Endocrine Disruptors:

Where are we?

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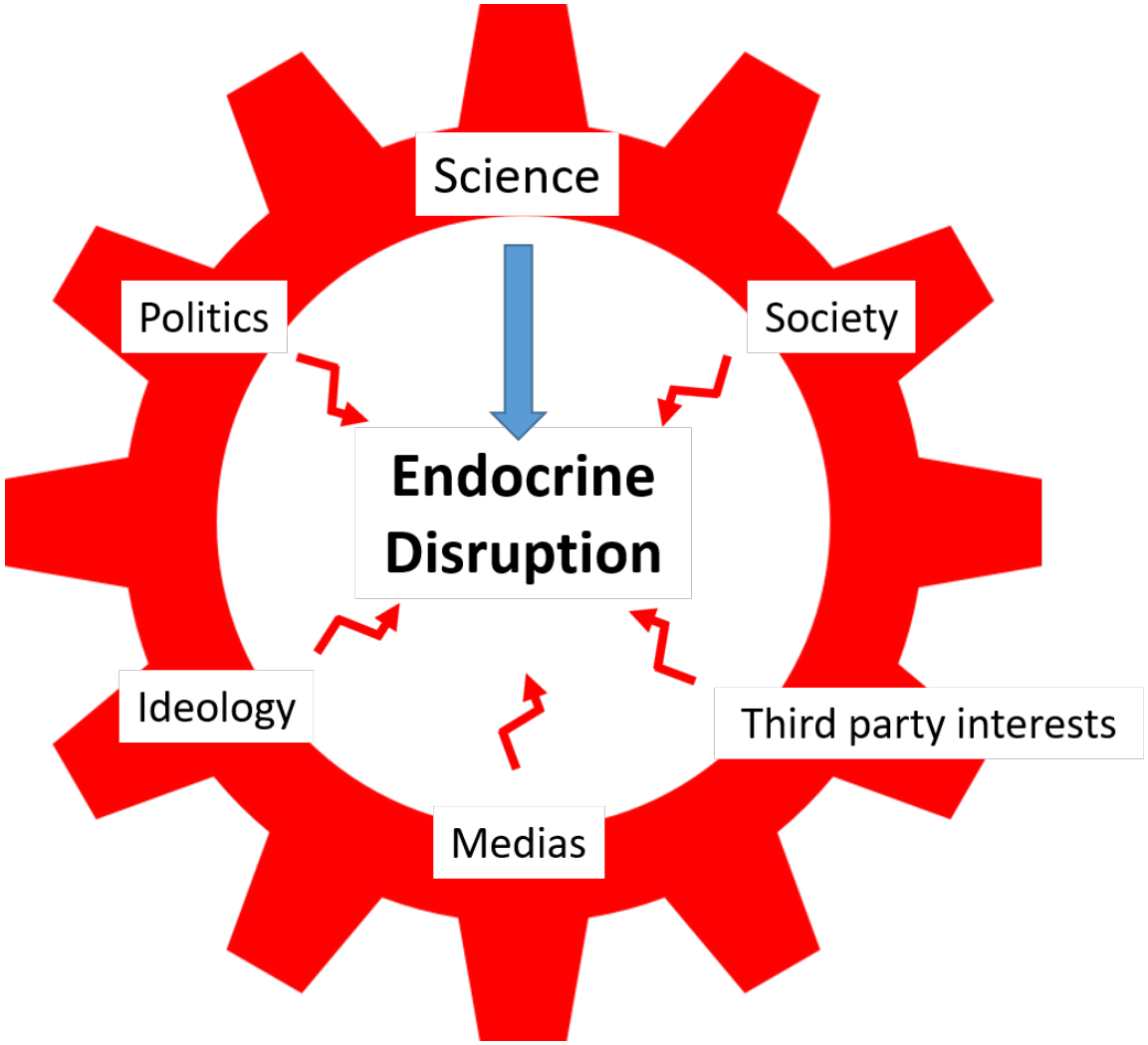
Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

irset
Institut de recherche sur la santé l'environnement et le travail

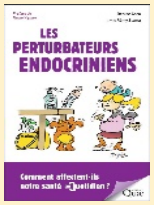
Worldwide

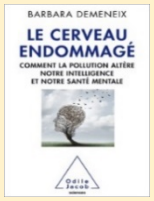

Science
Politics
Society
Endocrine Disruption
Ideology
Third party interests
Medias

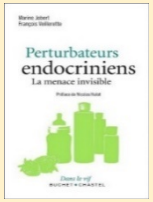
In France

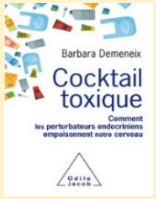
Press and Mass Media

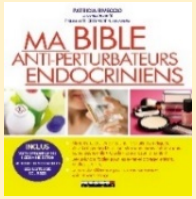

Text books

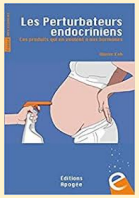


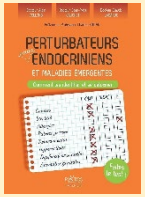












Government authorities

NGO

Advertising messages

Political campaigns

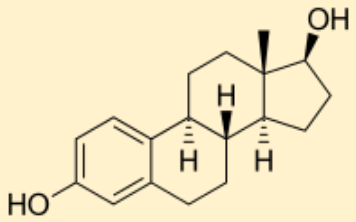
How did we get there?

1930s
Looking for synthetic estrogen analogs

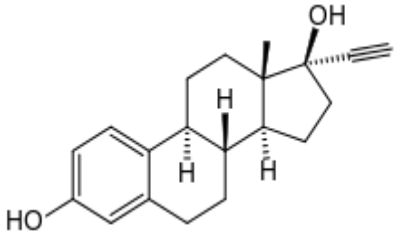
A synthetic Œstrus-Exciting compound
NATURE, January 14, 1933

Synthetic Oestrogènes Œstrogenic Agents without the Phenanthrene Nucleus
NATURE, June 13, 1936

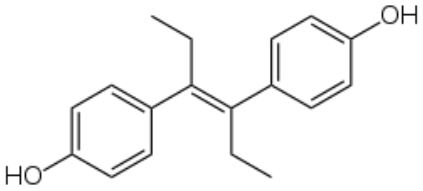
Œstrogenic Activity of Certain Synthetic Compounds
NATURE, February 5, 1938



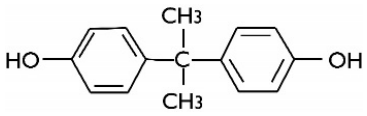
Œstradiol



Ethinyl oestradiol



Diethylstilbestrol



Bisphenol A

1940s to 1990s
Identification of environmental chemicals that interferes with endocrine systems

- **Identification of man-made and natural compounds**, in particular chlorinated hydrocarbons, having *in vitro* or *in vivo* hormonal activities, in particular steroidal properties.

- **Reproductive disorders in wildlife and domestic animals** (*gastropod species, reptiles, fish, birds, and mammals*) associated with man-made and natural compounds suspected to act as hormones

- **Reproductive disorders in humans** suspected to be associated with man-made and natural hormonal compounds

In 1991
Invention of the term Endocrine Disruptor

Statement from the work session on chemically-induced alterations in sexual development: the wildlife/human connection.

Wingspread Conference Center, Racine, Wisconsin, July 1991.

- **Synthetic Hormone Disruptors:** A large number of man-made chemicals that have been released into the environment, as well as a few natural ones, have the potential to disrupt the endocrine system of animals, including humans

- **The chemicals of concern** may have entirely different effects on the embryo, fetus, or perinatal organism than on the adult;

The particularity of this statement is that it intends **to sensitize the scientific community and health authorities** on the negative consequences of these chemicals on ecosystems, animal health and human health**.**

1990s
EDs: An attractive expression for the scientific community

- **A simple expression** that combines observational and experimental data on compounds that may affect reproductive health through an hormonal mode of action

- It brought together research perspectives on an **original mechanism of toxicity** of some natural or man-made compounds

Since the 1990s until today
EDs: a consensual but vague definition (WHO/IPCS 2002)

An endocrine disruptor is an exogenous substance or mixture that **alters function(s) of the endocrine system** and consequently causes **adverse health ef**fects in an intact organism, or its progeny, or (sub) populations

A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expressed to lead to endocrine disruption in an intact organism, or its progeny, or (sub) population

Since the 1990s until today
EDs: Growing complexity

The concept of endocrine disruption was first developed when it was observed that some environmental chemicals were able to mimic the action of the sex hormones (estrogens and androgens) and to induce reproductive adverse effects.

In the absence of a standardized and well-marked definition, the concept has evolved to encompass a range of modes of action incorporating:

the **whole endocrine-signaling**: all hormones and their specific receptors, transport proteins and associated enzymes.

the **non-endocrine signaling systems**

Since the 1990s until today
EDs: « Endocrine » is a broad topic and « Disruptor » is imprecise

- **Endocrine signaling pathways interact with one another but also interact to non-endocrine signaling systems:**

  Without discernement, any substance interacting with any signaling system in a living organism could be considered as an endocrine disruptor

- **The development of acquired / non-communicable diseases is always linked with changes in organism's signaling**:

  Without discernement, the list of endocrine-disruptors attributable diseases could be unlimited (the so-called endocrine-related diseases)

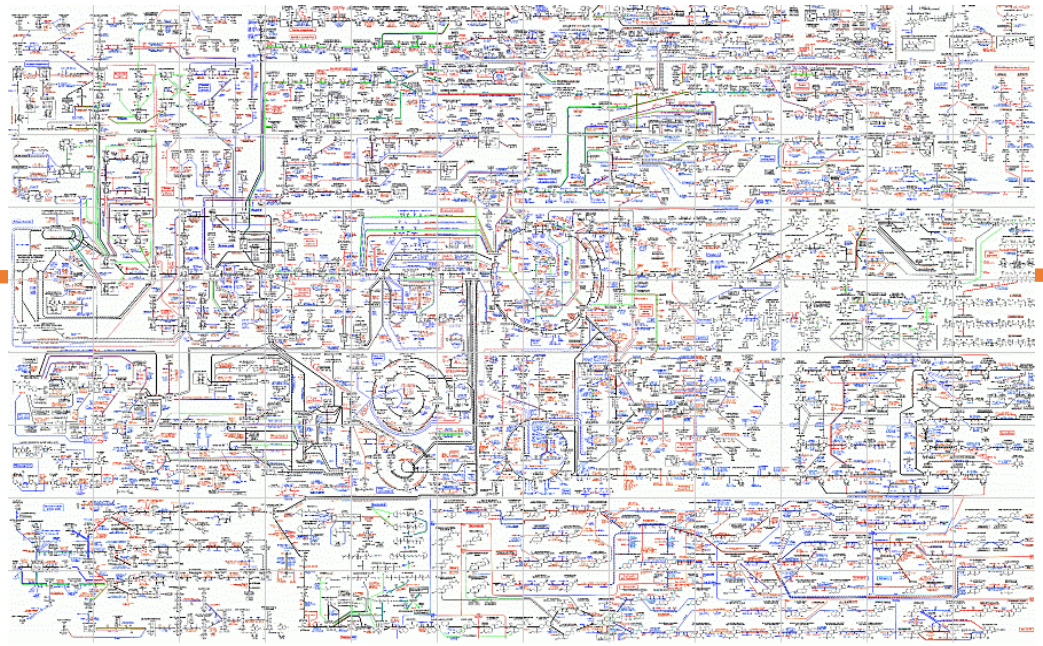
- **There is no clear-cut and precise definition or objective criteria to define them:**

  Without discernement, the list of endocrine-disruptors is imprecise and potentially unlimited

Since the 1990s until today
Eds: a mode of action

- **Endocrine diruptors refers to a mode of action likely to explain the occurrence of an adverse effect and not an adverse effect**

- **Is the presence of a mode of action sufficient to result in an adverse effect?**

EXPOSURE →  → ADVERSE EFFECT

COMPLEX BIOLOGICAL MECHANISMS

Since the 1990s until today
EDs: some non-specific and non-generalizable features

- Non-monotonic dose-response relationship
- Low-dose effects
- Synergistic effects
- Coktail effects
- Transgenerationnal effects
- Adverse effects not taken into consideration in regulated toxicological procedures

Since the 1990s until today
EDs: Looking for definition

Weybridge (1996), EPA (1996), WHO/IPCS (2002), BfR (2011), EFSA (2012), EU (2012), EPA (2012), Endocrine Society (2012), OECD (2012), EFSA (2013),…..

An endocrine disruptor is an exogenous substance or mixture that **alters function(s) of the endocrine system** and consequently causes **adverse health ef**fects in an intact organism, or its progeny, or (sub) populations

A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expressed to lead to endocrine disruption in an intact organism, or its progeny, or (sub) population

The WHO/IPCS definition have clearly two requirements for a substance to be defined as an endocrine disruptor, the demonstration of

1. an adverse effect
2. an endocrine disruption mode-of-action

Since the 1990s until today
EDs: Looking for regulation

USA

No regulatory definition

↓

EDs refer to modes of action and not to adverse effects already regulated elsewhere

↓

Development of tools to identify modes of action truly predictive of adverse effects

EU

Looking for a regulatory definition based on WHO/IPCS definition

↓

Proposal for a specific regulation excluding regulation by adverse effects

↓

Exposure must lead to a an adverse effect

The compound must have an endocrine mode of action

The adverse effect must be a consequence of the endocrine mode of action

Since the 1990s until today
EDs: The EU approach is criticized

1. Exposure must lead to a an adverse effect
2. The compound must have an endocrine mode of action
3. The ~~adverse effect must be a consequence of the endocrine~~ mode of action

If we conclude that adverse effect is the consequence of mode of action without proving it then we make a logical fallacy (*Post hoc ergo propter hoc)*

Misconceptions, beliefs, superstitions and magical thinking often result from this error

Since the 1990s until today
EDs: What is wrong?

- **Fuzzy concept with uncertain borders**
- **The scientific controversy exists and is still raging**
- **Scientists are largely responsible for these ambiguities**
  - **Some assume erroneously occasional peculiarities as generalizable truth**
  - **Some ignore risk assessment procedures (Hazard and Risk)**
  - **Some act as white knights**
- **This allows simplistic interpretations**
- **All these shortcomings plant the seed of third party interests**

  ***Damnant quod non intellegunt*.**
  They condemn what they do not understand. (Cicero)

  Recourse to the precautionary principle

THANK YOU FOR YOUR ATTENTION

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