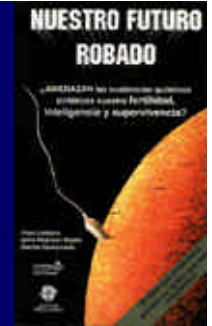




ENDOCRINE DISRUPTION: THE BASICS



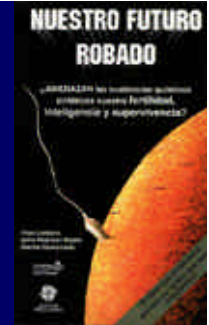
**Contaminants that interfere with the
body's natural signalling system**

**Affect the rates of synthesis or
breakdown of hormones**

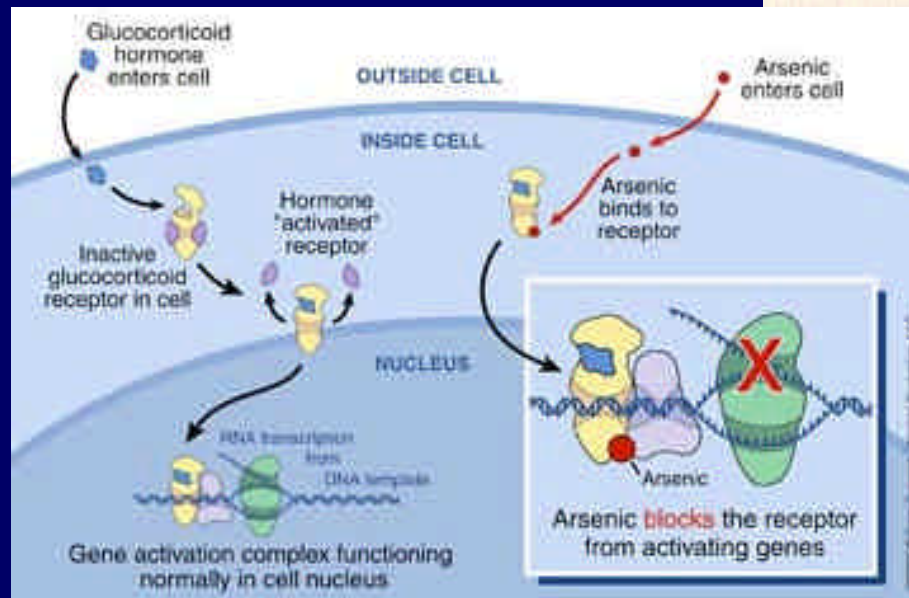
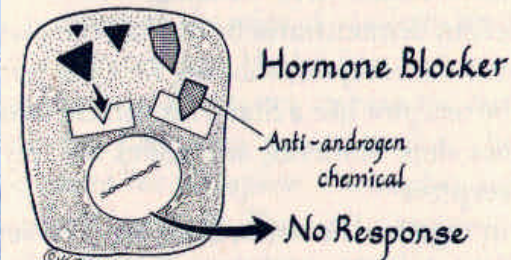
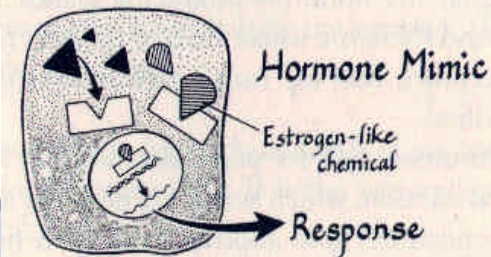
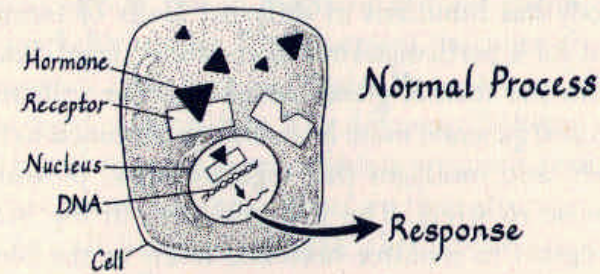
Block or mimic hormone messages

**Alter sensitivity to hormonal
stimulation**

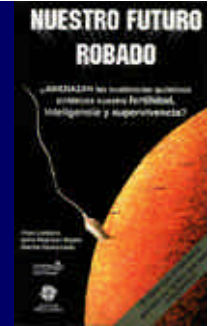
DISRUPTING HORMONE SIGNALS



Receptor Effects of Synthetic Chemicals

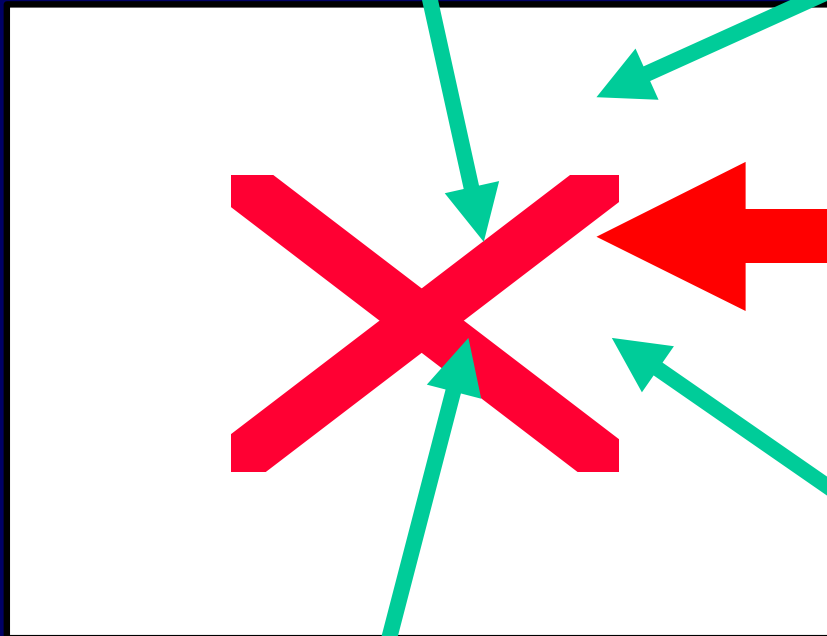


FETAL DEVELOPMENT IS ESPECIALLY VULNERABLE



Hormones

Growth factors



**Hormone
disruptors**

Neurotransmitters

Cytokines

www.OurStolenFuture.org

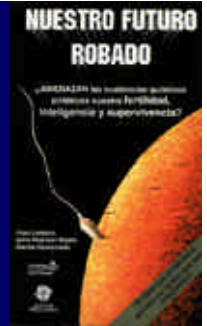
WHAT IS THE EVIDENCE?

Laboratory experiments

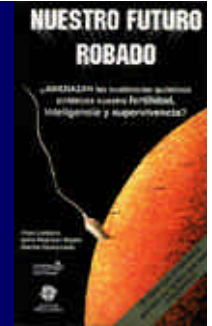
Wildlife observations

Well-studied human exposures

Epidemiology of people.



THE CASE OF THE ATLANTIC SALMON

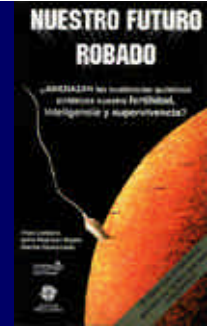


**Decline attributed to
traditional causes...**

**overfishing
habitat destruction
dams**

**Now, osmoregulatory
failure likely involved**

LAB STUDIES SHOW REPRODUCIBLE EFFECTS



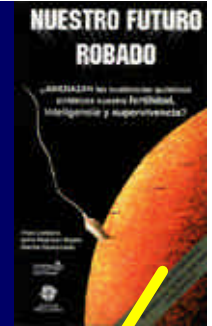
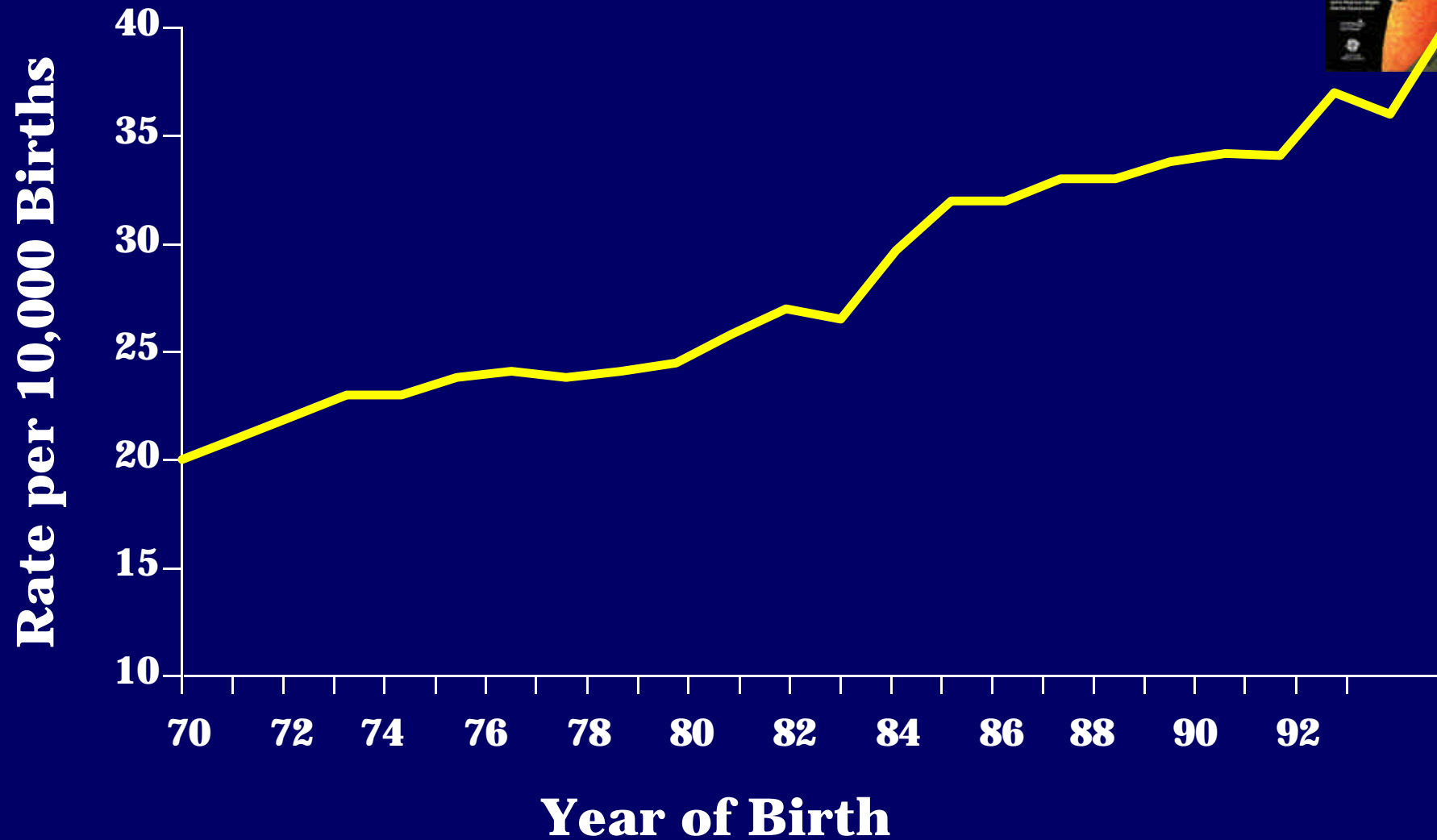
On many endpoints

**Reproductive birth defects and
reduced fertility**

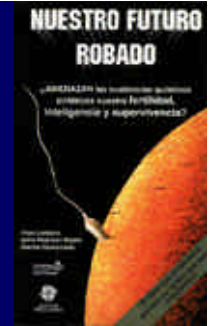
Behavioral disorders

Immune system impacts

HYPOSPADIAS in the US

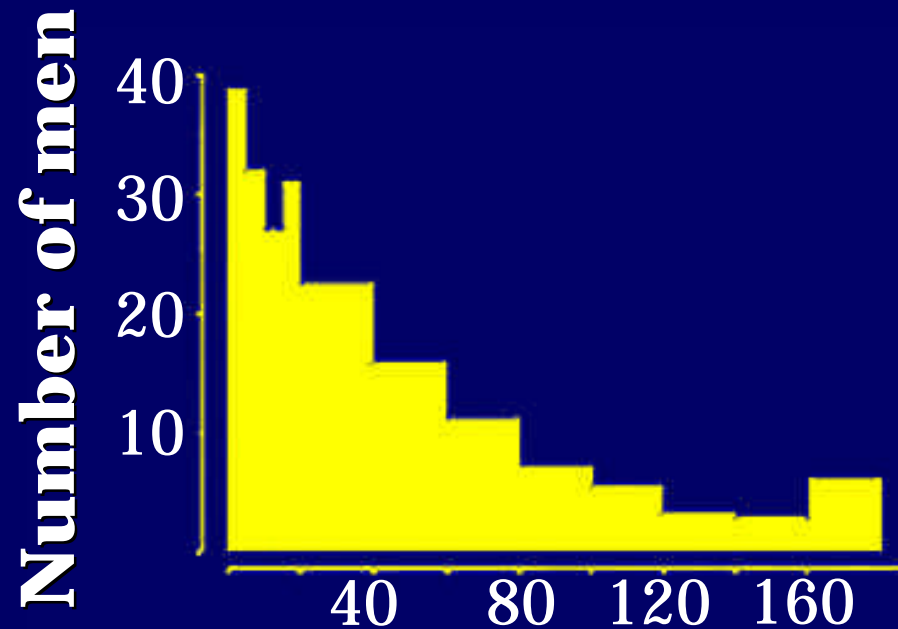
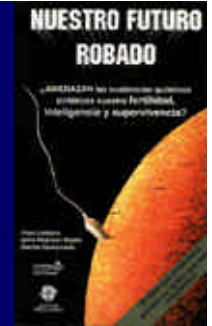


TRENDS IN SPERM COUNT



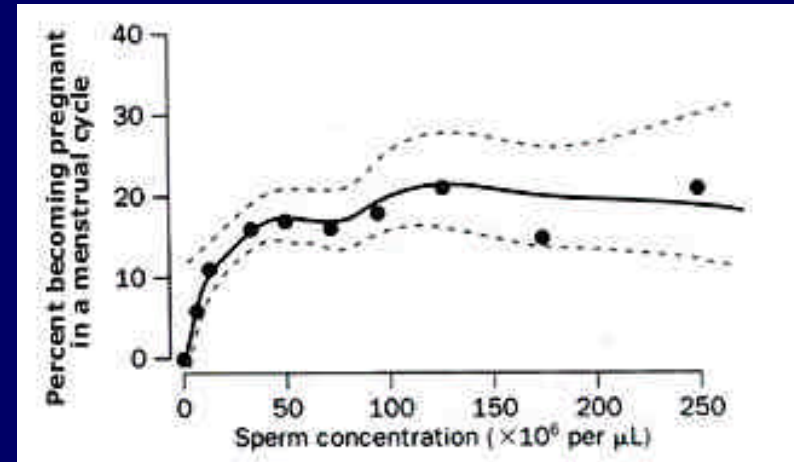
Swan et al., 2000

SPERM OF DANISH MEN



Sperm concentration

Andersen *et al.* 2000

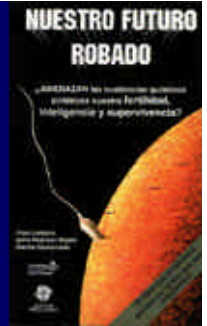


Bonde *et al.* 1998

SOME OBSERVED EFFECTS:

Wildlife

- **Male Gulls contaminated by DDT in their eggs grow up partially feminized.**
- **Many male fish in many rivers and estuaries are feminized; DDT reverses sex in medaka**
- **Low-level carbaryl changes frog tadpole behavior, making them less able to avoid predators**

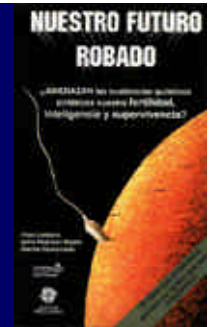


SOME OBSERVED EFFECTS

Laboratory:

- **Rats exposed to very low levels of dioxin display reduced motivation in standard behavioral tests**
- **Chimps exposed to very low levels of PCBs develop a syndrome analogous to attention deficit hyperactivity disorder.**
- **Male rats and mice exposed to phthalates in the lab are feminized**

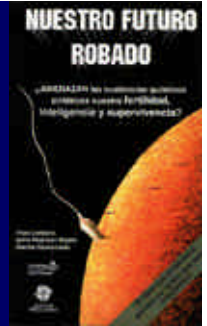
www.OurStolenFuture.org

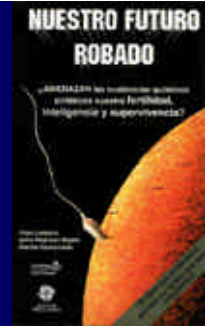


SOME OBSERVED EFFECTS

Exposed people:

- **DDT contamination strongly associated with preterm birth in the US.**
- **Reduced short-term memory and slower learning to read in children exposed to PCBs in the womb.**





WEAKENED IMMUNE SYSTEMS

Dutch children exposed *in utero* to relatively higher **background PCB levels by the age of 3½ years :**

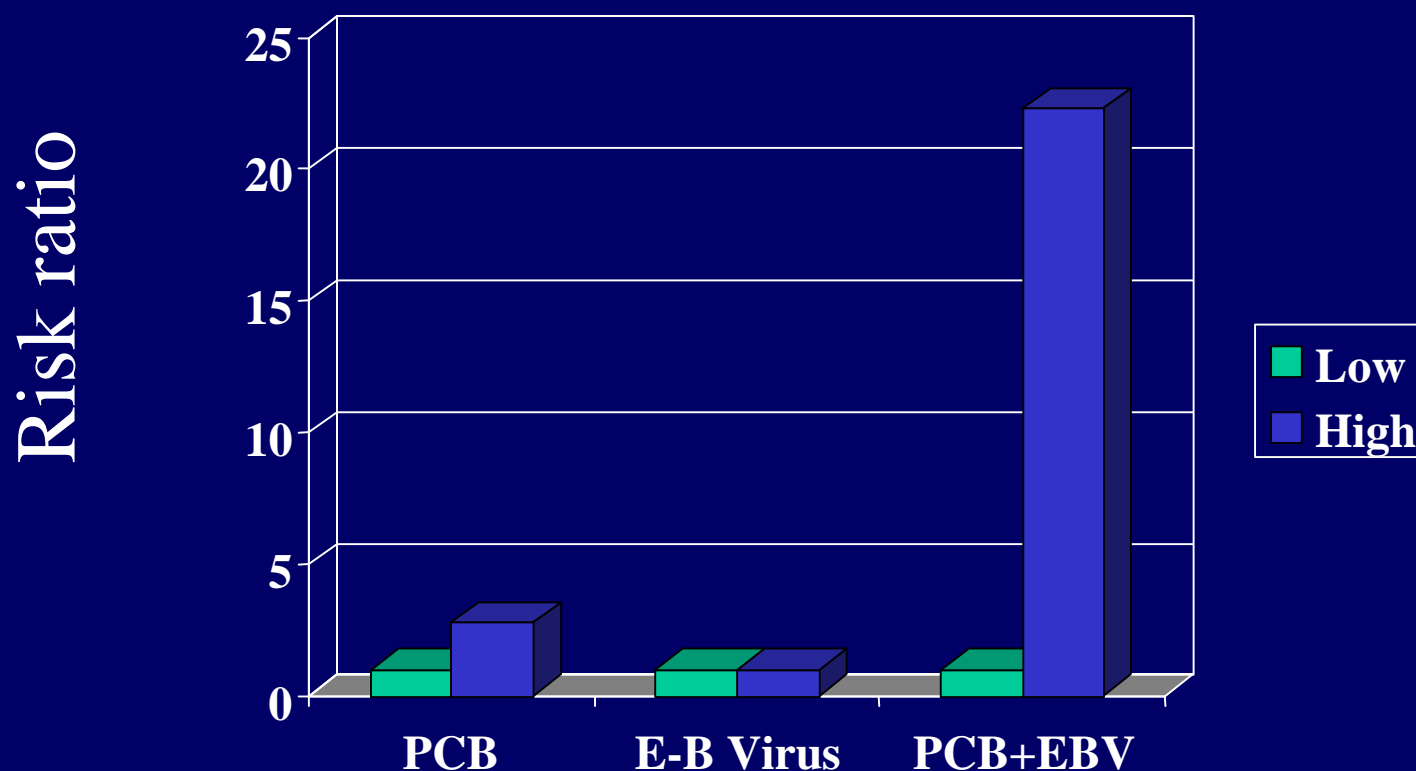
8 times more likely to have had chicken pox

3 times more likely to have had at least 6 ear infections.



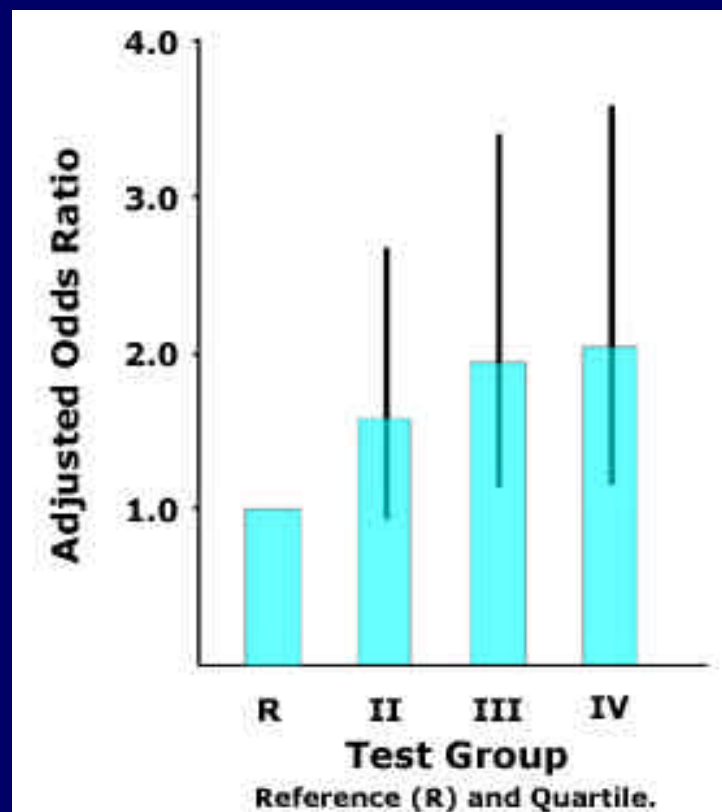
NON-HODGKINS LYMPHOMA

Interaction between contaminant and virus

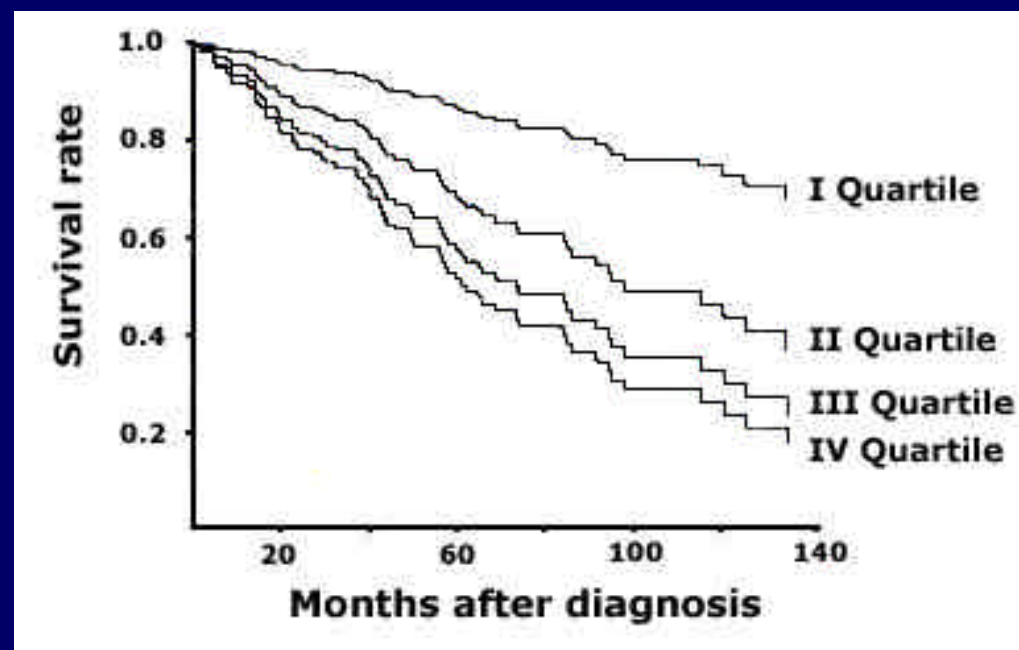




CANCER ENDPOINTS ALSO RELEVANT



Hoyer *et al.* 1998

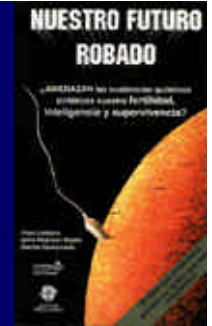


Hoyer *et al.* 2000

www.OurStolenFuture.org

Dieldrin and breast cancer

NEW RESULTS APPEAR EVERY WEEK



**Several major themes emerge if you
step back and look broadly at the
new research**

**Keep track of the details and
synthesis of this new research at
www.OurStolenFuture.org**

www.OurStolenFuture.org

MAJOR TRENDS...

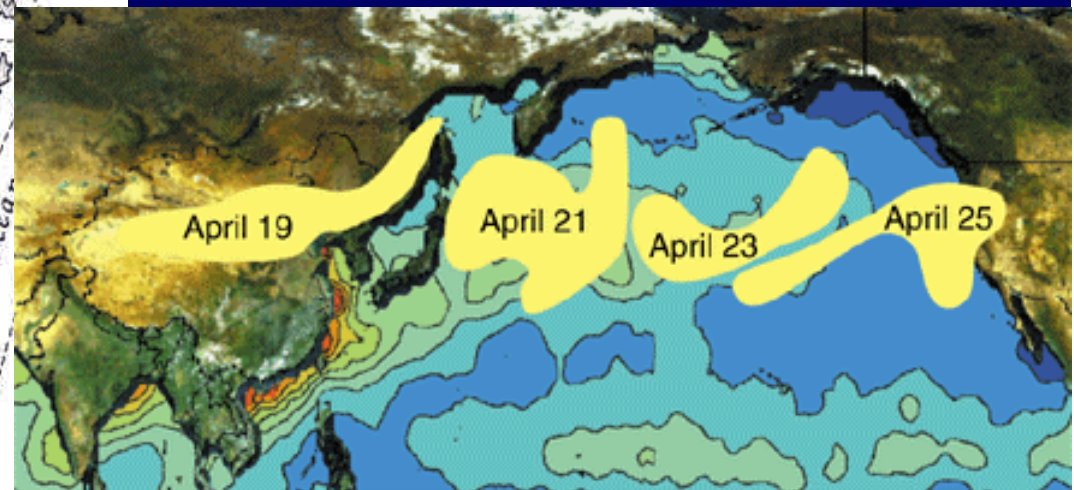
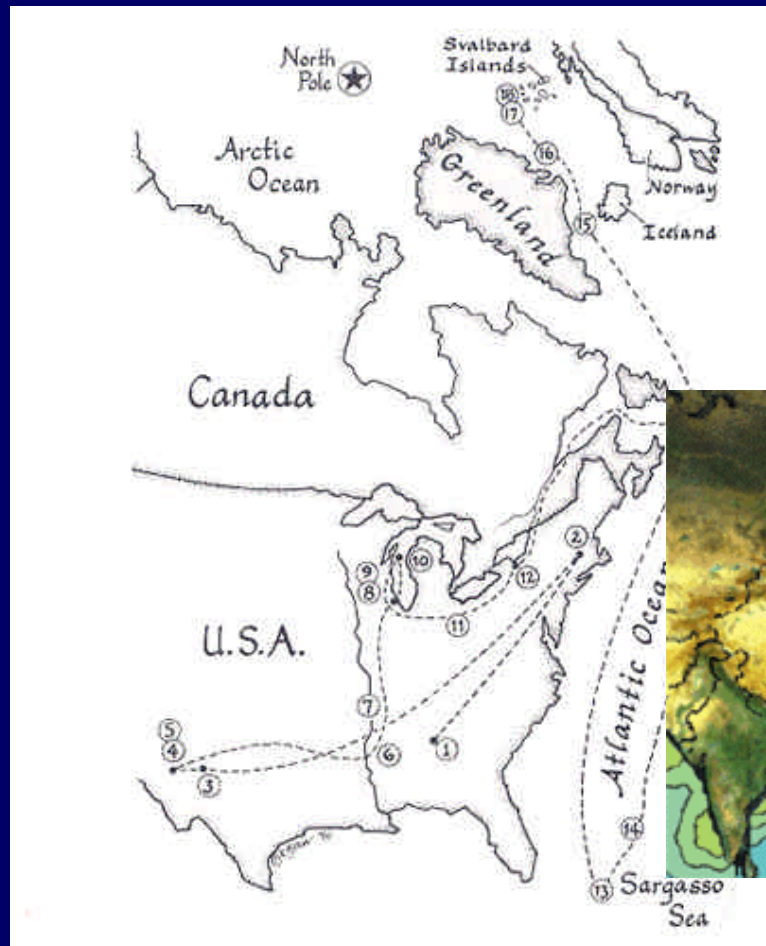
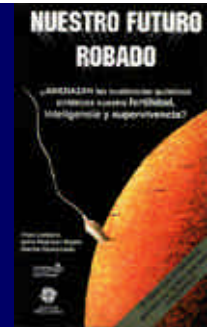
1. The geography of contamination has become global.



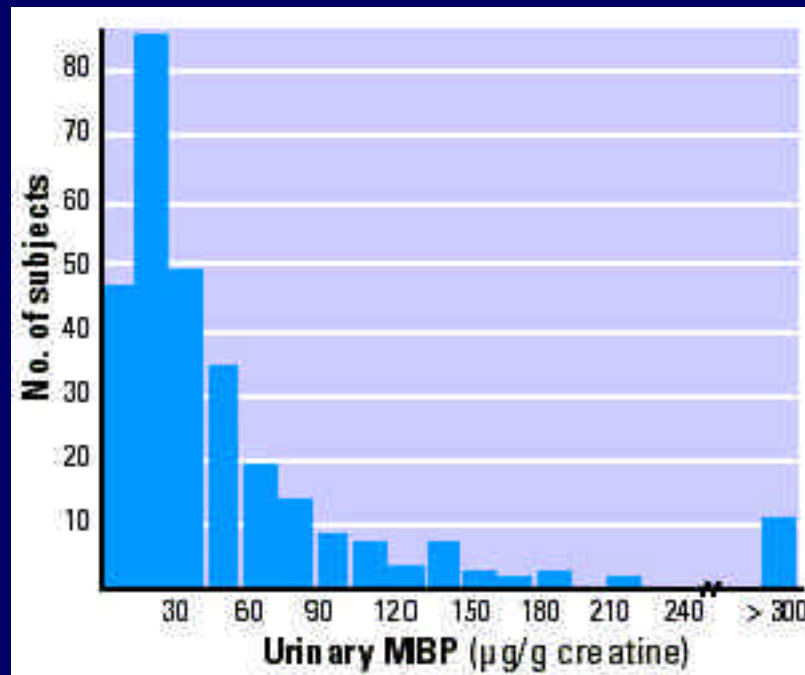
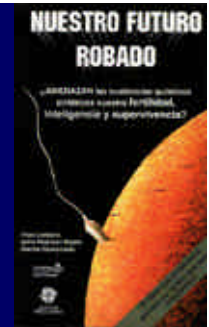
New York Times, 6 February 1999

www.OurStolenFuture.org

THE ODYSSEY OF A PCB MOLECULE



WIDESPREAD PHTHALATE CONTAMINATION



from Blount *et al.* 2000

EDCs ARE EVERYWHERE

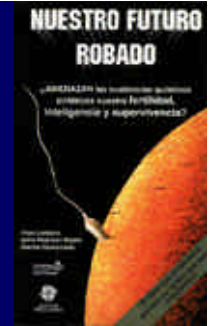


**They are found in the farthest
and deepest oceans**

**They are being remobilized by
global warming**

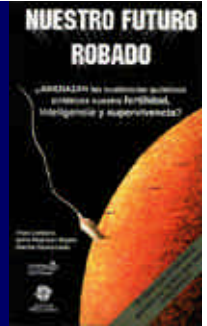
**In the US we are spreading them
onto agricultural fields**

WE UNKNOWLINGLY PUT THEM ON OURSELVES...



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EDCs ARE EVERYWHERE



As a result...

**No baby has been born in the last
generations without some
exposure in the womb.**

www.OurStolenFuture.org

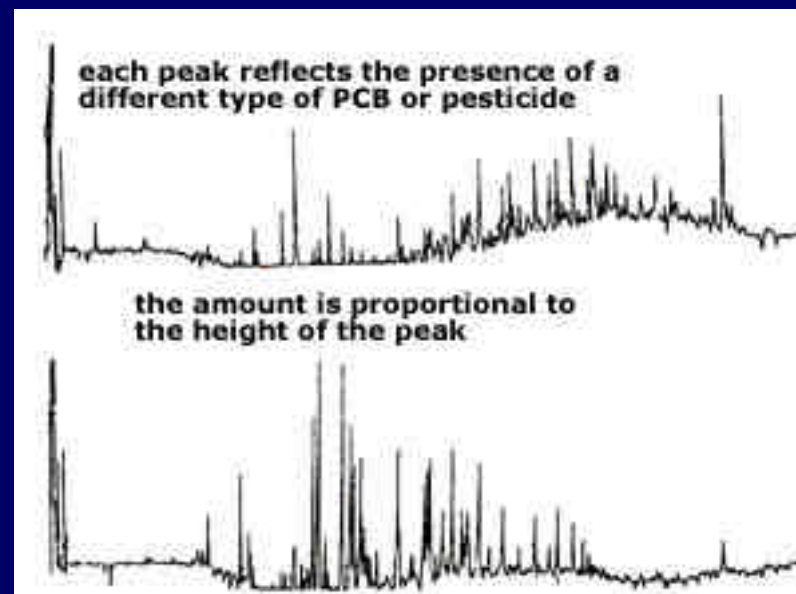
AND THEY DON'T OCCUR AS SINGLE CHEMICALS

Always mixtures...

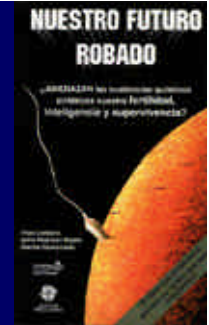
Gas chromatographs of human baby urine

Breast fed

Bottle fed

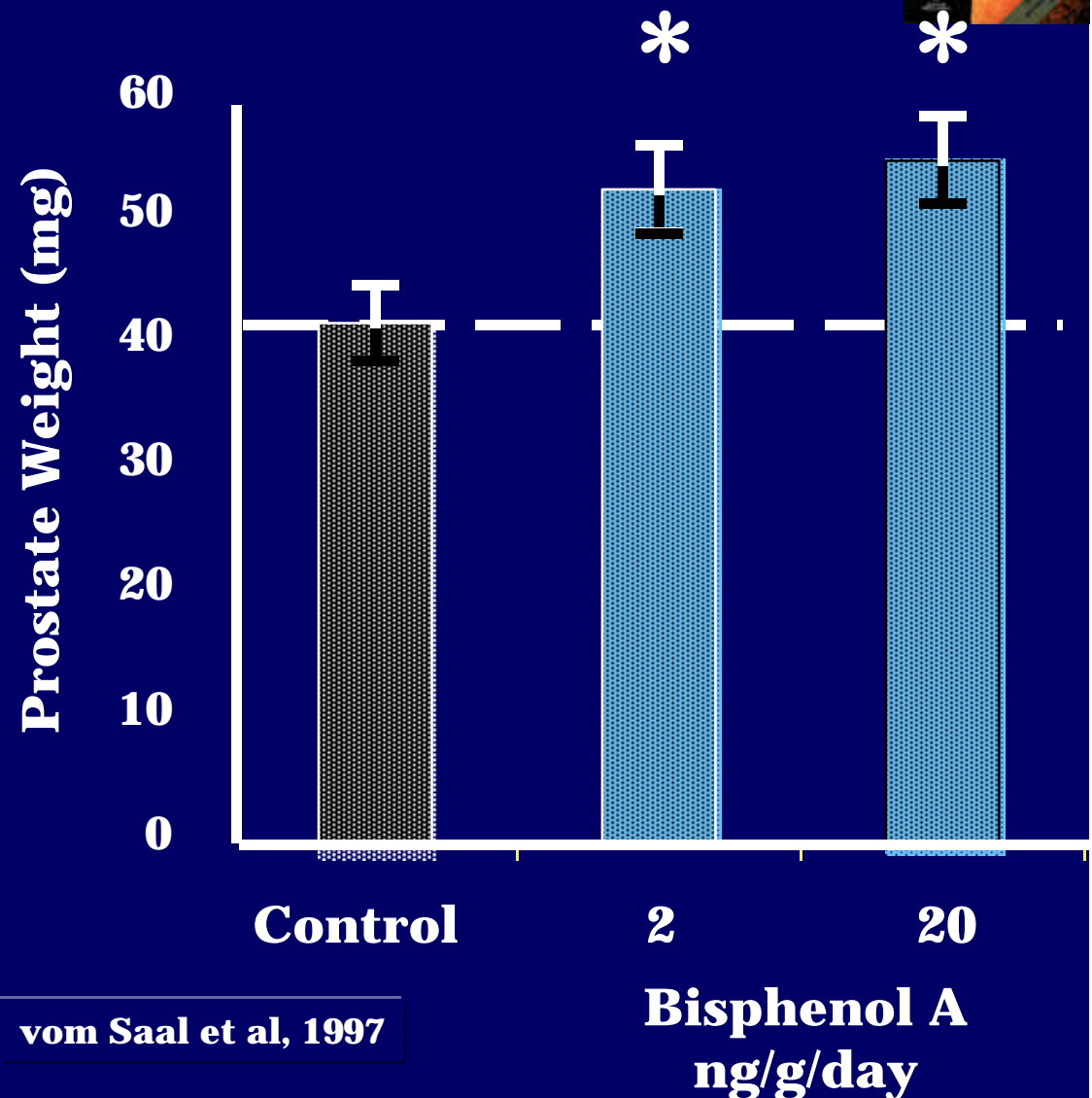


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MAJOR TRENDS...

2. The level of contamination at which risks become of concern has been lowered dramatically.



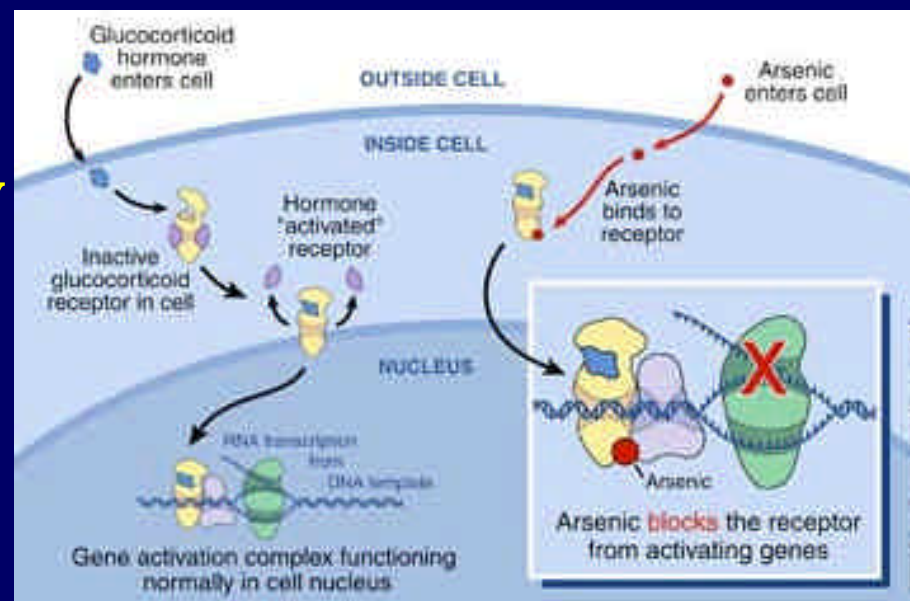


ARSENIC: a glucocorticoid disruptor

ED₀₁ activity at 10 ppb

Recommended: 10 ppb

cell culture that cause these endocrine-like effects are **well below any levels that caused any signs of toxicity in the cells**. In fact, we were down in what's called the nanomole range, or parts per trillion, and still seeing these effects.”

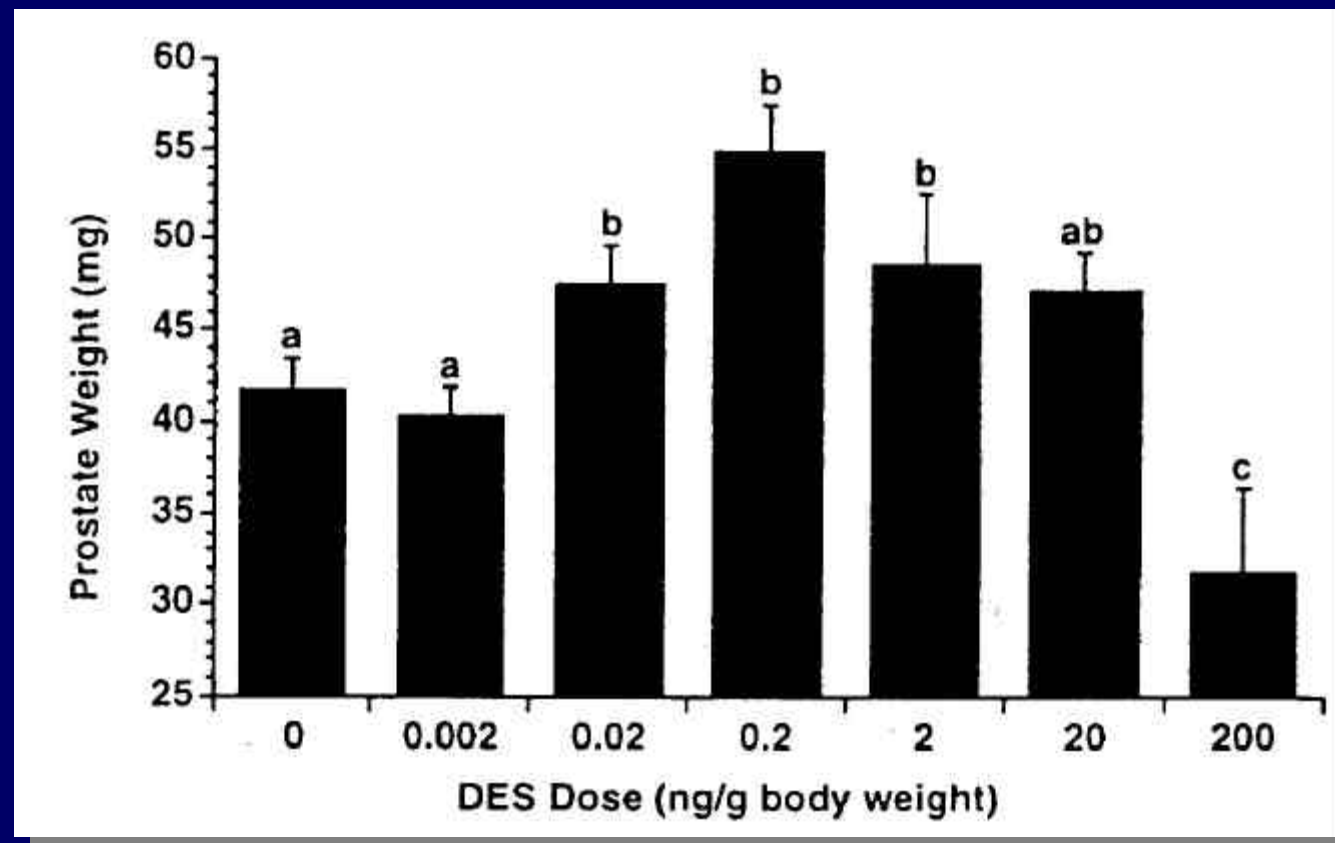
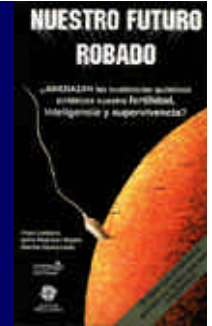


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GR activates PEPCK gene

LOW LEVEL DES

causes non-monotonic change in prostate weight



MAJOR TRENDS...



3. The message systems affected has been found to be much broader.

**Research focused first on with
estrogen mimickry.**

And then along came...

Estrogen blocking

Anti-androgens

**Interference
with
progesterone**

with retinoids

with thyroid

MAJOR TRENDS...



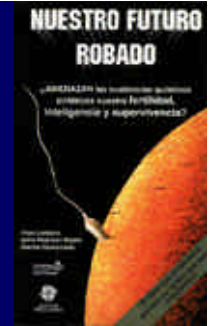
3. The message systems affected has been found to be much broader.

The early focus on sex and reproduction was too narrow...

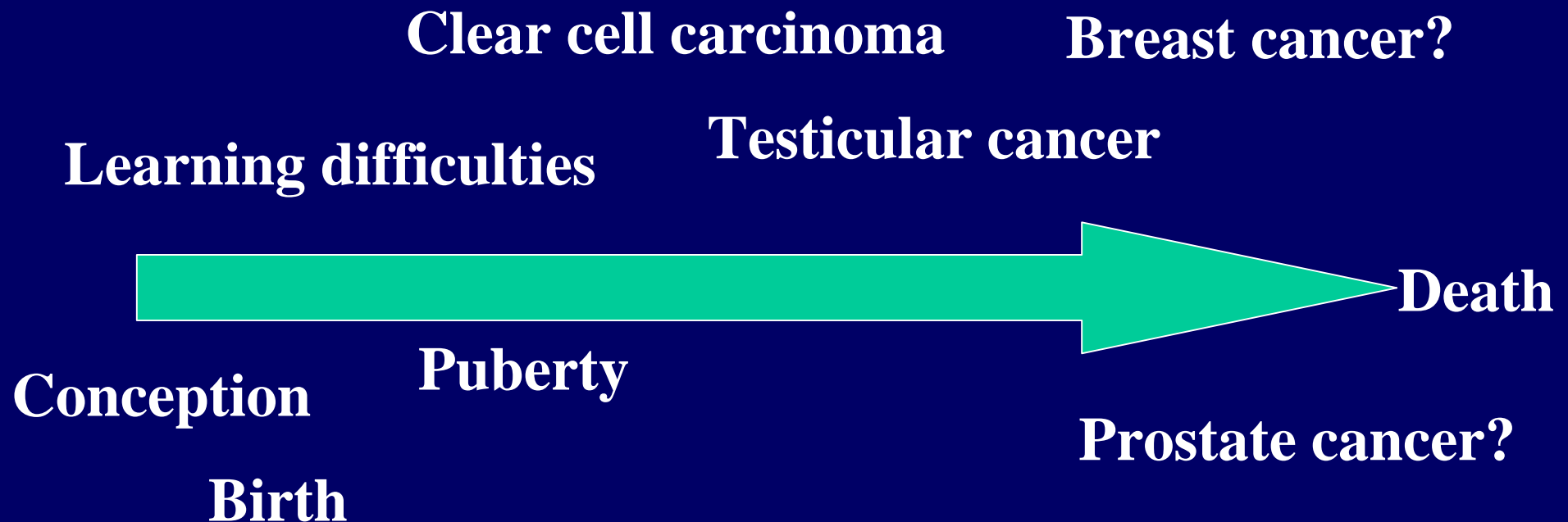
We must be looking for new endpoints

- **behavior/intelligence**
- **immune system function**
- **obesity?**
- **other dysfunctions?**

MAJOR TRENDS...

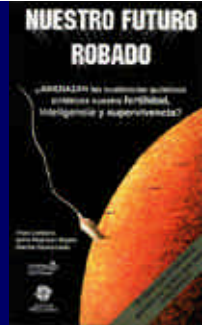
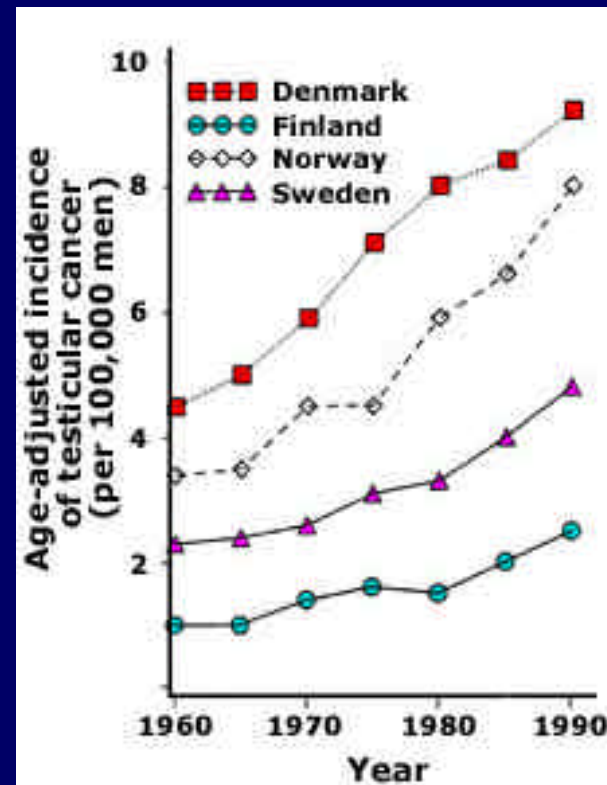


4. The time frame for concern has been extended to life-long impacts caused by fetal exposures.



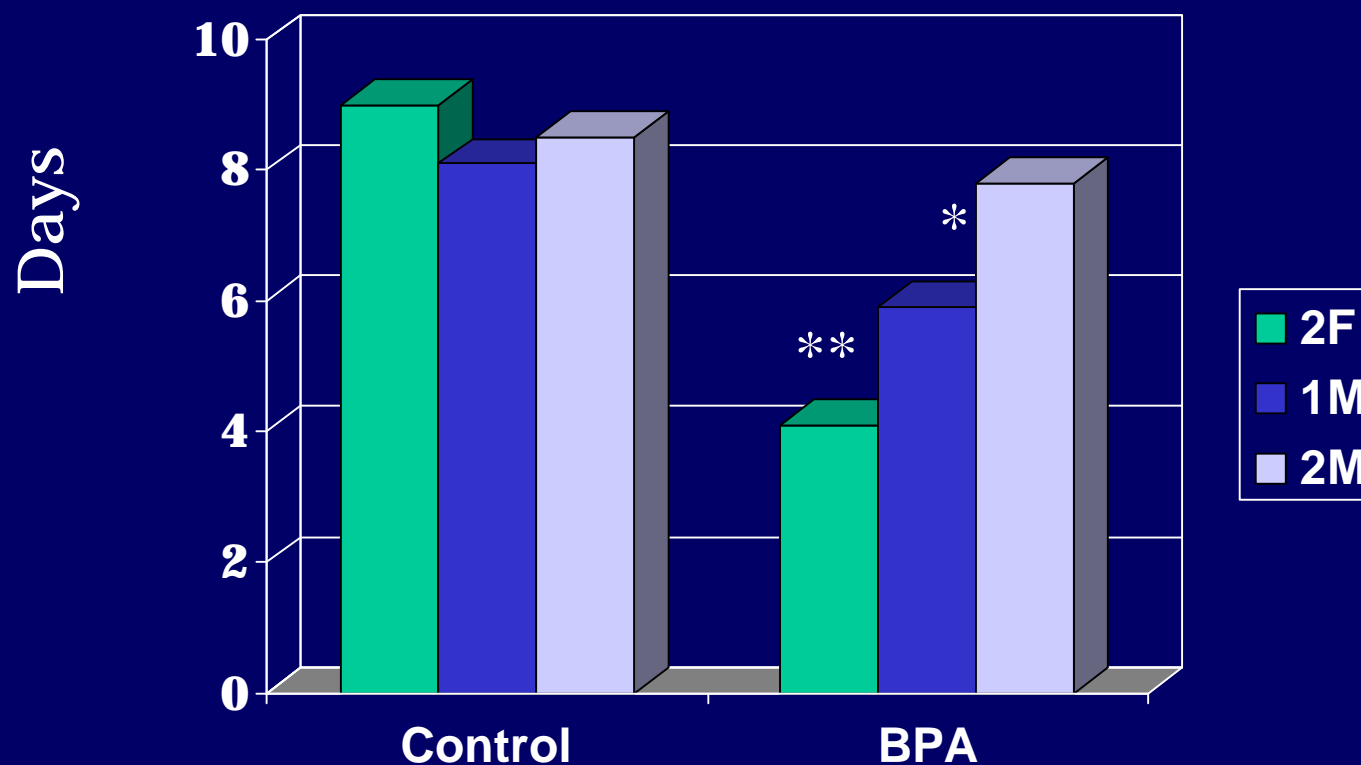
TESTICULAR CANCER

**Disrupted
development
of the fetal
testes**

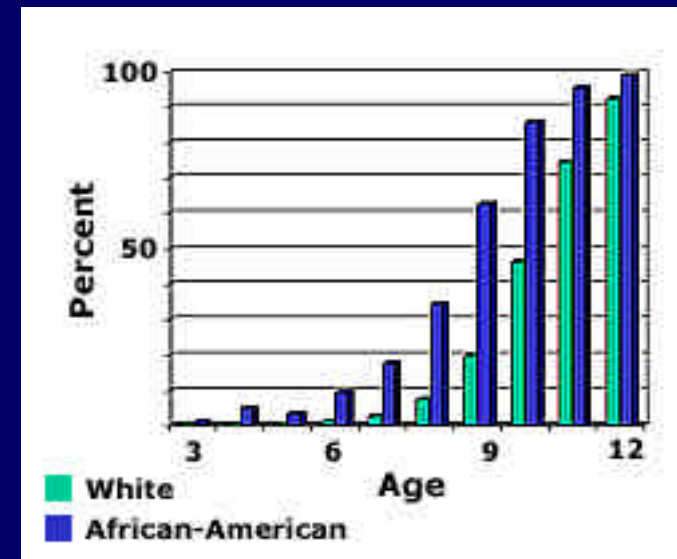
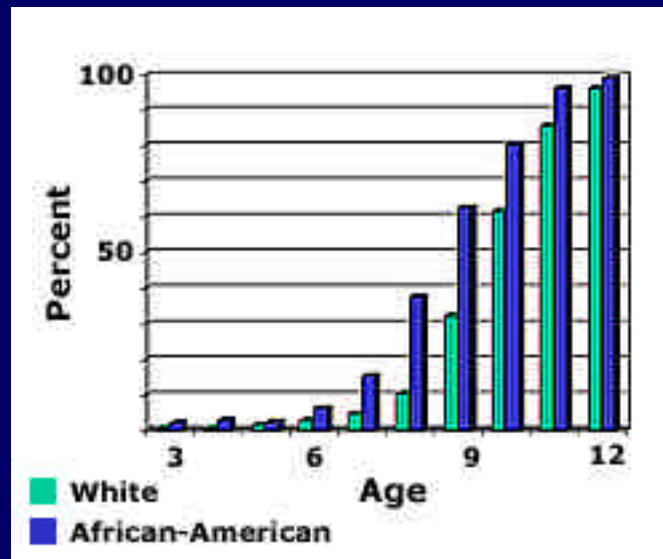
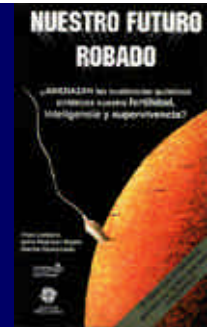


TIME TO PUBERTY

Altered by a plastic, bisphenol A.



SEXUAL MATURATION IN AMERICAN GIRLS



Breast development

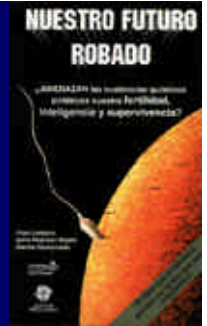
Pubic hair



FIVE CONCEPTUAL SHIFTS

- 1. Message disruption... not cytotoxicity**
- 2. Many endpoints...not just cancer**
- 3. Very low levels can have impact**
- 4. Fetal exposures cause life-long risks**
- 5. Exposure always occurs in mixtures**
- 6. Epidemiology is a blunt instrument**

CONCEPTUAL SHIFTS



Old ...traditional health endpoints...mutagenicity, carcinogenicity, cell death

New ...erosion of cognitive, immunological and reproductive function.

CONCEPTUAL SHIFTS



Old...only high levels
matter

New...impacts at everyday
levels...

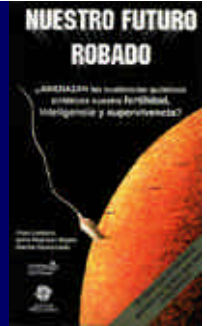
levels people had become
accustomed to calling
“normal,” background levels.

CONCEPTUAL SHIFTS



Old...exposure of a few to
high levels

New...exposure of many to
low but relevant levels

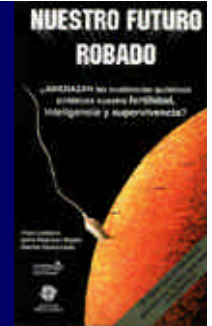


CONCEPTUAL SHIFTS-3

Old ...immediate cause and effect

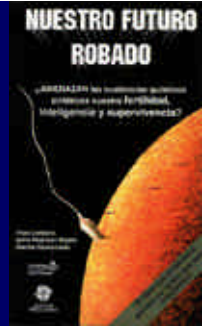
New ...long latencies following developmental exposure.

CONCEPTUAL SHIFTS



Old...take chemicals one at a time

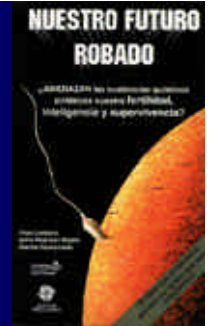
New...essential to consider the mixtures in which they ***always*** occur



CONCEPTUAL SHIFTS

Old... we should wait for epidemiological proof before acting

New... epidemiology may be incapable of confirming real impacts for a very long time



EPIDEMIOLOGY IS A BLUNT INSTRUMENT

In general... relatively good at rare events,

Less powerful for risk factors affecting more common endpoints.



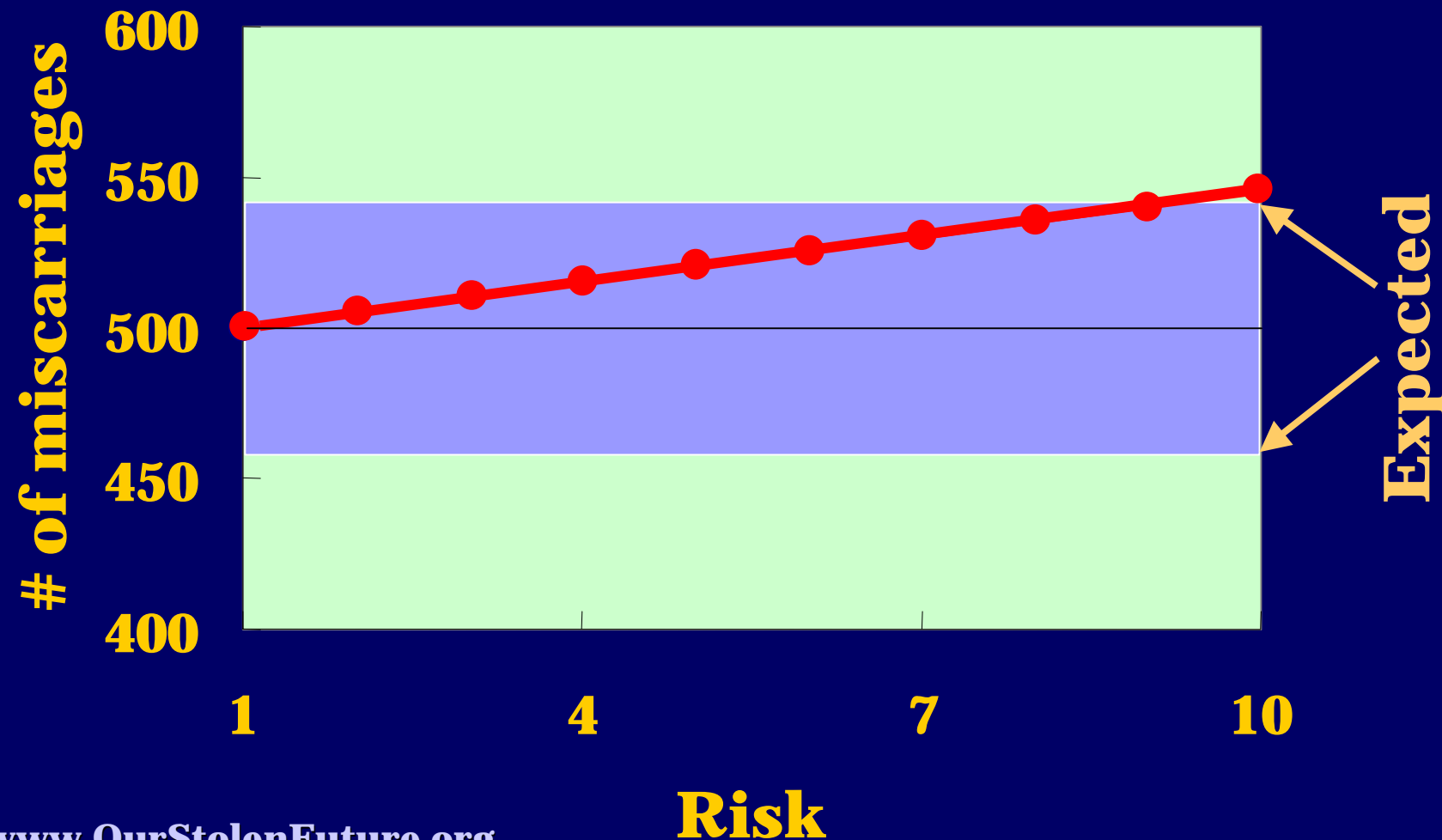
EPIDEMIOLOGY IS A BLUNT INSTRUMENT

A thought experiment

- * **Population of 5000 women**
- * **Background rate of spontaneous miscarriage of 10%. 500 +/- 42**
- * **Contaminant. 1% exposed.**
- * **How much increase in risk would be required to be evident?**



EPIDEMIOLOGY IS A BLUNT INSTRUMENT





EPIDEMIOLOGY IS A BLUNT INSTRUMENT

And it is even blunter for health endpoints whose causal mechanisms have the characteristics of endocrine disruption.

These characteristics create a strong, perhaps insurmountable bias toward false negatives.



EPIDEMIOLOGY IS A BLUNT INSTRUMENT

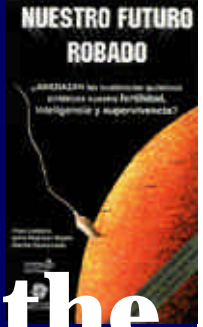
Low dose, non-monotonic D-R curves

Exquisite sensitivity to *in utero* timing

Mixtures that vary...but no controls

**One compound many possible effects;
multiple compounds cause same effect**

Long time lags; few if any fingerprints



EDC CHARACTERISTICS

These EDC characteristics inflate the variance in experimental and control populations.

Any one by itself may be tractable, with time.

...together perhaps insurmountable in any practical sense



EVEN WITH THESE CHALLENGES

**Intriguing findings are emerging in
the epidemiological literature.**

**Increased rate of fetal death from
congenital anomalies associated with
living near pesticide applications**

Bell *et al.* 2001 *Epidemiology* 12:148-156

www.OurStolenFuture.org



EVEN WITH THESE CHALLENGES

Intriguing findings are emerging in the epidemiological literature.

Women exposed in the womb to DES are less likely to have full-term births, and more likely to have spontaneous pregnancy losses or ectopic pregnancies.



EVEN WITH THESE CHALLENGES

**Intriguing findings are emerging in
the epidemiological literature.**

**Powerful association between in
utero exposure to DDE and pre-term
birth and pre-term weight**

Longnecker et al. 2001 The Lancet



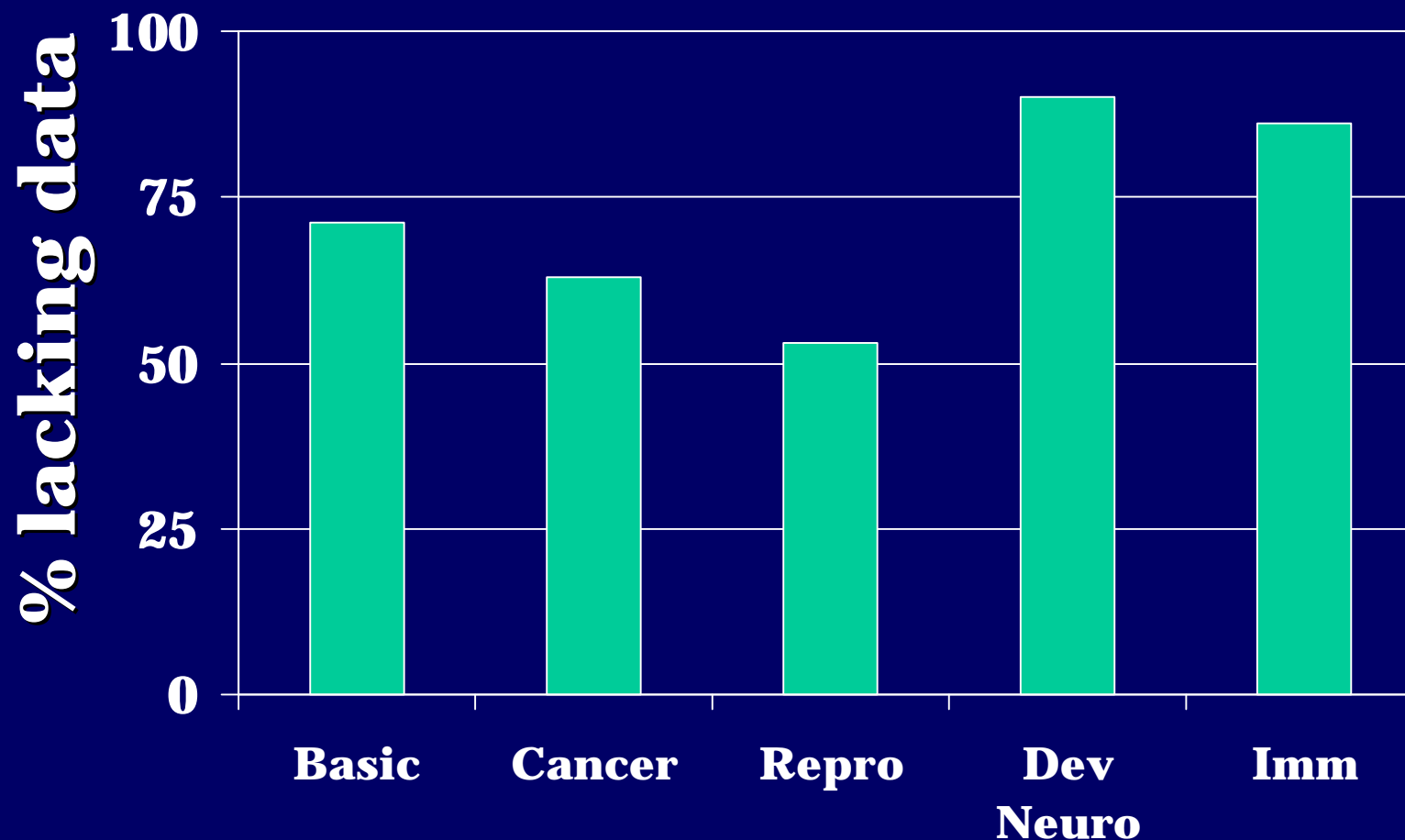
EVEN WITH THESE CHALLENGES

Intriguing findings are emerging in the epidemiological literature.

Exposure to polybrominated biphenyls in the womb advances the age of menstruation, up to a year earlier.

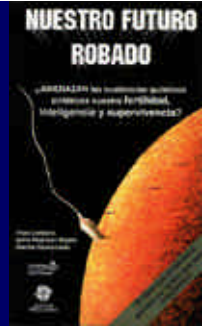
Blanck *et al.* 2000 Obstetrics & Gynecology 96

BUT WE REMAIN IGNORANT



3000 high volume chemicals lack data

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CONCEPTUAL SHIFTS

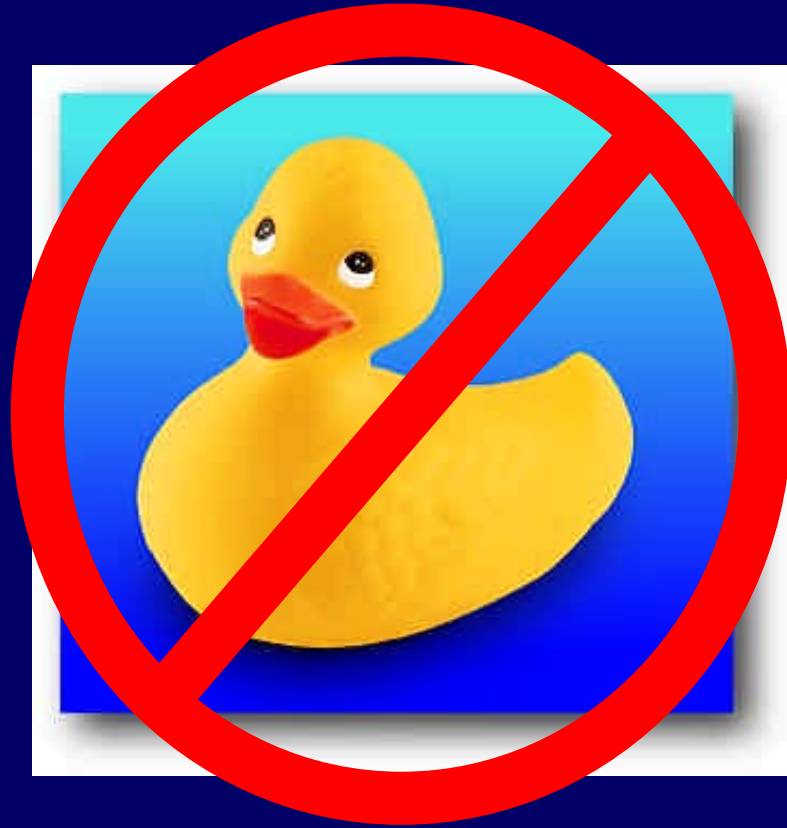
Old... we should wait for
epidemiological proof before acting

New... we need to act on a
precautionary basis

PHTHALATES IN KID'S TOYS



Banned



**First in Denmark, Austria, Greece,
France, the Netherlands, Sweden
and Norway... now EU-wide**

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POLYBROMINATED FLAME RETARDANTS

**Used in many consumer
products, industrial processes**

**Now being found widespread in
human and wildlife tissues**

e.g. de Boer et al. 1998

Potent thyroid disrupters

Ilonka et al. 2000

BISPHENOL A

Potent estrogen

**Widespread exposure via
polycarbonate**

**Significant low level effects in
animals**

www.OurStolenFuture.org





CONFIRMATION

Strong laboratory evidence showing low level impacts on reproductive, immune and behavioral endpoints

Observational evidence from wildlife revealing impacts at real-world exposure levels

Trends in human epidemiology consistent with predictions from the lab and from wildlife