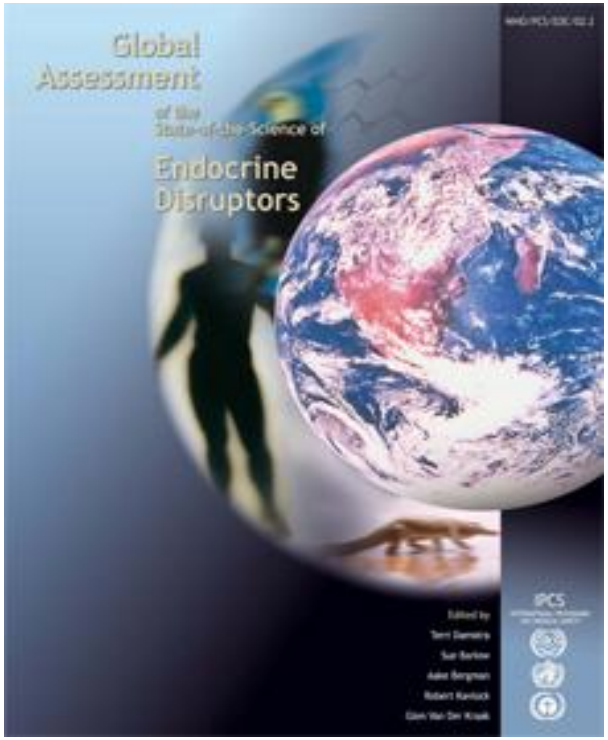
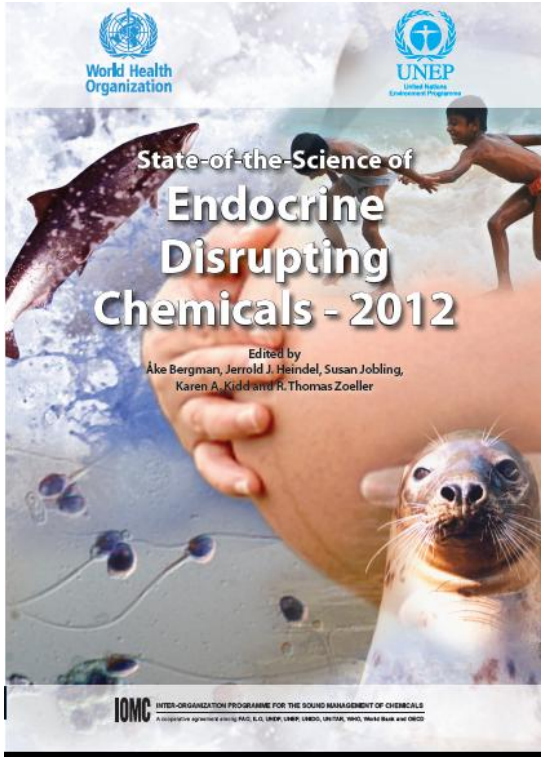
State-of-the-Science of Endocrine Disrupting Chemicals – 2012



IPCS 2002



UNEP/WHO 2012

Overview of Process

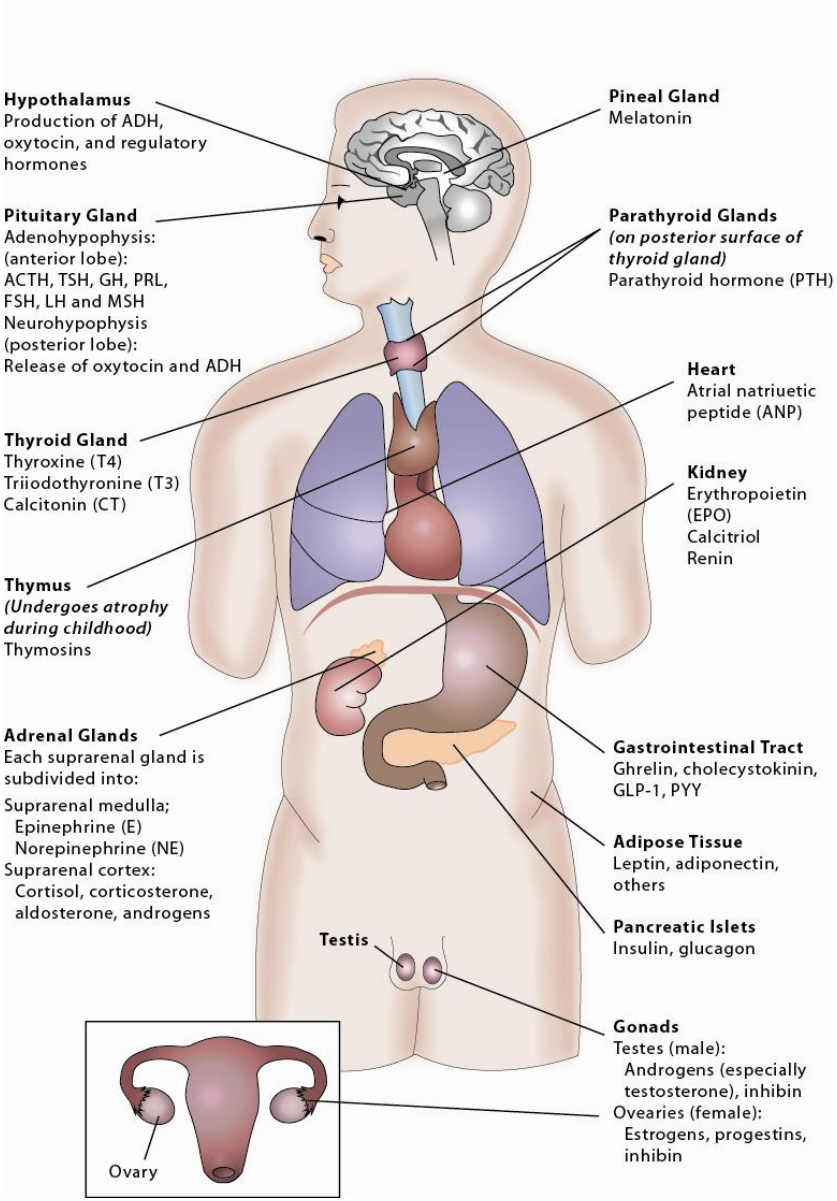
- December 2009, WHO and UNEP convened a meeting of the planning group for the development of an update to the 2002 IPCS “Global Assessment of the State-of-the-Science of Endocrine Disruptors”
- Working group members selected June 2010
- Working group (16) met
  - Stockholm in November 2010, in Copenhagen in May 2011 and in Geneva in December 2011
- Additional experts also contributed to sections of the reports
- Reviewed by 22 external reviewers

What advances have been made?

- WHO 2002
  - Evaluating cause-effect relationships for **specific chemicals**
- Today
  - Recognition of **complexity** of exposures
  - Progress with **experimental** studies
- Disease trends and epidemiology
  - Associations with summative exposure parameters
- **Sources of exposure**
  - Types measured in tissues
  - Spatial and temporal trends in exposure

Chapter 1 – What is endocrine disruption all about?

- What are hormones
- What are endocrine disruptors



There are approx. 50 hormone systems with around 100 signalling compounds

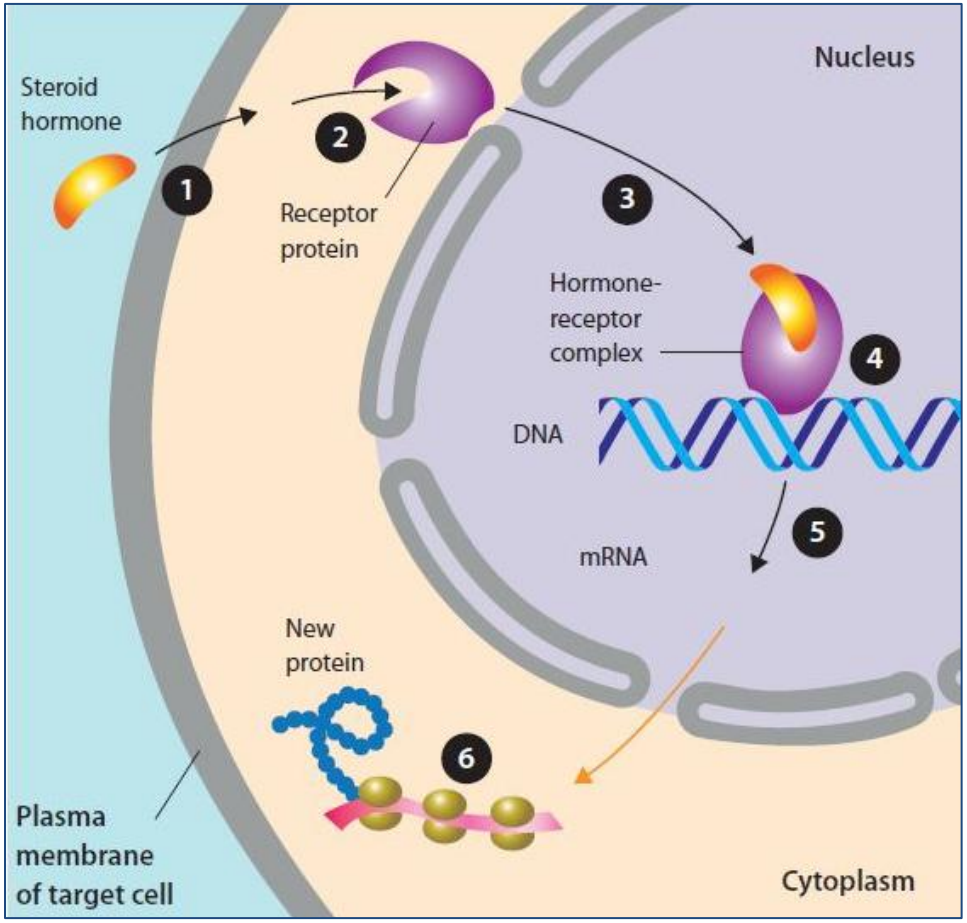
Very well preserved between & similar among species

EDCs Act like Hormones

- Hormones bind to specific receptors to trigger cellular responses such as protein synthesis.

- Some EDCs can act directly on hormone receptors as hormone mimics or blockers. Others act directly on proteins that control the delivery of a hormone to its normal target cell or tissue.

- EDCs have the ability to:
  - be active a low concentrations;
  - interact with multiple hormone receptors at once; and
  - work together to produce additive or synergistic effects.



Endocrine Disruption is not Endocrine Modulation

A change in blood level of hormone represents “disruption” only if the result is that hormone is not delivered (or is delivered inappropriately) to the target tissue (i.e., interferes with hormone action)

NORMAL ENDOCRINE FUNCTION:

Your favourite chocolate bar increases blood level of glucose

Increase in glucose causes insulin to be released

Insulin causes tissues to take up glucose (this is NOT “homeostasis”)

Thus, a chocolate bar is not an EDC

In contrast, an EDC would be an exogenous chemical, or mixture of chemicals, that interferes with:

- The ability of glucose to cause insulin release
- The ability of insulin to interact with its receptor
- The ability of insulin-receptor interaction to cause glucose uptake and/or utilization

LIKEWISE: An EDC is an exogenous chemical, or mixture of chemicals, that:

- Interferes with thyroid hormone action during brain development and reduces the intellectual potential of the individual and population
- Interferes with fat development, predisposing the individual and population to obesity and diabetes
- ETC!

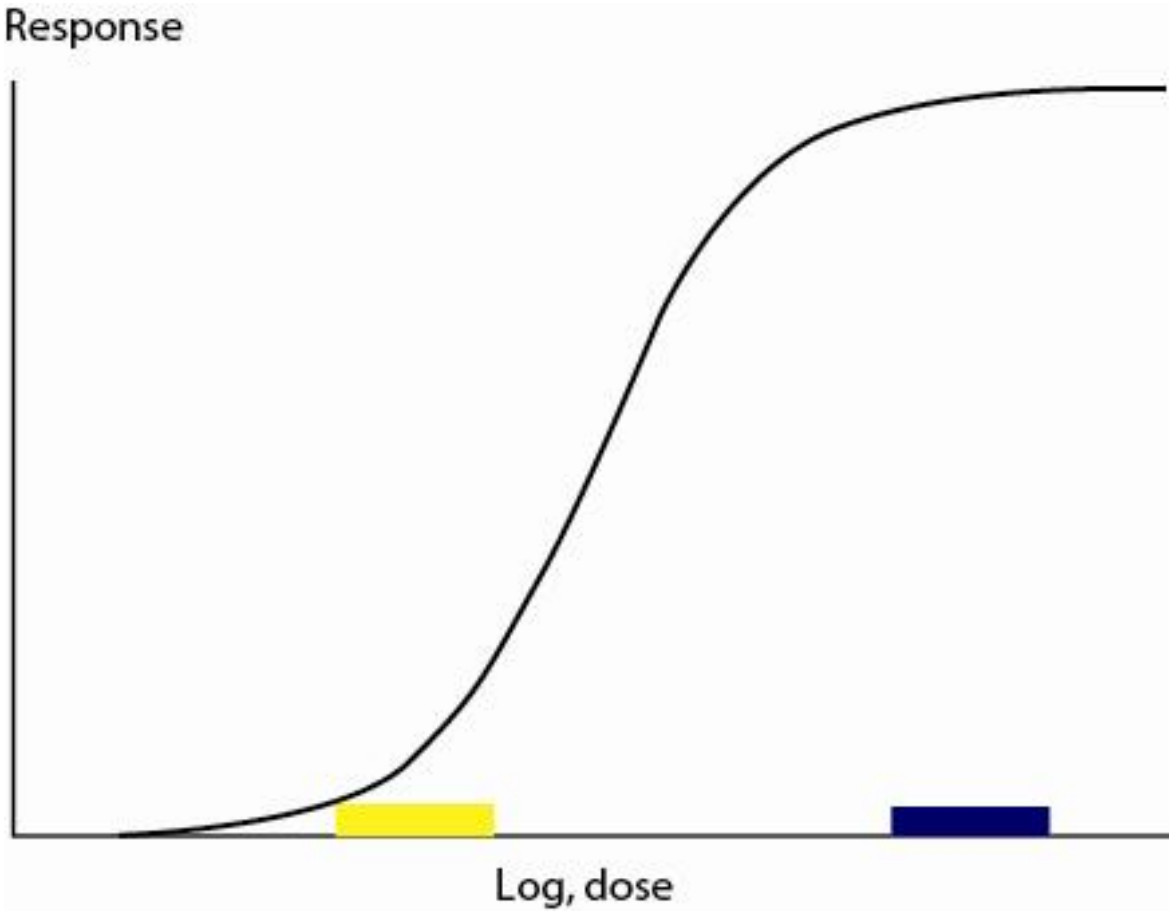


Figure 1.3A

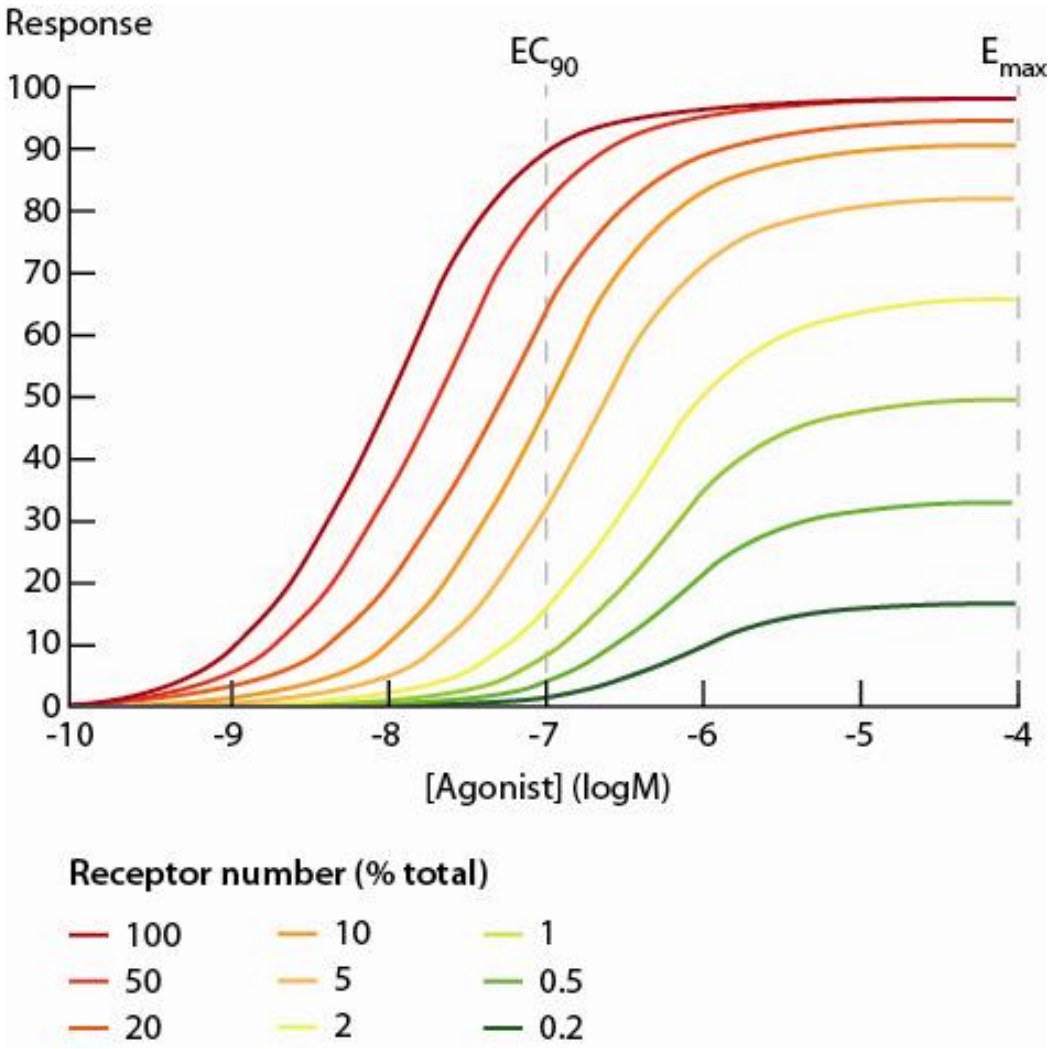
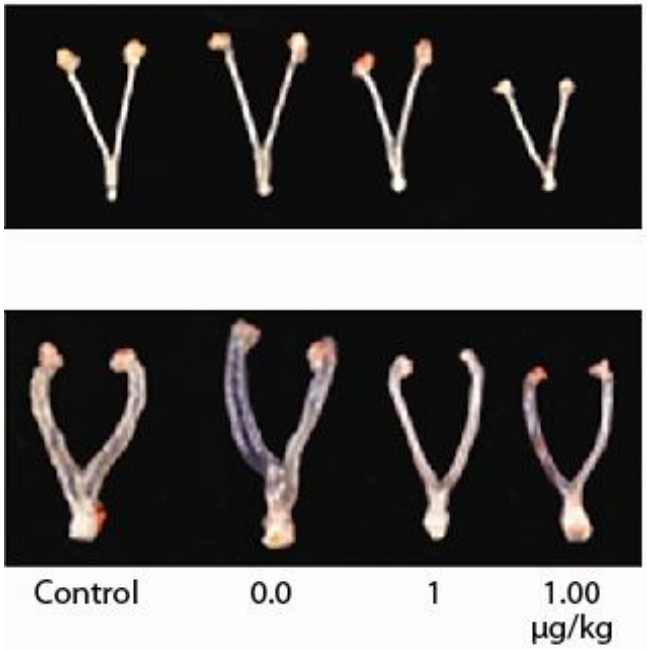
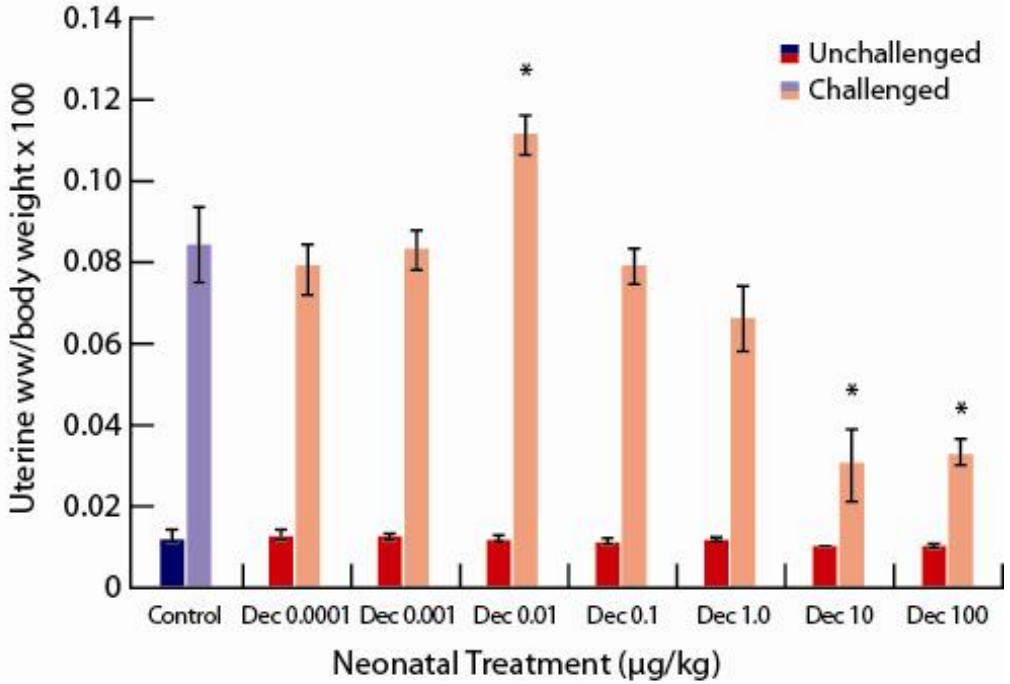

Response
EC90
Emax
100
90
80
70
60
50
40
30
20
10
0
-10
-9
-8
-7
-6
-5
-4
[Agonist] (logM)
Receptor number (% total)
100
50
20
10
5
2
1
0.5
0.2

Figure 1.3B

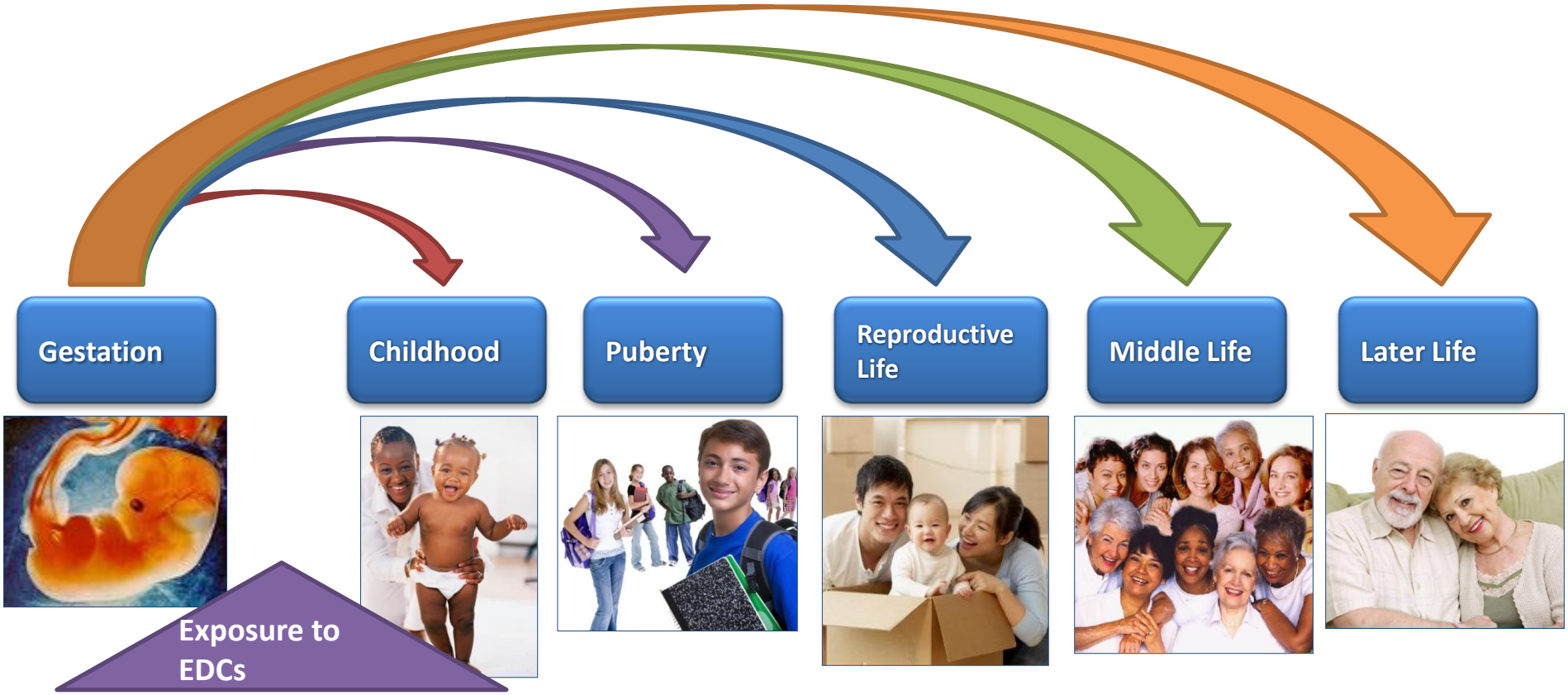




* Low doses of DES enhance estrogen responses while high doses dampen them.

Figure 1.5

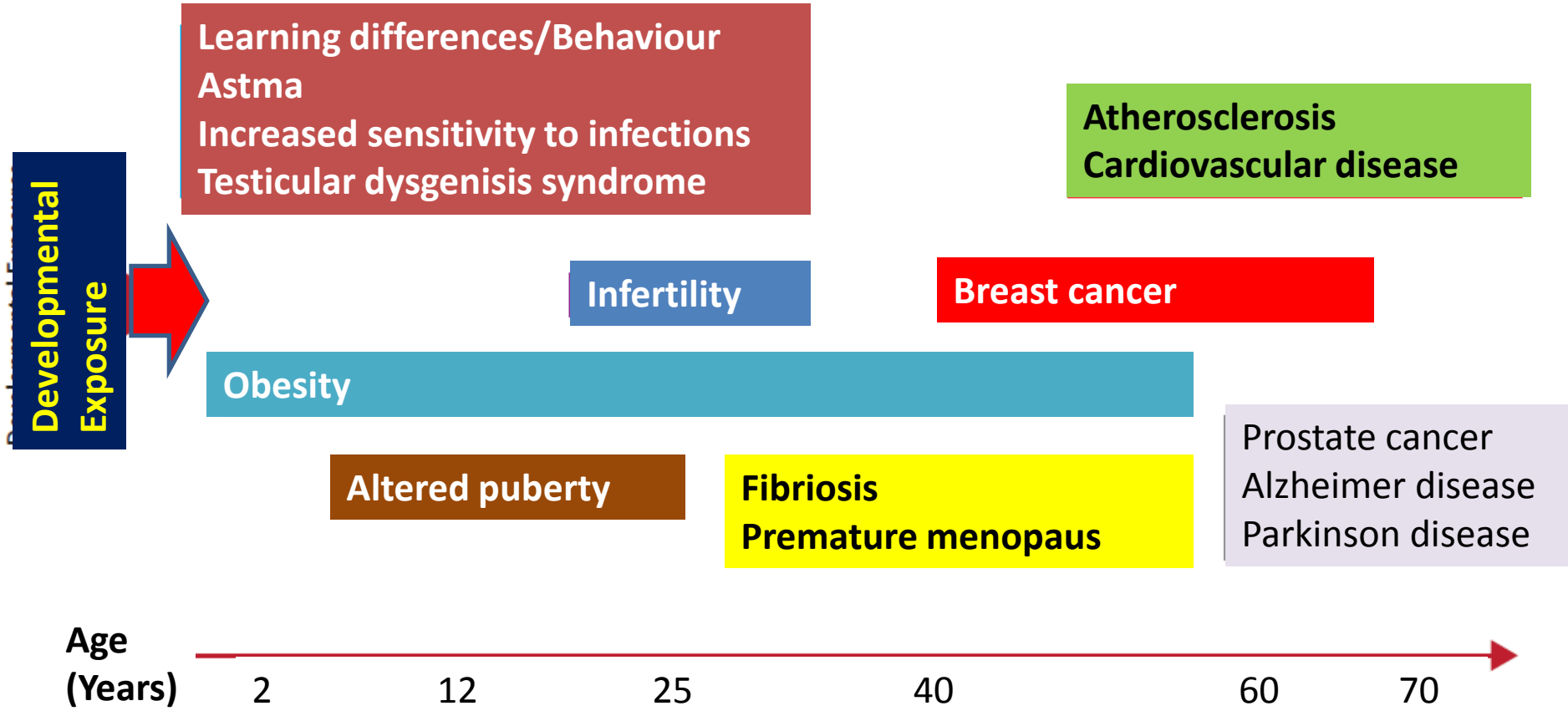
Early Life Exposure to EDCs



The effects of early exposures to EDCs – when organ systems are developing – may be manifested any time in life.

Why should we be concerned?

Developmental exposure to endocrine disruptors manifested later in life



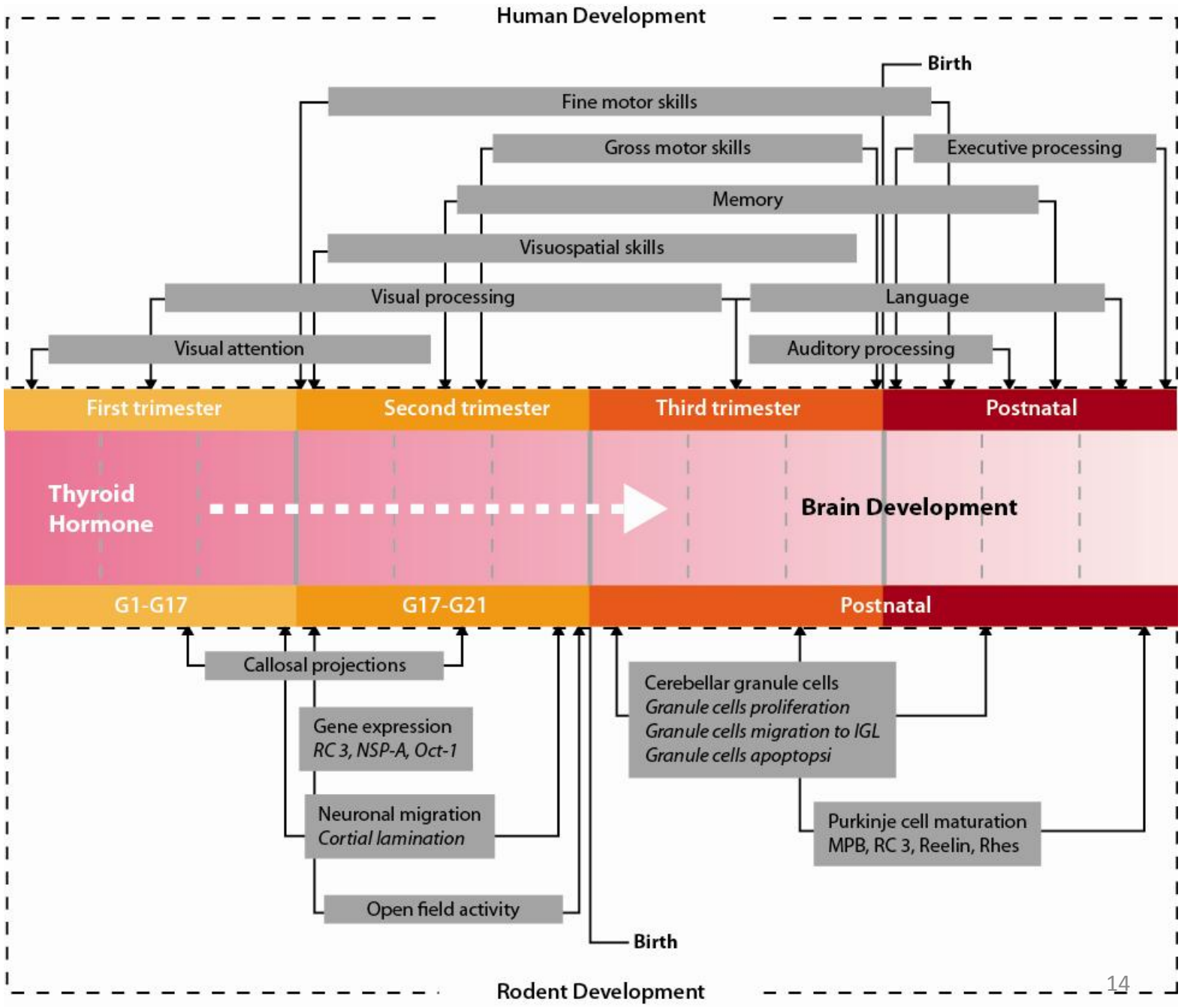

Human Development
Birth
Fine motor skills
Gross motor skills
Executive processing
Memory
Visuospatial skills
Visual processing
Language
Visual attention
Auditory processing
First trimester
Second trimester
Third trimester
Postnatal
Thyroid Hormone
Brain Development
G1-G17
G17-G21
Postnatal
Callosal projections
Gene expression
RC 3, NSP-A, Oct-1
Neuronal migration
Cortial lamination
Open field activity
Cerebellar granule cells
Granule cells proliferation
Granule cells migration to IGL
Granule cells apoptopsi
Purkinje cell maturation
MPB, RC 3, Reelin, Rhes
Birth
Rodent Development

Figure 2.14

More than 800 chemicals with ED properties

The majority of all chemicals in use are not tested

- Current use Pesticides
- Flame Retardants
- Plastics
- Herbicides
- Industrial byproducts
- Plasticizers
- Personal Care products
- Surfactants
- Cosmetics
- Solvents
- Sunscreens
- Antioxidants
- Heavy metals
- POPs
- Polycyclic Compounds

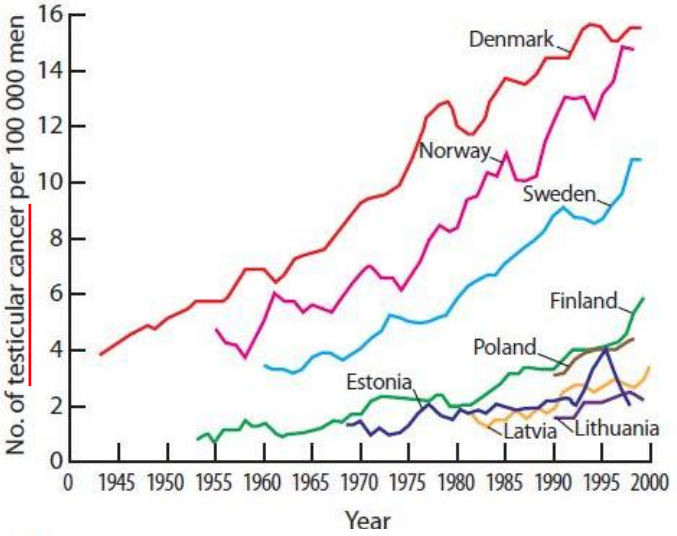
Chapter 2 – Evidence for endocrine disruption in humans and wildlife

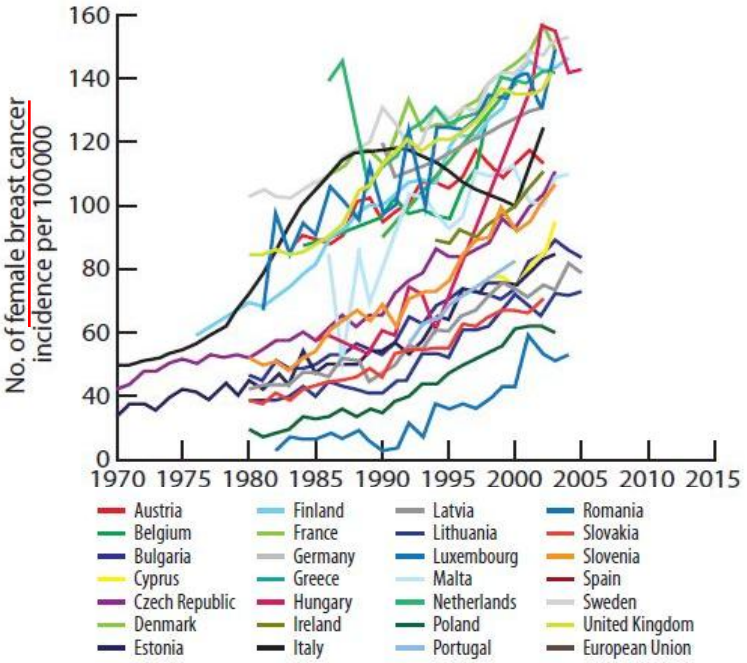
- Endocrine disruptors and:
- Female reproductive health
- Male reproductive health
- Sex ratios
- Thyroid related diseases and disorders
- Neurodevelopment
- Hormone related cancers
- Adrenal disorders
- Bone disorders
- Metabolic disorders
- Immune function, diseases and disorders
- Population declines

Human Disease Trends

Over recent decades there has been:

- significant increase in **reproductive problems** in some regions of the world, suggesting a strong role for unidentified environmental factors in disease etiology
- increase in **endocrine cancers**
- significant decrease in **human fertility** rates
- increase in use of assisted reproductive services
- increasing number of chemicals to which all humans in industrialized areas are exposed





Top: Richiardi et al., Cancer Epidem. Biomark. (2004);
Bottom: based on data from http://data.euro.who.int/hfadb/

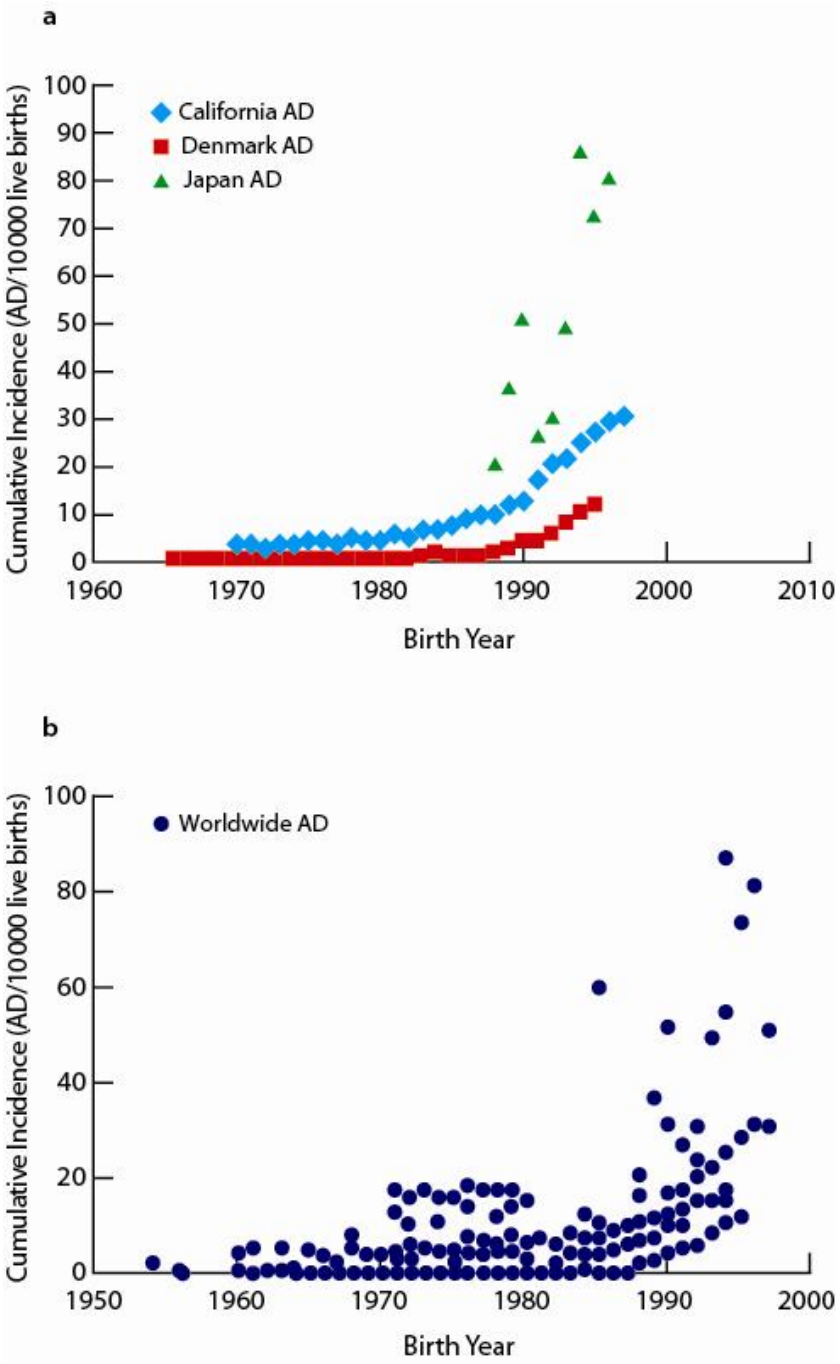

a
Cumulative Incidence (AD/10000 live births)
100
90
80
70
60
50
40
30
20
10
0
California AD
Denmark AD
Japan AD
1960
1970
1980
1990
2000
2010
Birth Year
b
Cumulative Incidence (AD/10000 live births)
100
80
60
40
20
0
Worldwide AD
1950
1960
1970
1980
1990
2000
Birth Year

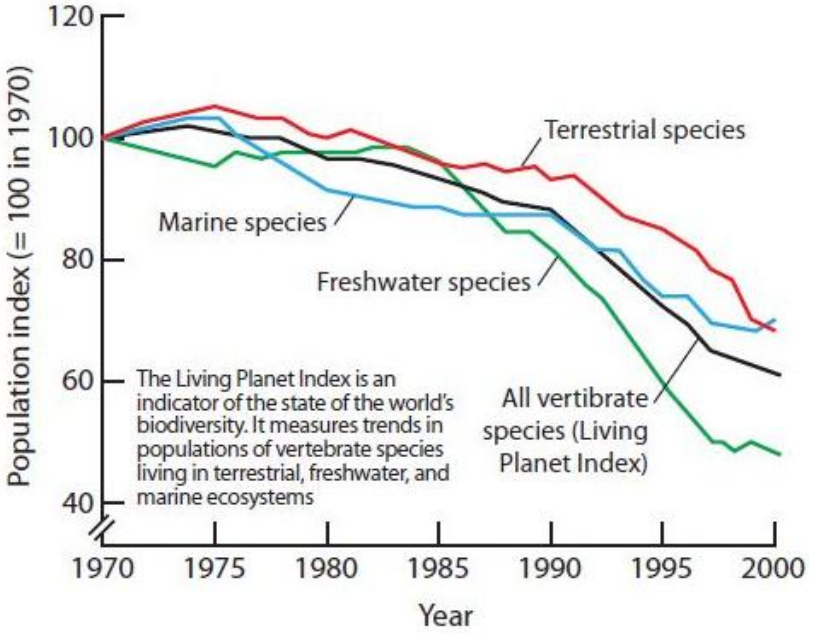
Figure 2.13

Parallels between human and wildlife health

- Hormones and signaling pathways are often quite similar across species.
- The increasing incidence of human disorders is similar to those observed in wildlife.
  - There is recent evidence that animals living near humans also have increasing body weight.
- Studies of PCB-exposed wildlife have provided important information on:
  - exposure levels;
  - early and subclinical effects; and
  - clinical neurotoxicity of PCBs.
- Mechanisms underlying the effect and outcomes of EDC exposure in wildlife are often similar to those in humans.

EDCs and Wildlife Population Declines

- There is a worldwide loss of species or reduced population numbers of amphibians, mammals, birds, reptiles, freshwater and marine fishes, and invertebrates.
- Demonstrating a clear link between EDCs and population declines is challenging because of the difficulty in isolating the effects of chemicals from the effects of other stressors and ecological factors.
- EDCs have been shown to negatively affect body systems that are critical for the health and survival for wildlife.



Population declines in vertebrates worldwide over 30 years.
(source: World Wide Fund for Nature and the World Conservation Monitoring Centre of UNEP)

- Given our understanding of EDCs and their effects on the reproductive system, it is extremely likely that declines in numbers of some wildlife populations are because of the effects of EDCs.
- As levels of EDCs decline, some wildlife populations have shown recovery.

Key Concerns

- Three strands of evidence fuel concerns over endocrine disruptors:
  - The high incidence and the increasing trends of many endocrine-related disorders in humans;
  - Observations of endocrine-related effects in wildlife populations;
  - The identification of chemicals with endocrine disrupting properties linked to disease outcomes in laboratory studies.

Chapter 3 - Human and wildlife exposures to EDCs

- EDCs of concern
  - Types, sources, environmental distribution, exposures
- EDCs found in humans and wildlife
  - Types measured
  - Spatial and temporal trends
- Emerging issues and EDCs of concern

Which are the Endocrine Disrupting Chemicals?

Property/Behaviour based grouping

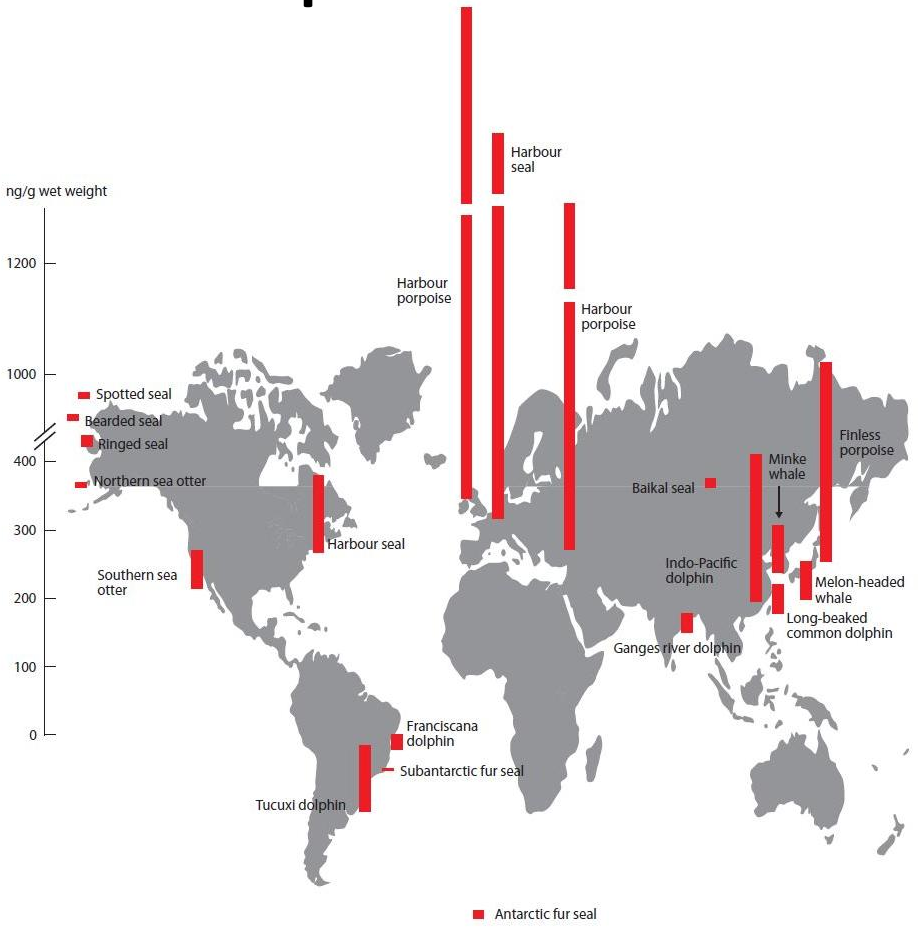
- Persistent & Bioaccumulative chemicals
  - POP (Stockholm Convention)
  - Other P and B chemicals (Lipophilic and Proteinophilic)
- Semi-persistent chemicals
  - Chemicals with high persistency but without bioaccumulation potential
- Pseudo-persistent chemicals
  - Chemicals for which continous exposure may occur, leading to stady state levels in exposed organisms
- Metals and metalloids

Multiple Routes of EDC Exposure

- EDC exposure occurs via:
  - ingestion of food, dust, and water
  - inhalation of gases and particles in the air
  - dermal uptake
- Pregnant females can transfer EDCs to the developing fetus through the placenta and to offspring in mother's milk, which may affect development of her offspring and also their offspring over several generations (i.e., transgenerational effects).
- Multiple routes of exposure to a variety of EDCs means that humans and wildlife are exposed to multiple EDCs at the same time.
- Animal studies show exposures to mixtures of EDCs produce additive effects, which can occur even when the chemicals do not produce effects individually.

Global EDC Exposure – Evidence from Wildlife Populations

- Levels of EDCs in humans and wildlife vary with location.
- Some levels of EDCs are higher in people and wildlife in urban or highly industrialized areas where, for example, disposal of e-waste occurs.
- Some levels of EDCs are higher in remote environments because of long-range transport by air and ocean currents and food web accumulation.

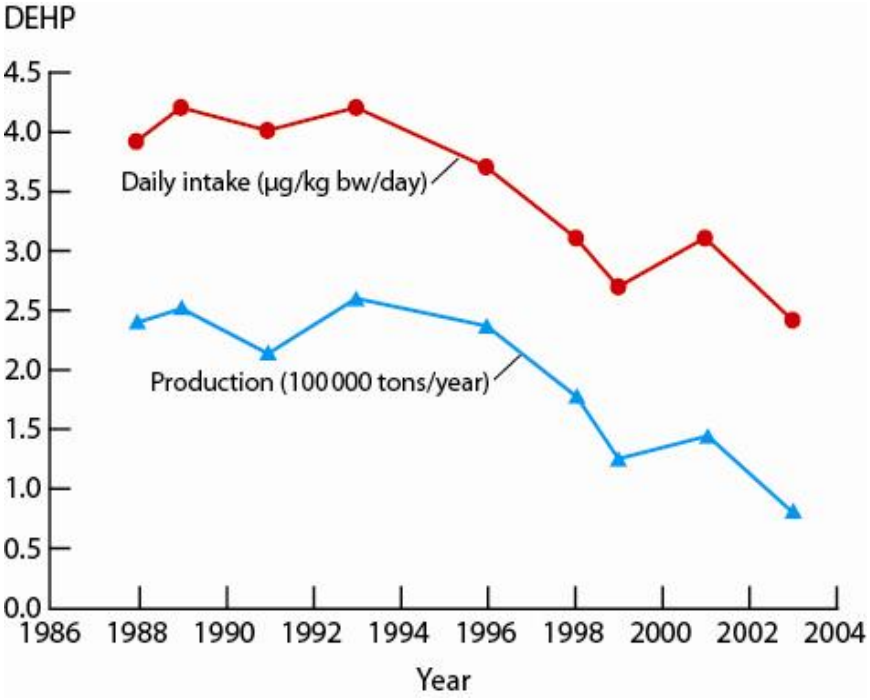


Concentrations (ng/g wet weight) of perfluorooctane sulfonante (PFOS) in liver of marine mammals.

Figure modified from: Houde et al., Environ. Sci. Technol. (2011)

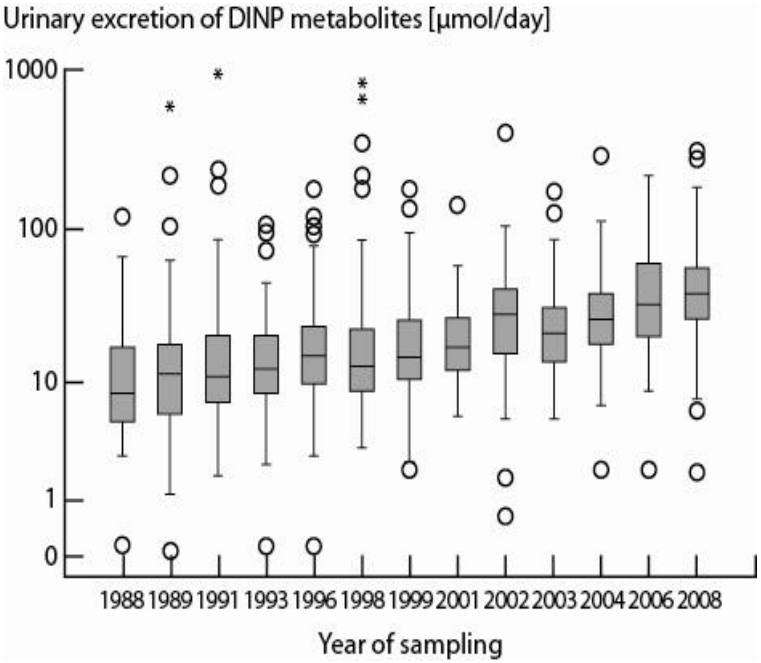
Exposure to EDCs is responsive to changes in production & use

DEHP production in Germany & median daily intake of DEHP



(Helm, STOTEN, 388, 2007)

Trend of urinary excretion (mmol/day) of DiNP metabolites



(Göen et al. J. Hyg. Env. Health, 215 (2011)

The Tip of the EDC Iceberg

- Only a small fraction of the hundreds of thousands of synthetic chemicals have been assessed for endocrine disrupting activity.
- Many chemicals in consumer products are not identified by the manufacturer.
- There are still many questions:
  - **How many EDCs are there?**
  - **Where do they come from?**
  - **What are the human and wildlife exposures?**
  - **What are their effects individually and in mixtures during development, adulthood, and across generations?**
  - **What are their mechanisms of action?**
  - **How can testing for EDCs be improved?**

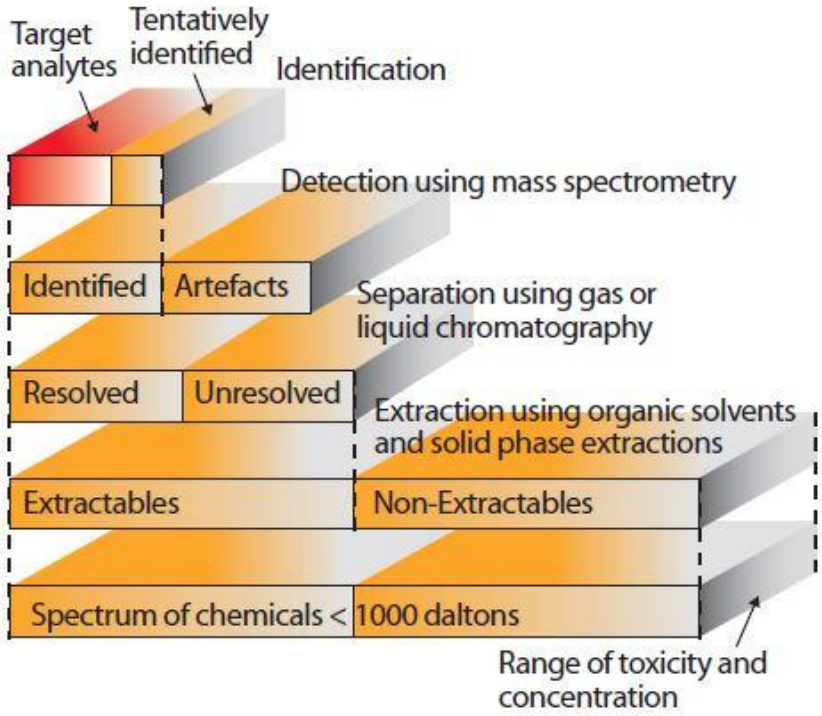
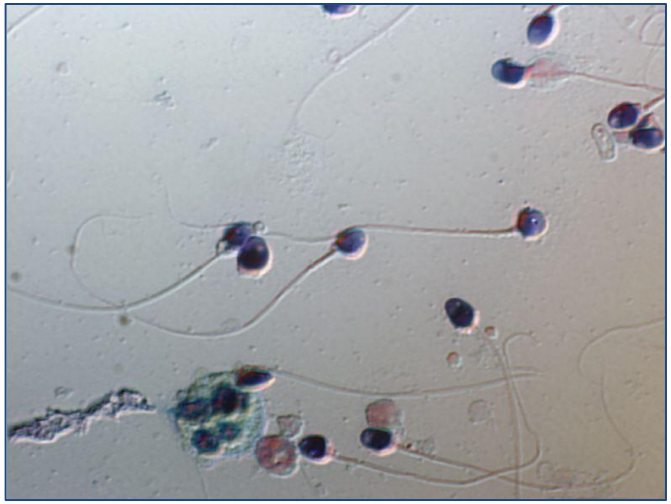


Illustration of the complexity of measuring chemicals, including potential EDCs, in environmental media.

Current Testing for EDCs



- Tests for the endocrine disrupting activity of a chemical usually determine the **no-observed-adverse-effect level**, or the level associated with no observable effects. This level is used to determine levels expected safe for humans or wildlife. **The doses declared safe are not actually tested, nor are the mixtures.**
- Studies assume:
  - there is a threshold for EDC effects; **but** there is no threshold for EDC effects due to the presence of active hormone pathways.
  - there will be no effects at low doses; **but** EDCs may have effects at low doses.
  - dose-response curves rise with increasing dose; **but** EDC dose-response curves will not necessarily rise in proportion to dose.
- Many studies focus on histopathology and organ and body weights as end-points; **but** EDCs can cause many diseases and affect many disease end-points.
- Risk assessment approaches do not always assess toxicity during development, or follow animals for their lifetime.

Thank you

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