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Notre métier, rendre le vôtre plus sûr

Endocrine disruptors and epidemiological evidences : methodological challenges

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. *Concerning occupational health*
. *Examples from reproductive system*

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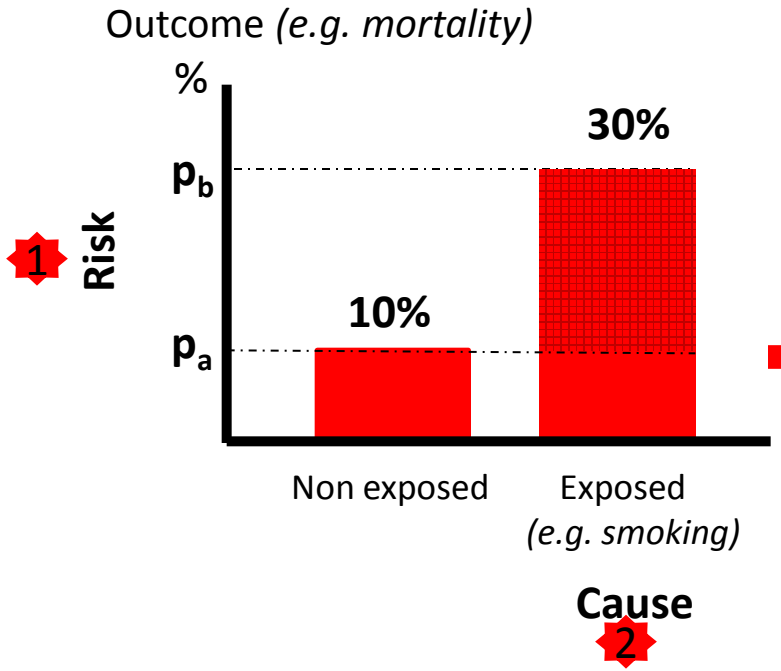
Introduction (1)

- Generally, an essential part of the evidence in establishing causality between a risk factor and a disease -> case-control or cohort studies
- All human observational studies have limitations
- But, studies of EDs have specific complications compared to studies
- Objective: to present some key issues about EDs which should be considered to design epidemiological studies

Introduction (2)

Causal epidemiological concepts : Risk – Cause - effect

1 2 3



3 Effect

$$\text{Relative Risk (strenght of effect)} = \frac{p_b}{p_a} = \frac{0{,}30}{0{,}10} = 3$$

The demonstration of the effect of a cause by comparing groups is a key principle of the causal epidemiology.

Hormones are active at extremely low doses

- Physiological levels of the endogenous hormones are extremely low : 10-900 pg/ml for oestradiol; 300-10,000 pg/ml for testosterone; 8-24 pg/ml for T4 [Vandenberg 2012]

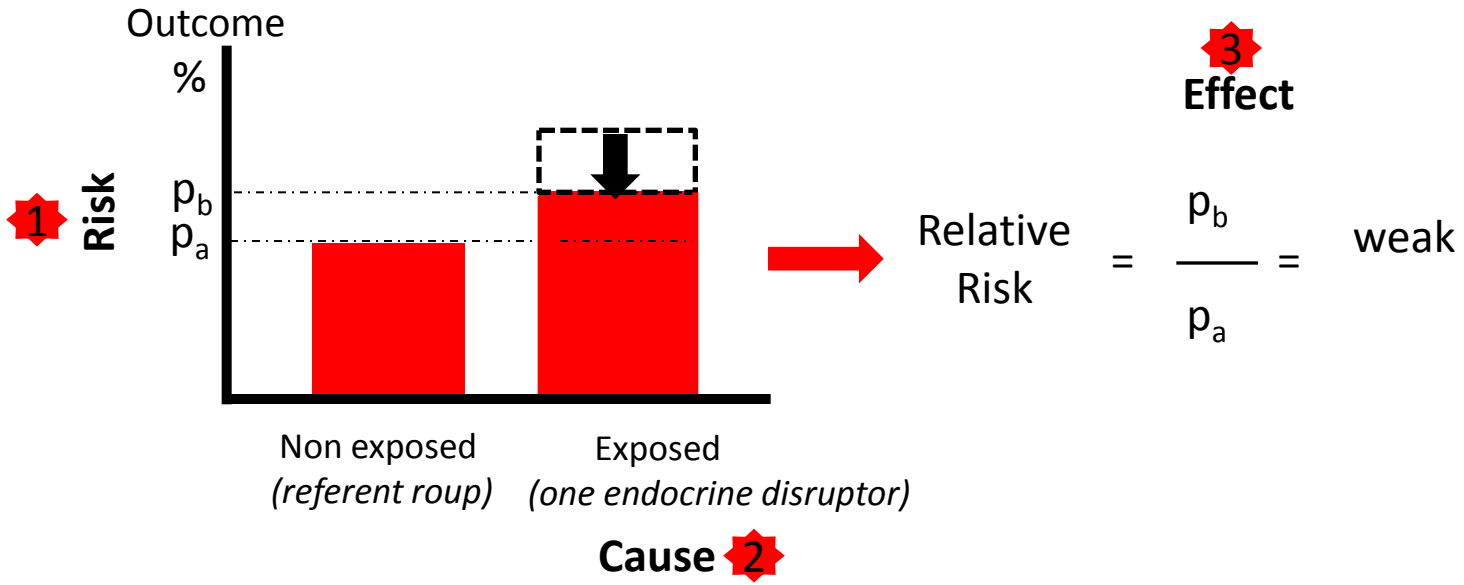
- Hormones have a strong affinity for their receptor

- A near-maximum biological response can be observed at low concentration without a high rate of receptor occupancy (0.1-10% of total receptors)

- Physiologically, all contribue to what natural hormones are active at extremely low doses

Expected weak effects

- **Difficulty** : EDs using physiological mechanism, effect sizes **<u>are expected to be weak to moderate</u>** in observational studies



- When RR is weak (from 1 to 1,5) → difficulty to argue a causality relationship (sampling fluctuation, problems of biases, …)
- Epidemiologist can : - ↑ size of studies (statistical power); multicenter studies
  ex: case-control study → RR=1,5 and exposition 10% => n=900 x 2
  exposition 5% => n=1700 x 2

Expected weak effects

weak RR in large population exposed at risk
→ numerous cases

Example: estimation of number of cases (low birth weight) according to the frequency of exposition at least one ED in pregnant women at work

RR	% Exposition	Number of Birth in working population 2010 *(France)*	Number of birth (<2500 g) *(6,4 %)*	Number of cases* due to exposure
1,25[$]	11[$]			1000
1,25	30	600 000	40 000	2800
1,25	50			4500
1,25	70			6000

[$] *From Birks L et al, occupational exposure to endocrine-disrupting chemicals and birth weight and length of gestation: a European meta-analysis. EHP 2016*

* *calculated with attributable fractions from Levin's method*

Low-dose hypothesis

- **Low dose -> operational definition** [Vandenberg 2012] **:**
  - doses that are in the range of human exposure
  - or/and doses below those traditionally tested in toxicological studies *(NOAEL / LOAEL)*
- **From this definition :**
  - for PEs -> from micro- to milligram/kg
  - for some PEs ->in the nanogram /kg (e.g. dioxin-like)
  - traditional approaches rather > at milligram/kg
- **From animal studies**: e.g. Vom Saal and Welshons et al, 2006
  - examined the low-dose BPA literature
  - ≈ 100 studies -> significant effects < 50 mg/kg/d *(LOAEL)*
  - ≈ 40 studies -> adverse effects < 50µg/kg/day

Low-dose hypothesis

- **<u>Therefore</u> : → need of accurate exposure assessment**
  - To limit misclassification errors : non differential → ↓ RR
    (questionnaire, self-reported, job exposure matrix…)
  - Rather quantitative approach of exposure
  - Often several routes (skin, inhaled, ingested) → internal dose
  - Dosage biologique ED or metabolites in biological matrice like blood, urine, other tissue ...

    . when half-life is long (POPs) may provide a reasonable exposure marker

    . But **<u>difficulty with short half-life +++</u>** *(like BPA, phtalate, alkylphenol, UV filter …)*
      - variability the day and across days / low reproducibility
      - difficult to estimate an internal dose that reflets interest exposure for given period and/or long term exposure
      - often need several samples

Environmental background noise

- Exposure occurs through the diet, personal care products (cosmetic, perfumes, lotions, and shampoos), detergents, PVC products, medecine…

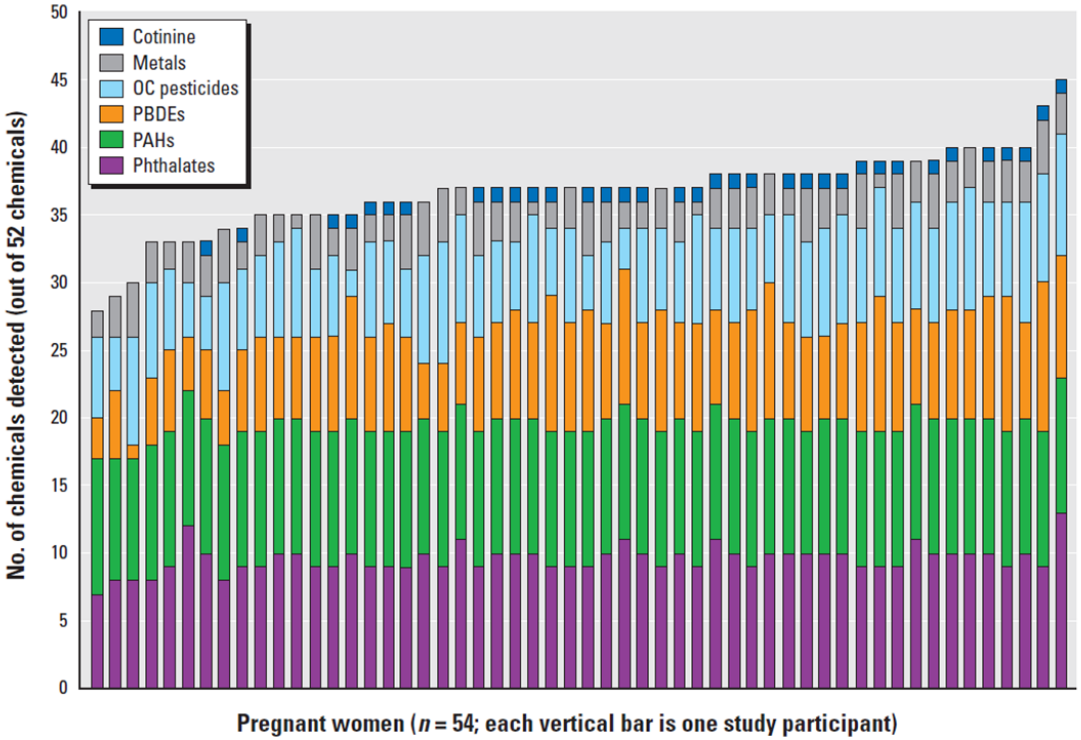
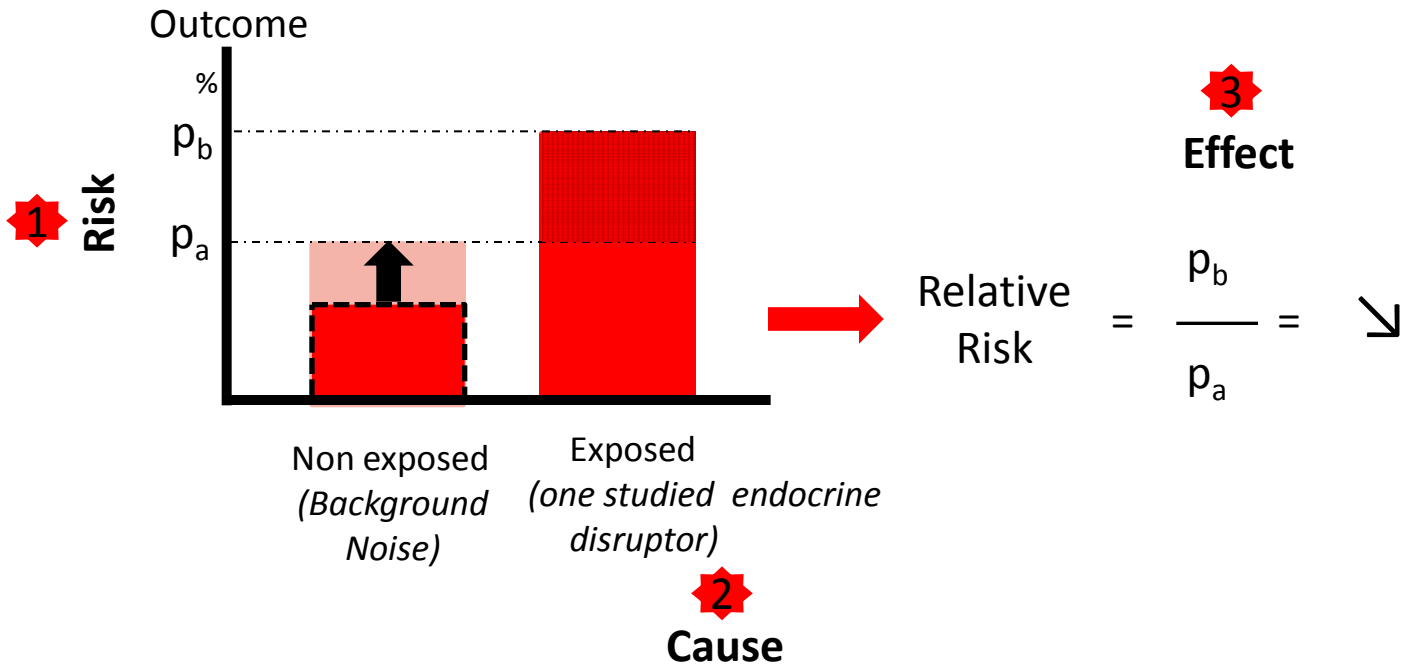


Figure 3. Number of chemicals detected by chemical class in U.S. pregnant women, NHANES subsample B [metals, cotinine, organochlorine (OC) pesticides, phthalates, brominated flame retardants (PBDEs), and PAHs], 2003–2004 (n = 54). Each vertical bar represents one study participant. Other subsamples showed similar results.

[Source : Woodruff TJ et al, 2011**]**

Environmental background noise

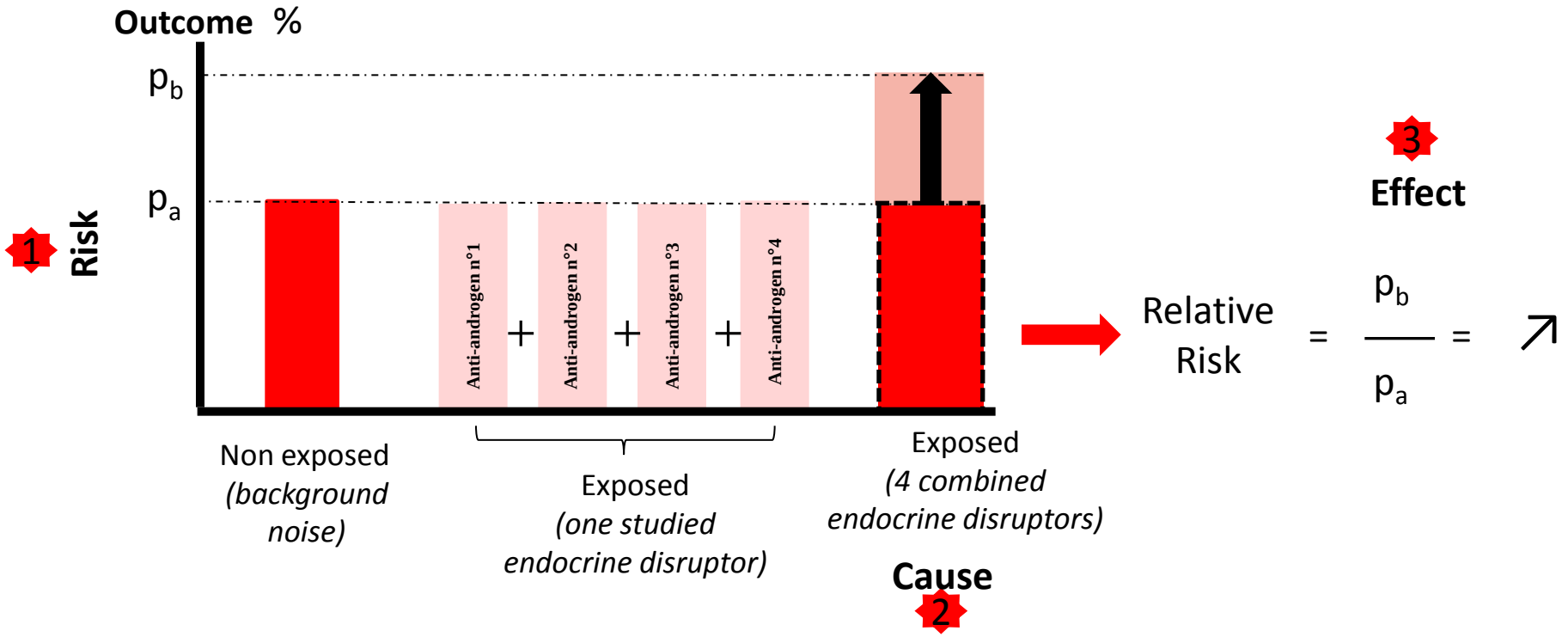
- **Difficulty** → detect a signal from the background noise for a study in the workplace :



- Problem +++ : **<u>often impossible to find unexposed control</u>** [Lee 2016]

Mixture effects

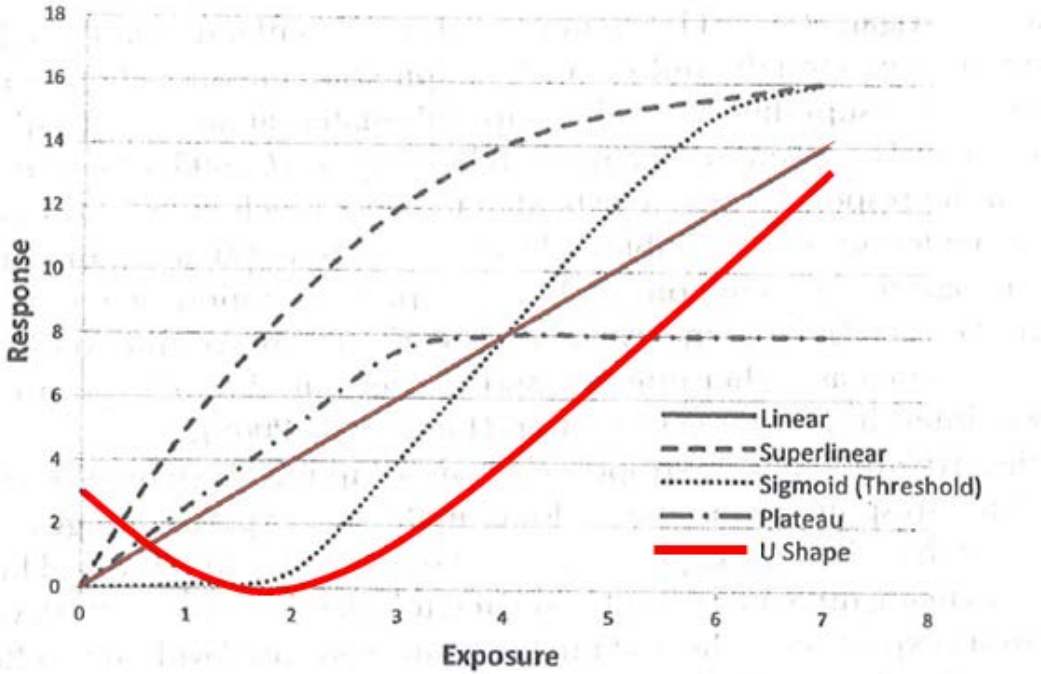
- **Issues of mixture** → in exposed group
- In general, epidemiological studies has focused on individual chemicals [Kortenkamp 2008]
- But EDs -> combinaison effects (experimental evidence) [Haas 2007, Silva 2002, Rajapakse 2002] -> Act through a common mechanism -> additive or synergic effects



- For example -> sector of hairdressers and cosmetologists
- Developed better tools for the investigation of cumulative exposed

Non monotonicity

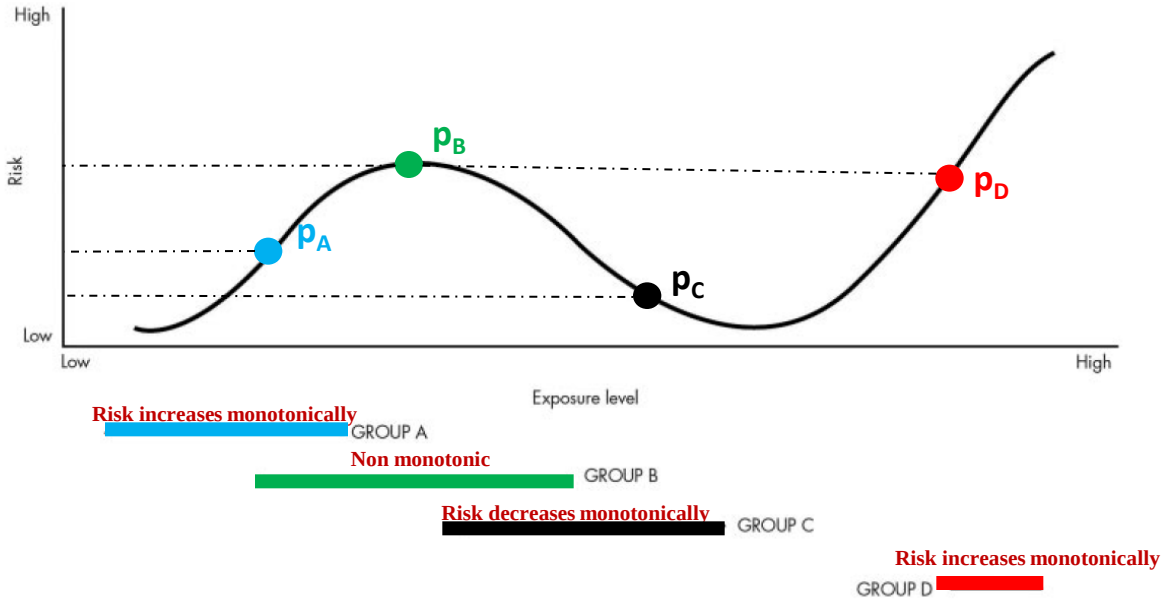
- A dose-response curve is nonmonotonic when the slope of the curve changes sign within the range of doses examined

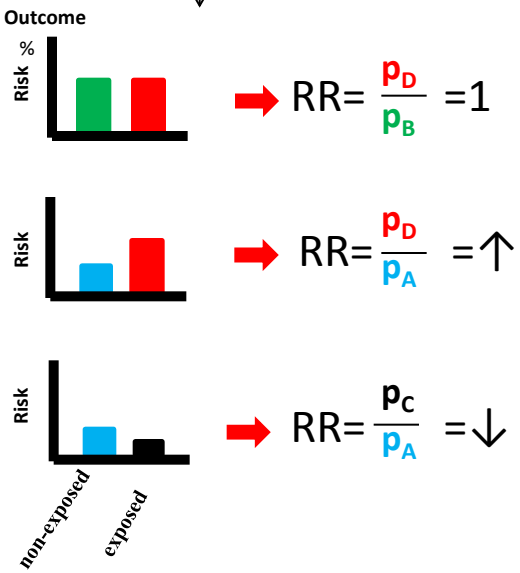


Examples of different exposure-response curves [Christensen 2015]

Low-dose and nonmonotonicity

- In observational epidemiology -> exposure distribution are given
- In different populations -> will have different ranges of exposure
- According to reference group -> a variety of possible findings





Source: Kortenkamp A *et al*, 2008

Importance of study size +++ -> the ability to detect NMDRCs, particularly in the low-dose range

Windows of susceptibility

Timing of exposure

- EDs can act at all times during life (fetus, infancy, puberty, adulthood, old age …)

- But the timing of ED action often determines the strength of their impact

- At least two perspectives :

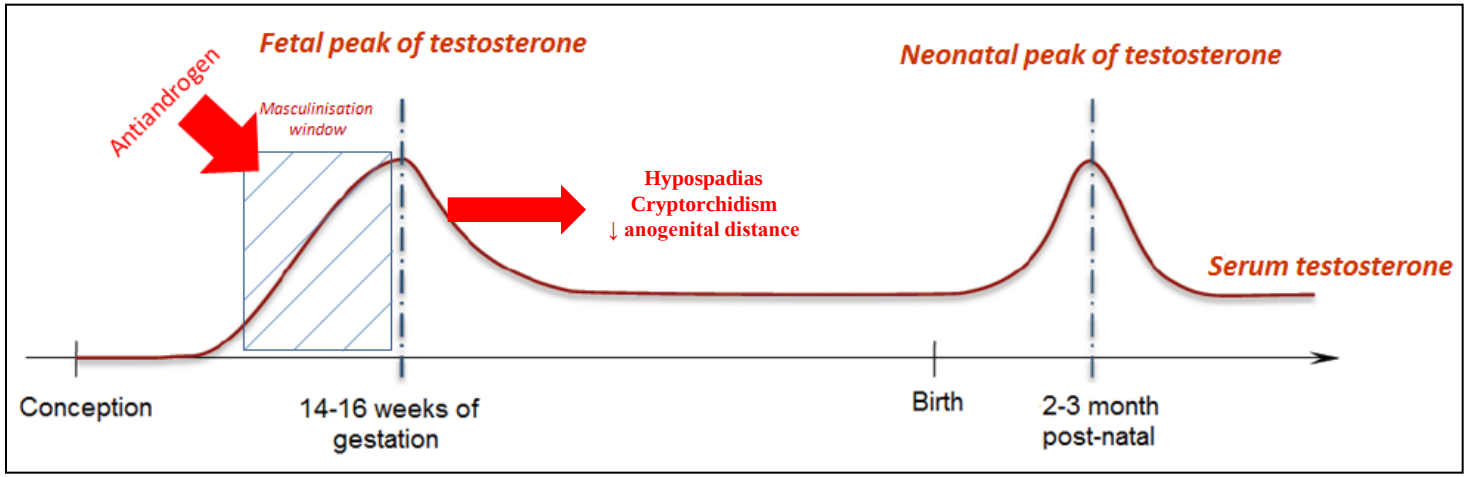
1- developmental effects

2- disturbance of homeostasis

Windows of susceptibility

- **1 - <u>Developing organisms</u>** are extremely sensitive to EDs -> occur at concentrations of the chemical that are far below levels that in the adult
  - During this period → possible direct effects (but as well as impacts much later in life)

ex: anti-androgen effect during pregnancy



Variation in serum testosterone levels during fetal and neonatal period [O'Shaughnessy PJ et al 2011

- Difficulties → to have accurate assessment of exposure during critical period (from example above -> during first trimester)
  → need cohorte starting from pregnancy

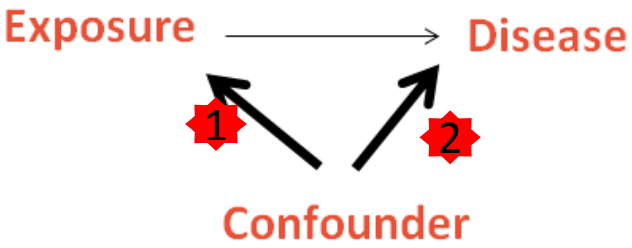
Windows of susceptibility

- **2 - <u>Disturbance of homeostasis</u>** »
  - The endocrine system plays an important role in the physiological response to environmental changes
  - **Disturbance of homeostasis** is not necessarily harmful → may or may not result in « adverse effects » → adaptative responses
  - But the response last as long as the PE is present
  - The concern is the impact of chronic exposure → change over the long term into adverse effects ?
  - Need for studies: → **first** : to confirm impact on intermediate biomarker,

    → **second** : long term follow-up with health outcomes is necessary

Confounding factors

- **Uncontrolled confounding is a major threat to validity in ED research**



3 *(without being an intermediary factor)*

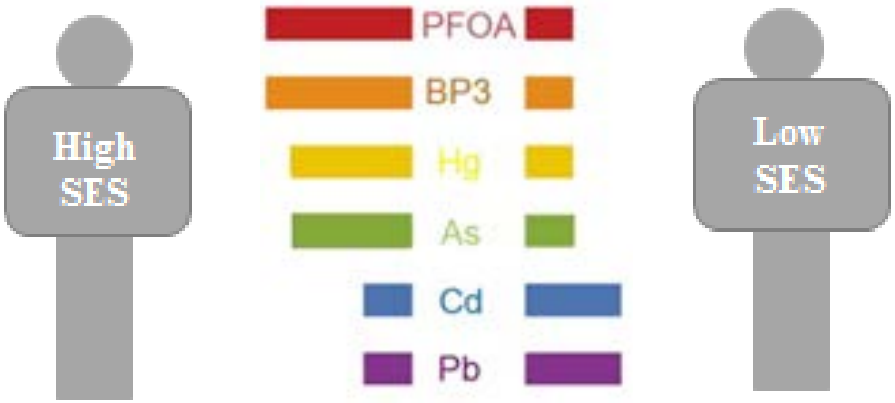
- To fully explain an association between E and D, the confounders must be moderately to strongly correlated with E or D) [Christensen 2015]

- But also, the distribution of the confounder must be very different between the exposed group and unexposed group to substantially change the effect estimate

- These conditions are rarely found : [Christensen 2015]
  → e.g. for studies of occupational exposures and lung cancer risks the adjustment for tobacco => impact on the RRs was rather moderate → ≈ ↓ 0,3
  → **researchers concluded : if RR> 1,5 or higher then RR unlikely to be entirely explained by uncontrolled confounding**

Confounding factors

- **<u>Concerns about compared groups</u>** *(exposed, unexposed)*
  - Exposure to EDs vary according to age, sexe, ethnic group, socioeconomicstatus, lifestyle …
  - e.g. study from USA to investigate the association between 179 toxicants and the poverty income ratio (PIR) → PIR was associated with 18 chemicals [Tyrrell 2013]



  - Important to account for potential differences in these factors between groups to compare (exposed, unexposed)

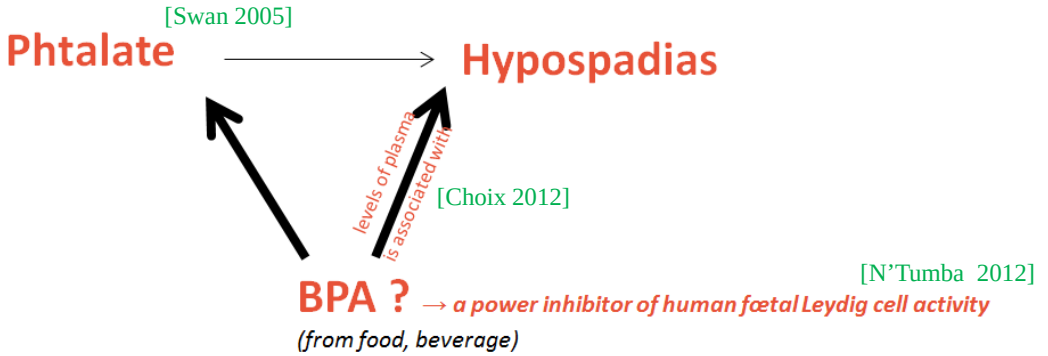
Confounding factors

Concerns about co-exposures :

- co-exposures with moderate correlation → as potential confounders

- can be isolated statistically
  (multi-variable regression, factor analysis …)

- If highly correlated (ρ > 0,8) may be difficult to analytically disentangle individual exposure effects



- In this situation, confounding may be difficult to address with statistical analysis for a given study

Conclusion

- Given this complexy, the evidence among epidemiology studies in humans is often inconsistent

- But there are :
  - many uncertainties surrounding the effects of EDs on human health
  - many limitations of extrapolation from in-vitro and in-vivo experimental findings to the human situation

- Despite methodological challenges, the conduct of epidemiological studies remains an essentiel component of the evaluation of possible human effects of EDs

- Key methodological issues must be known to develop new studies and raise the level of scientific evidence (new concepts ? new tools ? …)

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