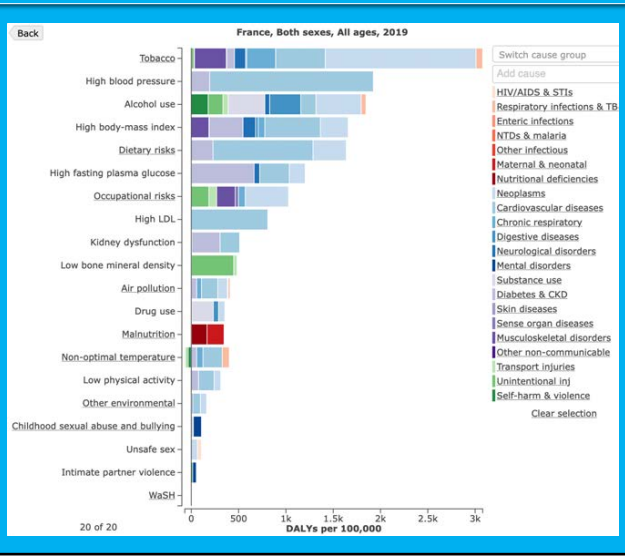
(Martin, *EHP*, 2017)

Assumptions: 1) All components have similar uptake, pharmacokinetics and toxicity and 2) the (log probit) dose response curves of the components are parallel

If HI ≤ 1, the mixture is said to be at an acceptable exposure level for the toxic effect of interest
If HI ≈ 1 then the mixture can be assumed to be equivalent to an exposure to a single compound leading to the effect of the benchmark dose (e.g., 10% change in the toxic outcome of interest)
If HI >>1 then the mixture cannot be considered to be safe.
(Teuschler & Hertzberg, *Toxicology*, 1995)

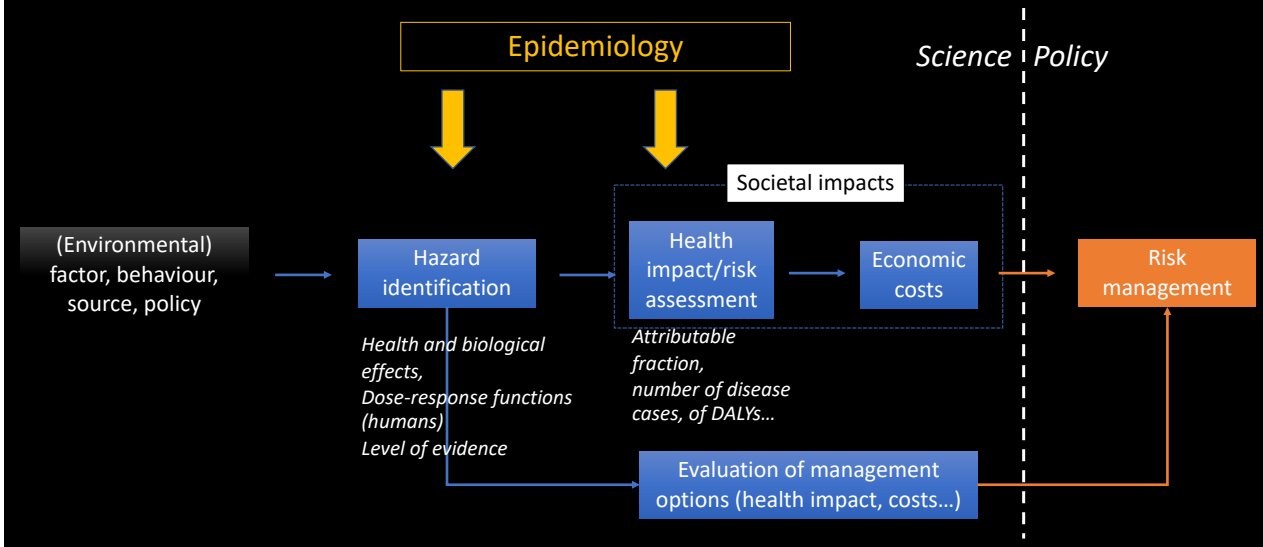
37

C. The epidemiological view to risk assessment



38

From hazard identification to risk management



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The simple case: counting identified items (*additions*)

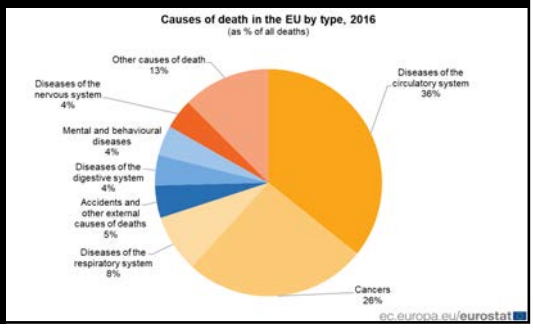
40

Estimating impacts by direct counts

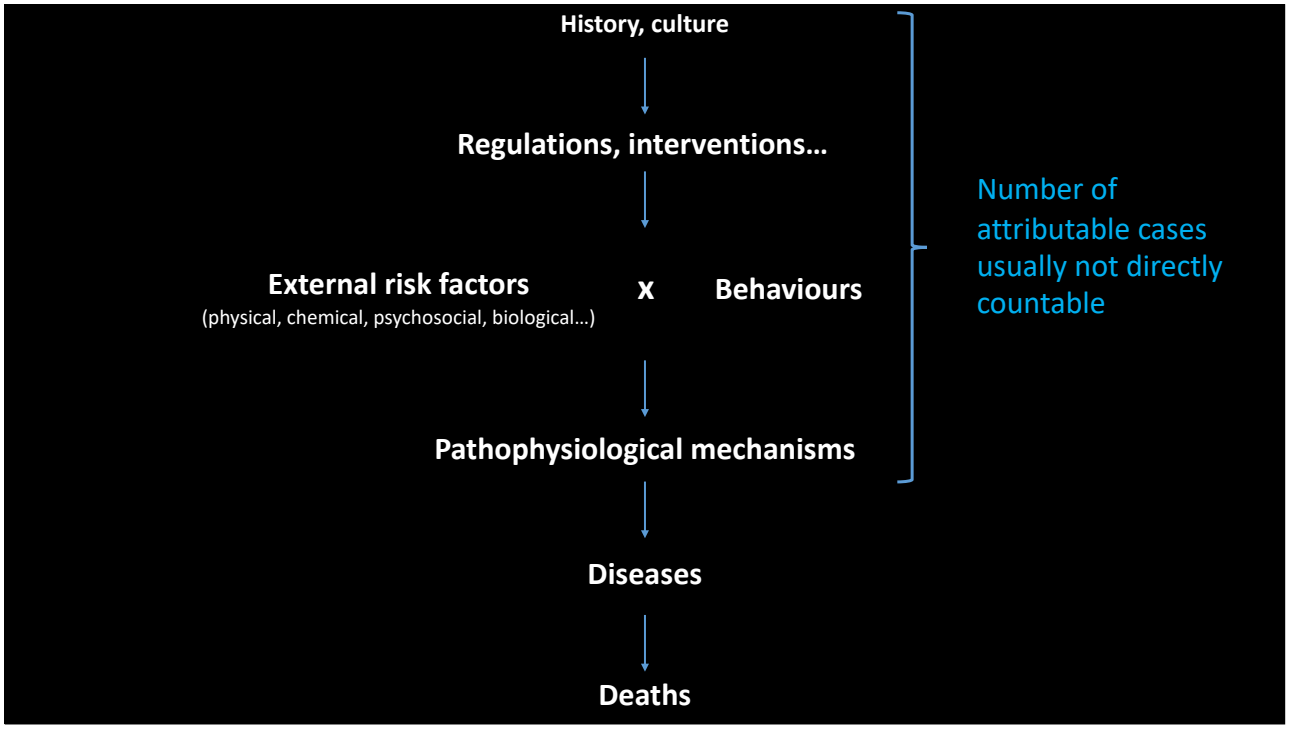
- Can only be done in the context of very simple causal models, i.e. when the cases induced by the factor of interest are directly visible or easily identifiable, e.g.,
  - To estimate the impact of a disease (counting the number of cases)

- Examples:
  - Violent deaths
  - Deaths by wounds
  - (Direct/*proximal*) causes of death (diseases)
  - Floodings, catastrophes, accidents
  - Extreme weather events

  - But not deaths by poisons
  - Extreme weather events due to climate change
  - And generally not *distal* causes of death (causes of causes)



41



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The less simple case: *before-after* estimates (*subtraction*)

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The less simple case: *before-after* estimates (*subtraction*)

- In the case of a specific event (e.g., strong change in the level of exposure of interest at the population level) occurring within a short period of time, comparing the health status of the population between *after* and *before* the event can be used as an estimate of the impact of this event.

$$\text{Impact} = \text{Deaths}(t_1) - \text{Deaths}(t_0)$$

- *Main assumption:*
  There was no (strong) change in health risk factors between the 2 compared periods t_1 and t_0 besides the event of interest (i.e., age structure, smoking rate… remained the same): *Flash event in an otherwise static society ("catastrophe")*

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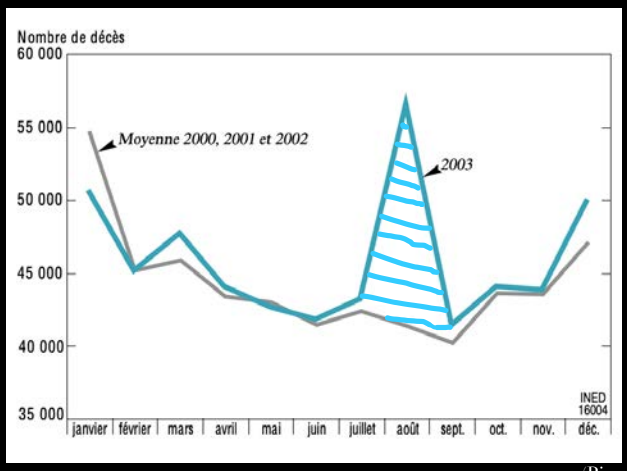
An estimation of the number of deaths attributable to the 2003 heat wave (France)

Monthly number of deaths



Impact = Deaths(August 2003) – Average(Deaths of August 2000, 2001, 2002) = 15,000 deaths

The focus on August allows to avoid the impact of within-year variations in mortality

Assumption: no strong change in the risk factors of mortality in the population between August 2000 and August 2003.
The impact is that of canicule and everything that came with it (e.g., possibly high ozone levels)

(Pison, *Pop & Soc*, 2003)

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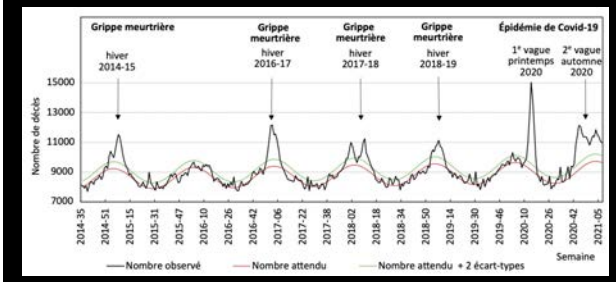
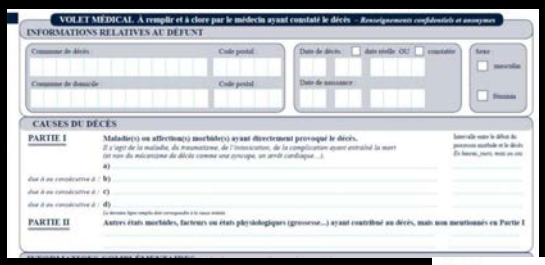
A comparison of *before-after estimates* and counts (Covid-19 attributable mortality in 2020)





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Inserm CépiDc

Estimated impact of *Covid-19* ***crisis (as a whole)***
Observed deaths – Expected deaths from past trends
= 55,000 deaths for 2020 (France)

Estimated impact of *Covid-19* ***disease*** *(as identified by MDs)*
(as counted from death certificates)
= 68,000 deaths for 2020 (France)

The difference may be due to decreases in deaths by other causes than Covid-19 in 2020

(Pison, *Pop & Soc*, 2021)

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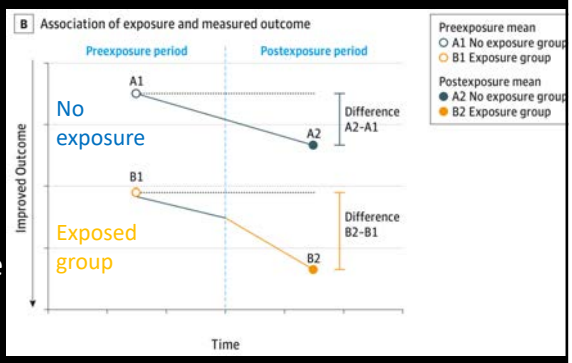
How to simply estimate the impact of an intervention in the context of temporal trends? The *Difference-in-differences* approach

- In the case of interventions spanning over several years (or whose impact cannot be observed on the short term), before-after comparisons may be biased by temporal trends in the health event of interest.
- It may be possible to control for these temporal trends if the intervention took place only in a few locations (which can be compared to locations without intervention, used to estimate the amplitude of the "natural" temporal trends

"Difference in differences" approach



(Dimick, *JAMA*, 2014)

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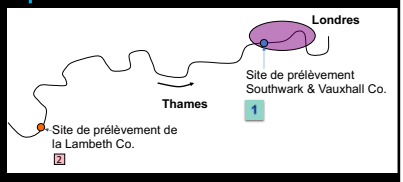
Can the "difference" approach also be used relying on *spatial* (rather than *temporal*) comparisons?

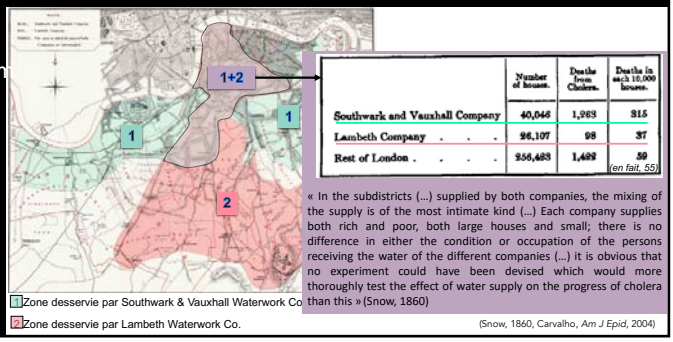
Space is generally a strong driver of (environmental) exposures. It is tempting to try to rely on spatial exposure contrasts to infer the impact of exposures.

This is generally not a rigorous idea (in the absence of specific effort against bias) because many other disease risk factors tend to also vary with space.

E.g., assessing the impact of a factory or highway by comparing the raw disease rate of subjects living nearby from subjects further away is likely biased by many other differences between the compared groups (*Note:* corresponds to a spatial ecological study design)

Exceptions exist: **(natural) experiments**: John Snow estimates of cholera deaths in London (1953). *Randomization* of water fluorination at the city level.





	Number of houses.	Deaths from Cholera.	Deaths in each 10,000 houses.
Southwark and Vauxhall Company	40,046	1,263	315
Lambeth Company . . .	26,107	98	37
Rest of London . . .	256,423	1,422	59 (en fait, 55)

« In the subdistricts (…) supplied by both companies, the mixing of the supply is of the most intimate kind (…) Each company supplies both rich and poor, both large houses and small; there is no difference in either the condition or occupation of the persons receiving the water of the different companies (…) it is obvious that no experiment could have been devised which would more thoroughly test the effect of water supply on the progress of cholera than this » (Snow, 1860)

(Snow, 1860, Carvalho, *Am J Epid*, 2004)

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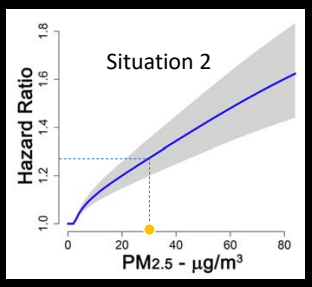
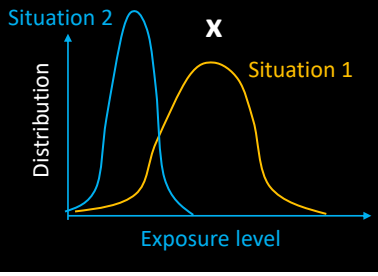
The more complex (general) case: *attributable risk assessment* from counterfactual scenarios (*estimation*)

Dose-response function





Impact
of an intervention shifting exposure from situation 1 to 2

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Health impact assessment: *Principle*

- Raw spatial comparisons in differences in disease risk cannot be directly attributed to spatial differences in exposure because of the potential for confounding bias
- However epidemiological studies (e.g., cohorts, case-controls studies…) allow providing *unbiased* estimates of dose-response functions (through specific designs and statistical adjustment)
- These dose response functions can be used to estimate the expected change in disease risk related to a specific change in exposure level (or in the distribution of exposure levels in the population)

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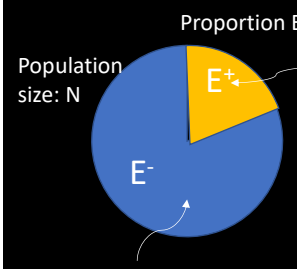
Health impact assessment using dose-response functions: the simple case

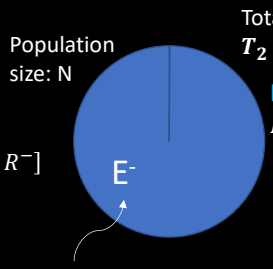
Assumptions

- Binary exposure (exposed E^+ *vs.* not exposed, E^-)
- An unbiased "dose-response function" (measure of association between exposure and disease) has been estimated (e.g., in the form of a relative risk, RR)



Total number of cases:
$\boldsymbol{T_1} = N[p \cdot RR \cdot R^- + (1-p) \cdot R^-]$

1. World in which exposure E exists (prevalence, p)



Total number of cases:
$\boldsymbol{T_2} = N[R^-]$

Impact of exposure:
$\boldsymbol{I} = \boldsymbol{T_2} - \boldsymbol{T_1} = N[p(RR-1)] \cdot R^-$

2. World in which exposure *E does not* exist (prevalence, 0)

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The population attributable number of cases and fraction (PAF)

Impact of exposure:
$\boldsymbol{I} = \boldsymbol{T_2} - \boldsymbol{T_1} = N[p(RR-1)] \cdot R^-$

Absolute value

$$\boldsymbol{PAF} = \frac{Number\ of\ cases\ due\ to\ E}{Total\ number\ of\ cases} = \frac{p(RR-1)}{p(RR-1)+1}$$

Fraction

Can be estimated for any hypothetical prevalence of exposure
Only valid in the absence of confounding!

Example assuming an exposure with a relative risk of 10 and a prevalence of 30%

$$\boldsymbol{PAF} = \frac{0.3(10-1)}{0.3(10-1)+1} = \frac{2.7}{3.7} = 73\%$$

Example assuming an exposure with a relative risk of 1.4 and a prevalence of 80%

$$\boldsymbol{PAF} = \frac{0.8(1.4-1)}{0.8(1.4-1)+1} = \frac{0.32}{1.32} = 24\%$$

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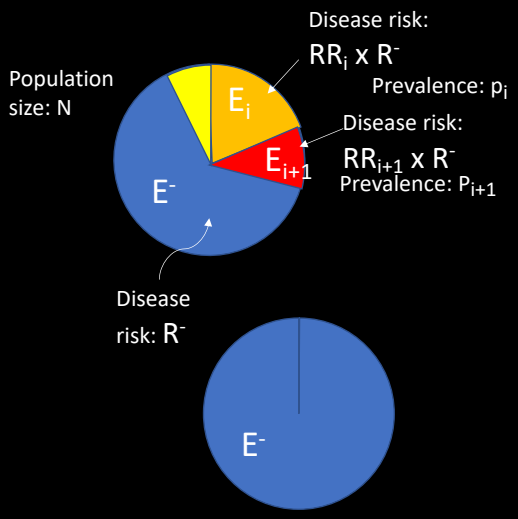
Generalization to exposures with more than 2 exposure levels

Impact of exposure:

$$\boldsymbol{I = T_2 - T_1 = N\left[\sum_{i=1}^{k} p_i \cdot (RR_i - 1)\right] \cdot R^-}$$

$$\boldsymbol{PAF = \frac{\sum_{i=1}^{k} p_i \cdot (RR_i - 1)}{\sum_{i=1}^{k} p_i \cdot (RR_i - 1) + 1}}$$



Counterfactual situation: World in which exposure *E does not* exist (prevalence, 0)

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The health impact of a multicategorical (or continuous) exposure

$$\boldsymbol{I = T_2 - T_1 = N\left[\sum_{i=1}^{k} p_i \cdot (RR_i - 1)\right] \cdot R^-}$$

Distribution of exposure in the population

Dose-response function

"Baseline" disease risk

1. This formula is actually not valid when confounding exist (even replacing RR$_i$ by adjusted RRs)
2. In practice, one has to consider the time-scale hidden behind the relative risk (RR). If they originate from a cohort analysis based on Cox survival model, they correspond to hazard rates (HR, ratio of the instantaneous disease rate). In this case, it is advised to simulate the various cohorts and apply the HR to each exposure group, and let them age over time to integrate impacts over long time periods.

See also (Poole, *Epid Rev*, 2015; Rockhill, *Am J Pub Health*, 1998)

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The health impact of a multicategorical (or continuous) exposure

$$I = T_2 - T_1 = N\left[\sum_{i=1}^{k} p_i \cdot (RR_i - 1)\right] \cdot R^-$$

Distribution of exposure in the population

Dose-response function

"Baseline" disease risk

The exercise can then be repeated for all diseases and troubles induced by the exposure considered,
The number of cases of each disease can then be converted e.g.into DALYs (disability-adjusted life years) to obtain a synthetic measure.

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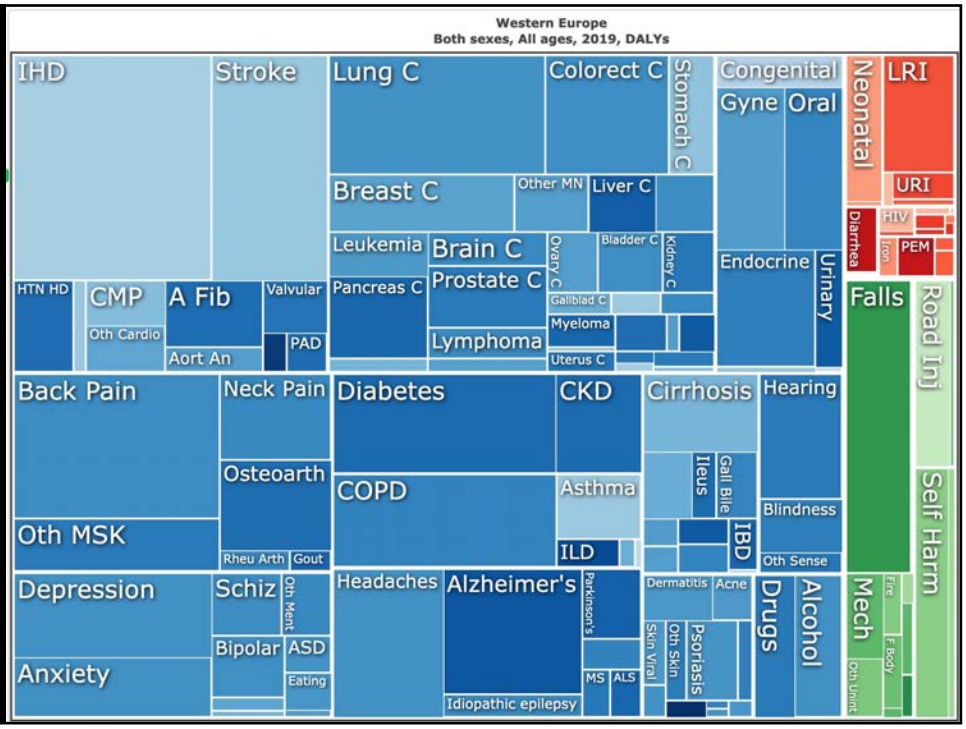
Burden of disease

Western Europe, 2019

Source: Institute for Health Metrics and Evaluation (IHME)
https://vizhub.healthdata.org/gbd-compare/

DALYs: Disability-adjusted life year
DALYs equal the sum of years of life lost (YLLs) and years lived with disability (YLDs). One DALY equals one lost year of healthy life.



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Main steps of (quantitative) *Health Impact Assessment (HIA)* studies

- Public involvement
- Description of the counterfactual situations compared (policies…)
- Definition/identification of the environmental factors/policy/plan… considered (including *hazard identification* and *assessment of the level of evidence*)
- Assessment of the level of evidence for each exposure-outcome pair
- Definition of the study area, study population and time period
- Assessment of "exposures"
- Characterization of the health impact
- Characterization of the social and economic impacts
- Uncertainty analyses
- Reporting/recommendations and evaluation.

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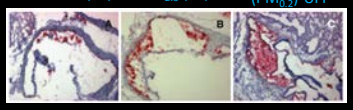
PM and ischemic diseases: Body of evidence from populations to particles

Molecular scale

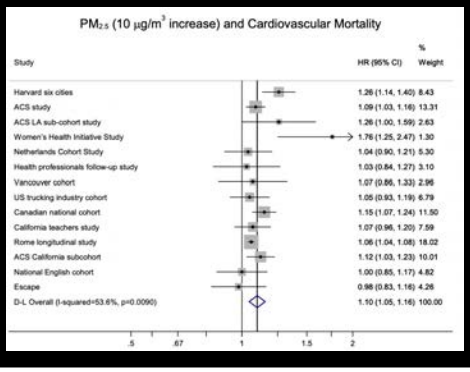
Individual scale (cohorts)

Individual scale (in vivo toxicology)

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



Cellular scale (in vitro toxicology)

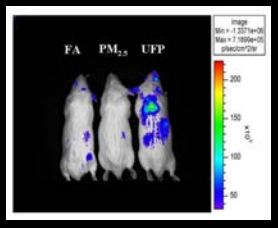


Lipid metabolism

Autonomic nervous system imbalance

Inflam-mation

Oxidative stress



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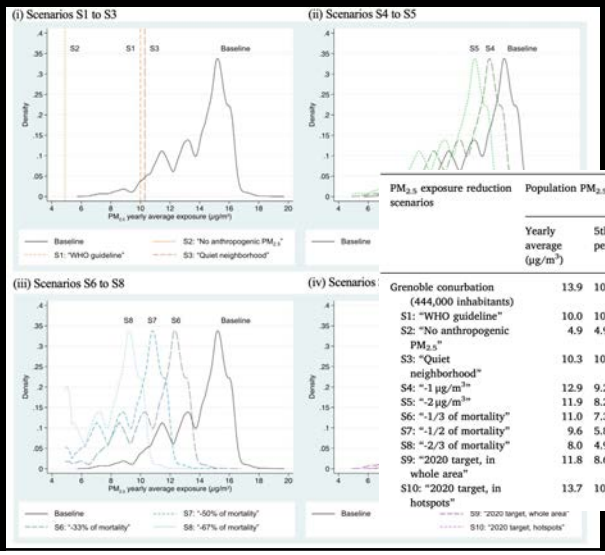
Health impact assessment tools can be used to test any hypothetical scenario (intervention)



$PM_{2.5}$ exposure reduction scenarios	Population $PM_{2.5}$ exposure		Health benefits concerning all-cause non-accidental mortality							
	Yearly average ($\mu g/m^3$)	5th–50th–95th percentiles ($\mu g/m^3$)	Δ_{NAC}[a,f]	95% CI	% of S2[b]	% of baseline cases[c]	95% CI	Mortality rate gain[a,f]	95% CI	Gain in life expectancy months[e]
Grenoble conurbation (444,000 inhabitants)	13.9	10.2–14.6–16.2								
S1: "WHO guideline"	10.0	10.0–10.0–10.0	65	40–90	45%	2.5%	1.5–3.5%	25	15–34	4.5
S2: "No anthropogenic $PM_{2.5}$"	4.9	4.9–4.9–4.9	145	90–199	Ref.	5.6%	3.5–7.7%	55	34–76	10.0
S3: "Quiet neighborhood"	10.3	10.2–10.3–10.3	61	38–84	42%	2.3%	1.5–3.2%	23	14–32	4.3
S4: "-1 $\mu g/m^3$"	12.9	9.2–13.6–15.2	16	10–23	11%	0.6%	0.4–0.9%	6	4–9	1.1
S5: "-2 $\mu g/m^3$"	11.9	8.2–12.6–14.2	33	20–45	23%	1.3%	0.8–1.7%	12	8–17	2.1
S6: "-1/3 of mortality"	11.0	7.3–11.7–13.3	47	29–66	33%	1.8%	1.1–2.5%	18	11–25	3.0
S7: "-1/2 of mortality"	9.6	5.8–10.2–11.8	71	44–98	50%	2.7%	1.7–3.8%	27	17–37	4.6
S8: "-2/3 of mortality"	8.0	4.9–8.6–10.2	95	59–132	67%	3.7%	2.3–5.1%	36	22–50	6.3
S9: "2020 target, in whole area"	11.8	8.6–12.4–13.8	34	21–48	23%	1.3%	0.8–1.8%	13	8–18	2.3
S10: "2020 target, in hotspots"	13.7	10.2–14.1–15.9	4	2–5	3%	0.2%	0.1–0.2%	1	1–2	0.3

(Morelli, *Env Int*, 2019)

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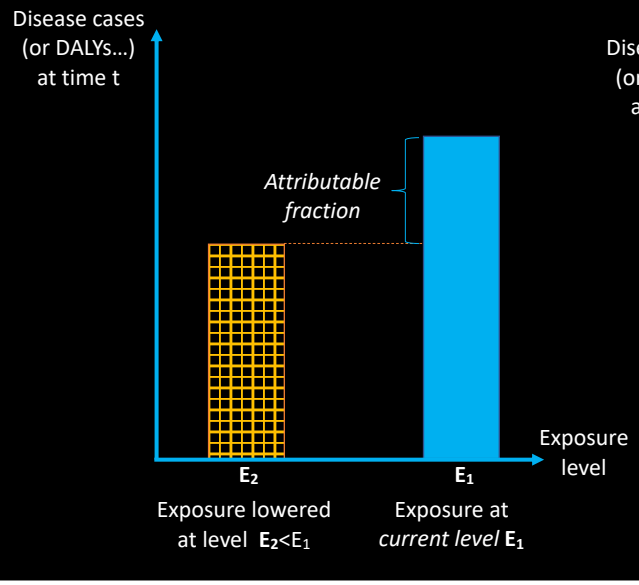
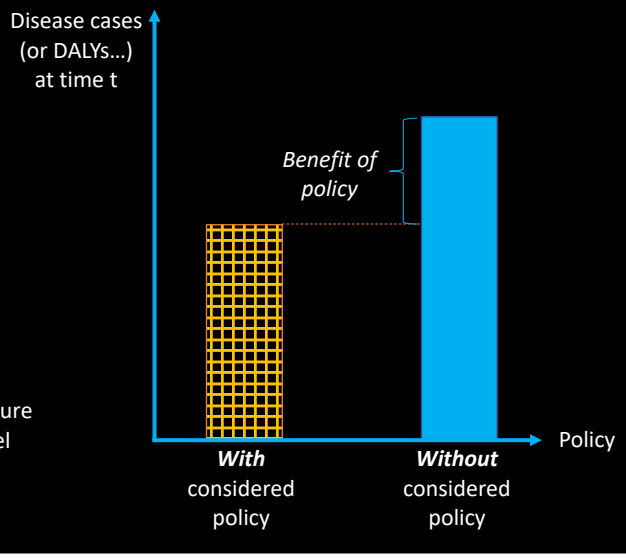
Risk assessment study

(*Sometimes used in relation to the estimation of the impact of existing exposures*)



Health Impact Assessment (HIA) study

(*Sometimes used in the context of the evaluation of hypothetical policies*)



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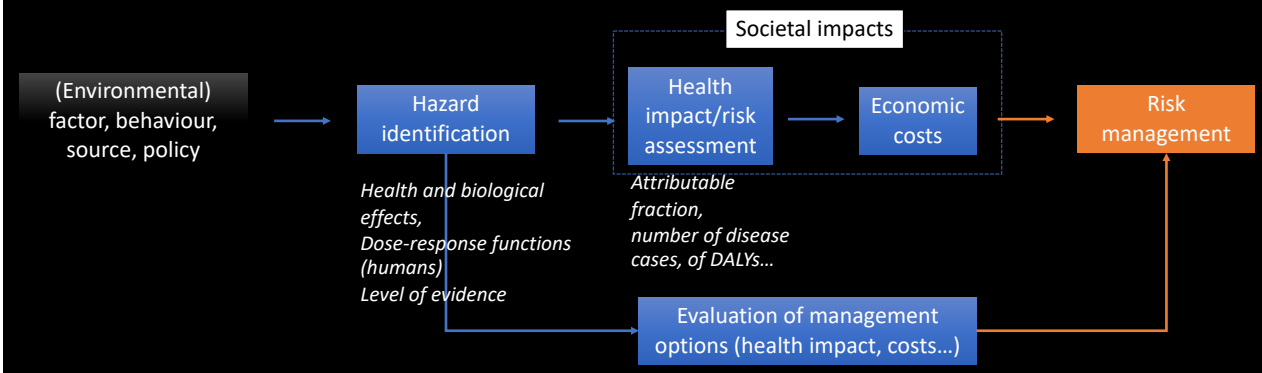
Comparing various management options



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- Characterization of the social and economic impacts
- Uncertainty analyses
- Reporting/recommendations and evaluation.

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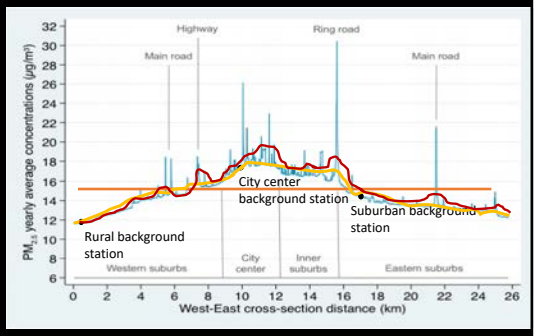
Issues related to exposure assessment

- Exposure misclassification is (also) an issue of HIA studies
  - Spatial resolution and population density matter

(Finest model)

Hypothesis (spatial resolution)	$PM_{2.5}$ exposure: 5th–50th–95th percentiles ($\mu g/m^3$)	PAF (%) (95% CI) (Lung cancer attributable fraction)
Main model	8.2–13.8–21.8	3.6 (1.7–5.4)
Sensitivity analyses		
H1: median of population-weighted $PM_{2.5}$ exposure		
(a) Department	9.7–13.8–19.1	3.6 (1.7–5.4)
(b) Country	13.8–13.8–13.8	3.2 (1.5–4.9)
H2: median of raw $PM_{2.5}$ concentration		
(a) Department	6.0–11.1–16.4	2.4 (1.1–3.6)
(b) Country	11.2–11.2–11.2	1.0 (0.5–1.6)



(Kulhanova, *Env Int*, 2018)

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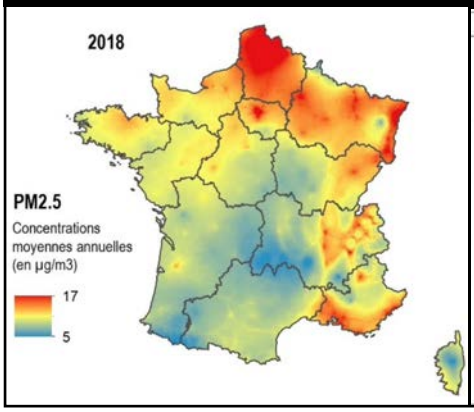
The health impact of atmospheric ($PM_{2.5}$) pollution (Medina, Santé Publique France, 2021)

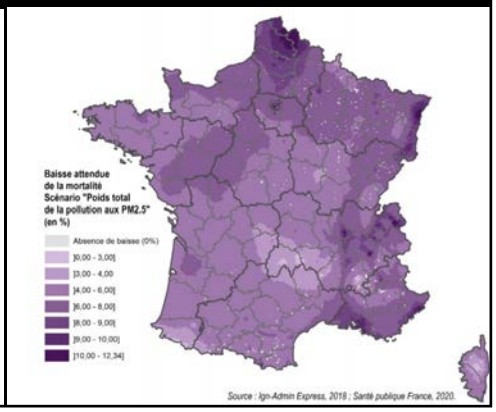
*Counterfactual scenario:
$PM_{2.5}$ concentrations lowered to 5 µg/m³

Environmental exposure *(observed/modelled)*



Population density *(observed)*

Gain in mortality (%)* *(estimated)*



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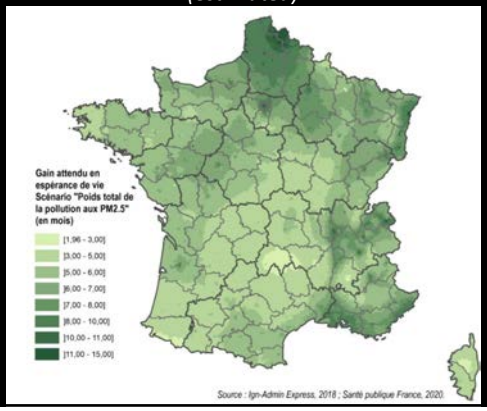
(Medina, Santé Publique France, 2021)

Various metrics of impact

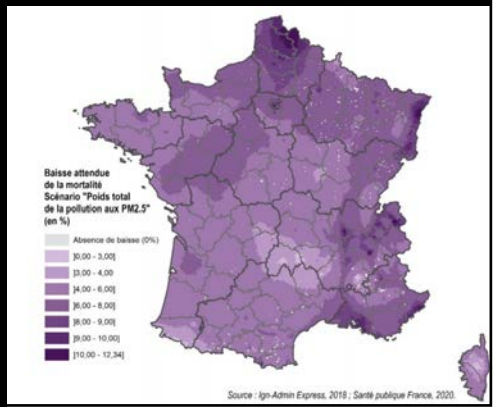
Life years lost due to exposure
Healthy life years lost du to exposure
DALYs: Disability-adjusted life-years

Gain in life expectancy (months)*
(estimated)



Number of cases

Gain in mortality (%)*
(estimated)



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Estimated *impact* of $PM_{2.5}$ exposure
(France and world)

Health endpoint	Human evidence	Mechanistic evidence	Attributable fraction or nb of cases*	Reference
Mortality	Certain	Certain	40,000 deaths/year (France), about 6.5% of deaths	(Medina/Santé publique France, 2021)
			4.1 M deaths/year (world)	(Fuller, *Lancet Plan Health*, 2022)
Lung cancer	Certain	Certain	3000 cases, 7.6% of all cases (France)	(Kulhanova, *Env Int*, 2018)
Breast cancer	Very likely	Moderate	3% (France)	(Gabet, *EHP*, 2021)

Overall cost of $PM_{2.5}$ exposure in France (2010s): 100 billion €/year (Aïchi, *Sénat*, 2015)

*Fraction of all disease cases attributable to atmospheric pollution exposure, considering a specific counterfactual situation (typically, a mean $PM_{2.5}$ level of 5 µg/m^3)

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From health impact to societal costs

Tangible costs

Those paid by society
Include
Direct costs
(e.g., related to the treatment of diseases)
Indirect costs
Tangible costs on relatives

Intangible costs

Those impacting society but not paid in money (e.g., costs related to grievance, suffering, quality of life…)
Require specific approaches to be estimated (e.g., willingness to pay)

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Total estimated cost (France)
€100 Billion/year

(French Sénat, Husson & Aïchi, 2015)

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- The estimation of the cost of the intervention can be compared to its expected benefit
  ➔Cost benefit analysis
- These estimates can be repeated for various management options (including the "business as usual" option)
  ➔ Allows comparisons of various risk management options

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Some issues with (regulatory) impact assessment studies

- Sometimes the health or environmental benefit of interventions is ignored/poorly estimated because of (alleged or real) uncertainties
- Sometimes the economic cost of interventions is over-estimated because the costs to a single producer is mistaken with the cost to society
  - Example: what are the costs and benefits associated with the ban of a specific pesticide?
- Depending on the way these costs are considered, the cost-benefit ratio of specific interventions (e.g., use of pesticides in crops) can strongly vary (see e.g., Bourguet and Guillemaud, *Sust Agr Rev*, 2016)

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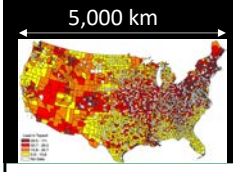
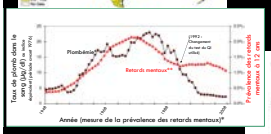
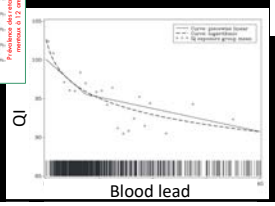
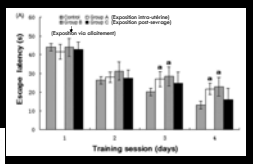
Neurological effects of lead: from populations to ions

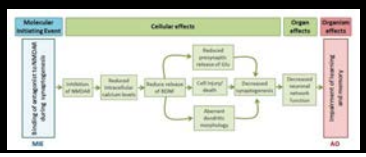
Population scale (ecological studies) | Individual scale (cohorts) | Individual scale (in vivo toxicology) | Cellular scale (in vitro toxicology) | Molecular/atomic scale











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

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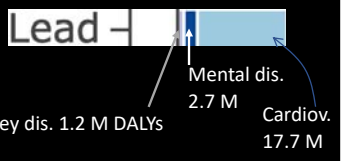
Estimated impact of lead exposure



Health endpoint	Human evidence	Mechanistic evidence	Attributable fraction or nb of cases*	Reference
Mortality	Certain	Certain	900,000 deaths/year (world)	(Fuller, *Lancet Plan Health*, 2022)
DALYs (cardiovascular, kidney and mental disorders)	Certain	Certain	21.7 Million DALYs (world)	IHME Seattle https://vizhub.healthdata.org/gbd-compare/
IQ loss and associated impacts	Certain	Certain	€22.7 Billion/year in France based on 2008 exposure estimates	(Pichery, *Env Health*, 2011)

Benefit of decreased lead level in the USA following the phasing out of leaded gasoline: $110 to 319 billion/year (Gosse, *EHP*, 2002)

Reducing exposure of French children down to 15 µg/l would lead to yearly gains of €22.7 billion. Abatement costs ranged from €0.9 billion to 2.95 € billion (Pichery, *Env Health*, 2011)

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D. The epidemiological view (2): Integration of multiple exposures

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Percentages don't add up…

Hypothetical *incidence rates (e.g., cases per million person.years)* of a specific disease according to alcohol and tobacco consumption

		Tobacco: No	Tobacco: Yes
Alcohol	No	**1**	**4**
	Yes	**3**	**12**

In the exposed group, 2/3 of disease cases are attributable to alcohol consumption

In the exposed group, 3/4 of disease cases are attributable to *tobacco* consumption

2/3 + 3/4 > 100%: in the case of multifactorial diseases, population attributable fractions do not add up… In the group exposed to both alcohol and tobacco, these 2 factors together explain a fraction of cases corresponding to 11/12.

(Rothman, Oxford Univ Press, 2002; Rockhill, *Am J Pub Health*, 1998)

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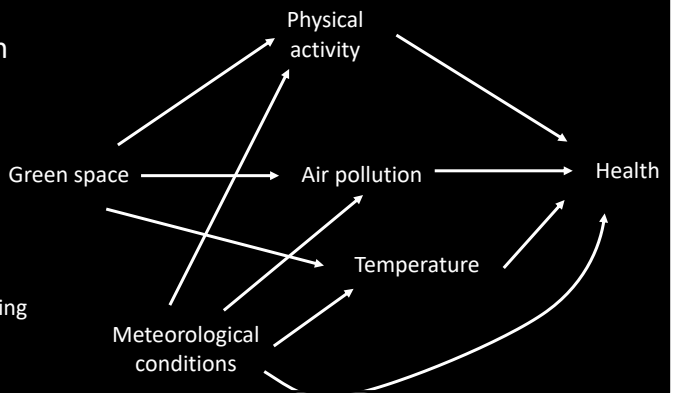
Problems with additions…

- One cannot add up cases of a specific diseases due to different risk factors
  - Many technical issues related to the estimation of "attributable fractions" in the context of multiple exposures
  - Mediation/interaction: If one factor is on the causal pathway of the other, controling this risk factor will also control (part of) the cases induced by the other factor
  - Co-occurrence of risk factors

Many previous health impact assessment studies considering multiple exposures ignored these issues.



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Number of yearly deaths attributable to selected risk factors (world)

(GBD collaborators, Lancet, 2020; Fuller, *Lancet Plan Health*, 2022)

	Female	Male	Total
Total air pollution*	2·92 (2·53–3·33)	3·75 (3·31–4·25)	6·67 (5·90–7·49)
Household air†	1·13 (0·80–1·50)	1·18 (0·79–1·66)	2·31 (1·63–3·12)
Ambient particulate‡§	1·70 (1·38–2·01)	2·44 (2·02–2·83)	4·14 (3·45–4·8)
Ambient ozone‡	0·16 (0·07–0·25)	0·21 (0·09–0·33)	0·37 (0·17–0·56)
Total water pollution*	0·73 (0·40–1·26)	0·63 (0·46–0·95)	1·36 (0·96–1·96)
Unsafe sanitation†	0·40 (0·23–0·68)	0·36 (0·26–0·54)	0·76 (0·54–1·09)
Unsafe source†	0·66 (0·35–1·15)	0·57 (0·39–0·88)	1·23 (0·82–1·79)
Total occupational pollution*	0·22 (0·17–0·28)	0·65 (0·54–0·79)	0·87 (0·74–1·02)
Carcinogens‡	0·07 (0·05–0·09)	0·28 (0·22–0·35)	0·35 (0·28–0·42)
Particulates‡¶	0·15 (0·10–0·21)	0·37 (0·27–0·47)	0·52 (0·42–0·64)
Lead pollution*‡	0·35 (0·19–0·53)	0·56 (0·36–0·77)	0·90 (0·55–1·29)
Total modern pollution*	2·28 (1·86–2·67)	3·55 (3·08–4·04)	5·84 (5·03–6·61)
Total traditional pollution*	1·85 (1·39–2·42)	1·81 (1·36–2·38)	3·66 (2·82–4·63)
Total pollution*	3·92 (3·39–4·47)	5·09 (4·57–5·68)	9·01 (8·12–10·0)

Data are N in millions (95% CI). *Custom aggregate from Institute for Health Metrics and Evaluation corrected for overlap. The totals for air, water, modern, traditional, and all pollution are less than the arithmetic sum of the individual risk factors within each of these categories because their contributions overlap (eg, household air and ambient air pollution each can contribute to the same diseases). †Traditional pollution risk factor. ‡Modern pollution risk factors. §Ambient particulate matter is $PM_{2.5}$. ¶Occupational exposure to respirable, thoracic, or inhalable particulate matter.

Table: **Global estimated pollution-attributable deaths (millions) by type of pollution and sex, 2019**

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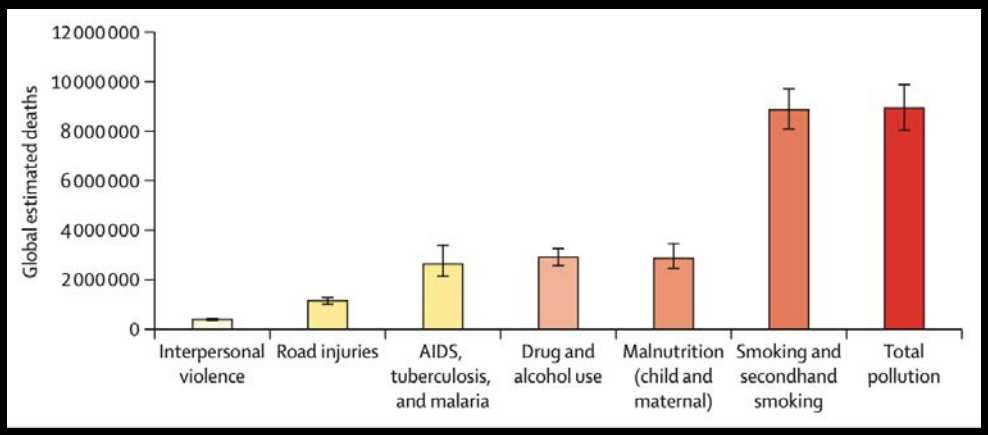

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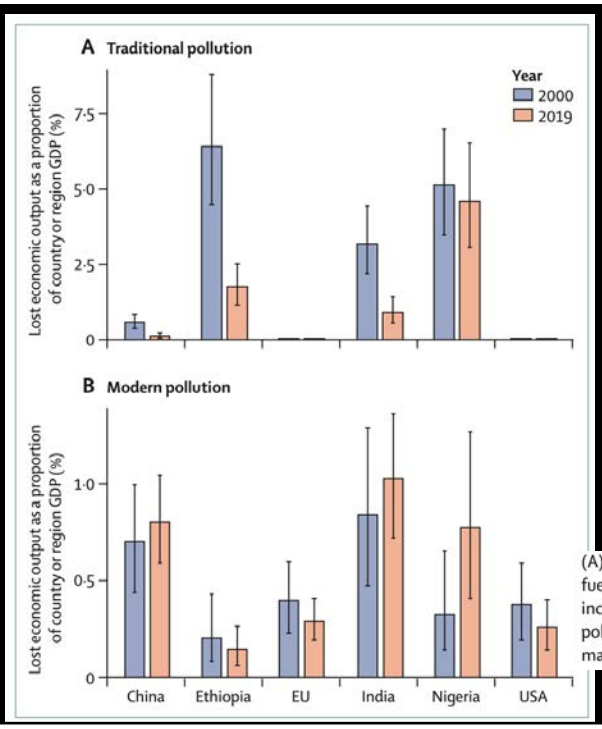

(A) Traditional pollution includes deaths from household air pollution from solid fuels and unsafe water, sanitation, and hand washing.[6,56,57] (B) Modern pollution includes deaths from ambient ozone pollution, ambient particulate matter pollution, lead exposure, occupational carcinogens, occupational particulate matter, gases, and fumes.[6,56,57] GDP=gross domestic product.

(Fuller, *Lanc Plan Health*, 2022)

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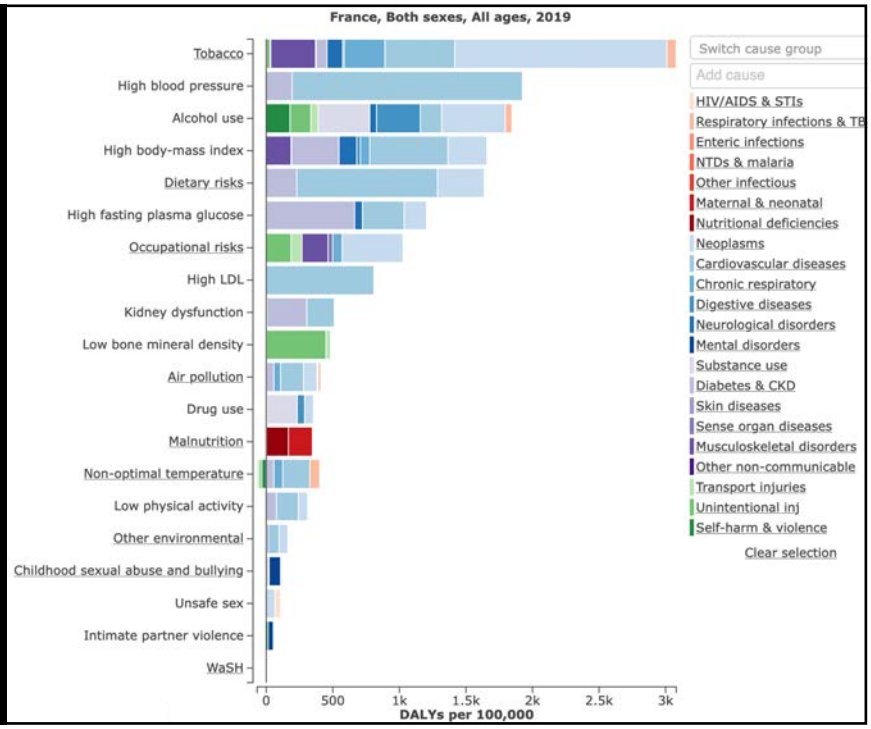
Identified causes of DALYs (Disability-adjusted life years lost, France 2019)



(Institute for Health Metrics and Evaluation, Seattle University, https://vizhub.healthdata.org/gbd-compare/

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How to handle the level of proof?

- Historically, only factors for which the level of evidence was deemed very high were considered in HIAs (e.g., lead, PM…)
- Specific situation of the (numerous) chemicals factors for which the level of evidence is intermediary, or without robust dose-response function in humans (because most of the evidence comes from animal studies)
  - In the context of a "slow" science with limited funding in relation to the large number of factors to evaluate, some of these levels of evidence will eventually increase
  - Excluding these factors may underestimate the impact
  - Including all of them possibly overestimates the impact
  - One option is to (try to) estimate their impact and weight this impact according to the level of evidence regarding the exposure-effect pair (see Trasande, *JCEM*, 2015)

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Cost of exposure to some endocrine disruptors in the EU

Exposure	Outcome
Polybrominateddiphenyl ethers (PBDE)	IQ Loss and Intellectual Disability
Organophosphate pesticides	IQ Loss and Intellectual Disability
Dichlorodiphenytrichloroethane (DDE)	Childhood obesity
Dichlorodiphenytrichloroethane (DDE)	Adult diabetes
Di-2-ethylhexylphthalate (DEHP)	Adult obesity
Di-2-ethylhexylphthalate (DEHP)	Adult diabetes
Bisphenol A	Childhood obesity
Polybrominateddiphenyl ethers (PBDE)	Testicular cancer
Polybrominateddiphenyl ethers (PBDE)	Cryptorchidism
Benzyl and butylphthalates	Male Infertility, Resulting in Increased Assisted Reproductive Technology
Phthalates	Low testosterone, Resulting in Increased Early Mortality
Multiple exposures	ADHD
Multiple exposures	Autism
Dichlorodiphenyldichloroethylene (DDE)	Fibroids
Di-2-ethylhexylphthalate (DEHP)	Endometriosis

Distributions of exposure

Combined to dose-response function

Estimated total cost: €163 Billion/year

(Trasande, *Andrology*, 2016)

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E. Perspectives and conclusion

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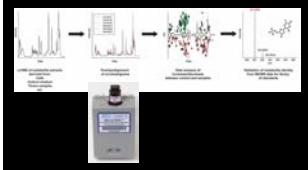
The ambitious road of *environmental health* research

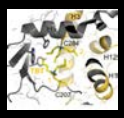
Exposome

Quantification
Platforms
TD-TK modeling
Dosimeters
« Exposome-ready » cohorts



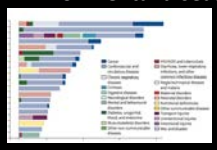
Link with socio-territorial characteristics
« Environmental justice »

Mechanisms of action
Cross-omics studies
In vitro and in vivo toxicology, cohorts



Health effects
In vivo toxicology (AOPs), Cohorts

Health impact
Environmental disease burden



Act on the exposome
Individual interventions
Governance / regulatory framework

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A need to clarify terminology

- Multiplicity of related terms: Health Impact Assessment (**HIA**), comprehensive HIA, analytical HIA, **risk assessment**, safety assessment, **burden of disease** (BoD), Environmental Health Impact Assessment (EHIA), Integrated Environmental Health Impact Assessment (IEHIA), Human Impact Assessment (HuIA)…
- The multiplicity of terms relates to the **multiple origins of the approach**
  - epidemiology (population attributable fraction…), chemical safety and regulatory toxicology (risk assessment), regulatory assessment of future policies (impact assessment).
- Some differences exist between some types of studies in terms of aims
  - E.g. risk *vs.* safety assessment (is there a risk *vs.* can I be sure that we are safe?)
- Some real (methodological) differences exist between studies relying on human dose response functions as opposed to purely toxicological dose response functions or threshold values/benchmark doses
  - Not sure however that this justifies to use different names for the corresponding designs, if they share a similar aim
- Similarly, there is no compelling reason to use different terms for impact studies according to the family of evaluated factors (e.g., evaluating a complex policy *vs.* evaluating the impact of exposure to a single chemical)
- Further effort needed to build a consensus across research and users communities.

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As a conclusion

- Environmental health burden assessment is essential to quantify the burden associated with the effects identified by environmental health research and translate it in a way easy to handle for society (number of cases, costs…)
- It may allow to provide a way to hierarchize environmental factors (in terms of disease burden, healthy life years lost, cost…)
- It is essential to anticipate the possible impact and efficiency of public health interventions
- It can also quantify to which extent the health burden associated with an environmental factor or intervention will differ socially or spatially (and hence the potential for interventions and policies to reduce social health inequalities)
- Environmental health burden assessment is very intensive in terms of required entry data (dose-response functions, representative exposure data, level of evidence, possibly baseline disease risk…)
- It remains challenging methodologically (e.g., to consider inter-related exposures)
- Currently, most of the available estimates regarding the environmental health burdens deals with infectious diseases and well-studied and strong risk factors such as tobacco, alcohol, particulate matter.

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The relations between human health and the environment in the Anthropocene

COLLÈGE DE FRANCE 1530

Course overview

#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: Protéger la santé des populations exposées aux substances chimiques - Enseignement et perspectives du programme national de biosurveillance
Dr. Clémence Fillol, Santé publique France

#8 – 1 June 2022
A Global Vision: The Burden of Disease Attributable to the Environment

Seminar: Causal pluralism and public health
Pr. Federica Russo, Philosophe des Sciences, Techniques, et Information, Université d'Amsterdam

#9 - 8 June 2022
Climate change and human health

Seminar: L'anthropocène est un accumulocène
Dr. Jean-Baptiste Fressoz, CNRS et EHESS

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