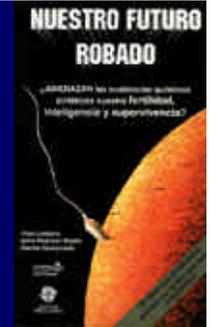


[www.OurStolenFuture.org](http://www.OurStolenFuture.org)

# **ENDOCRINE DISRUPTION: THE BASICS**



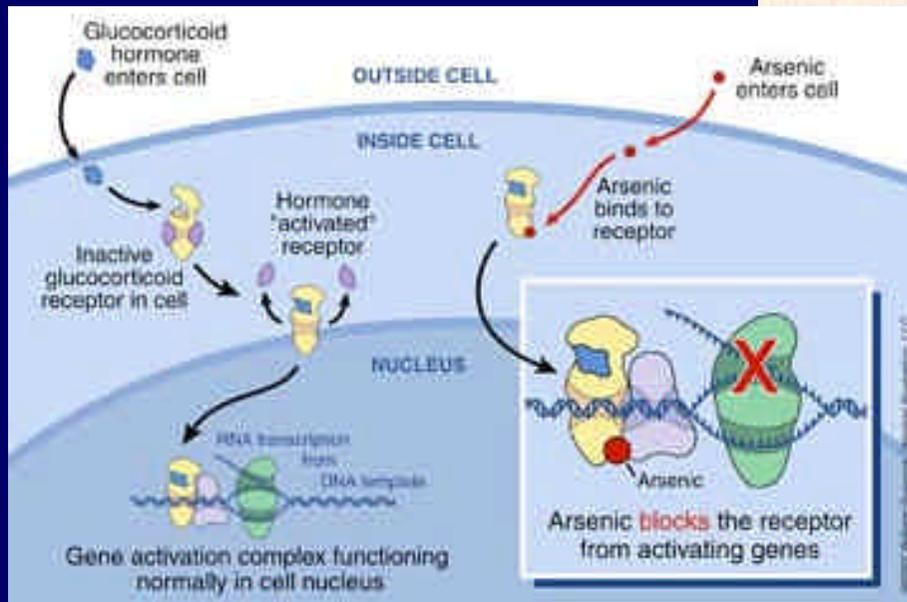
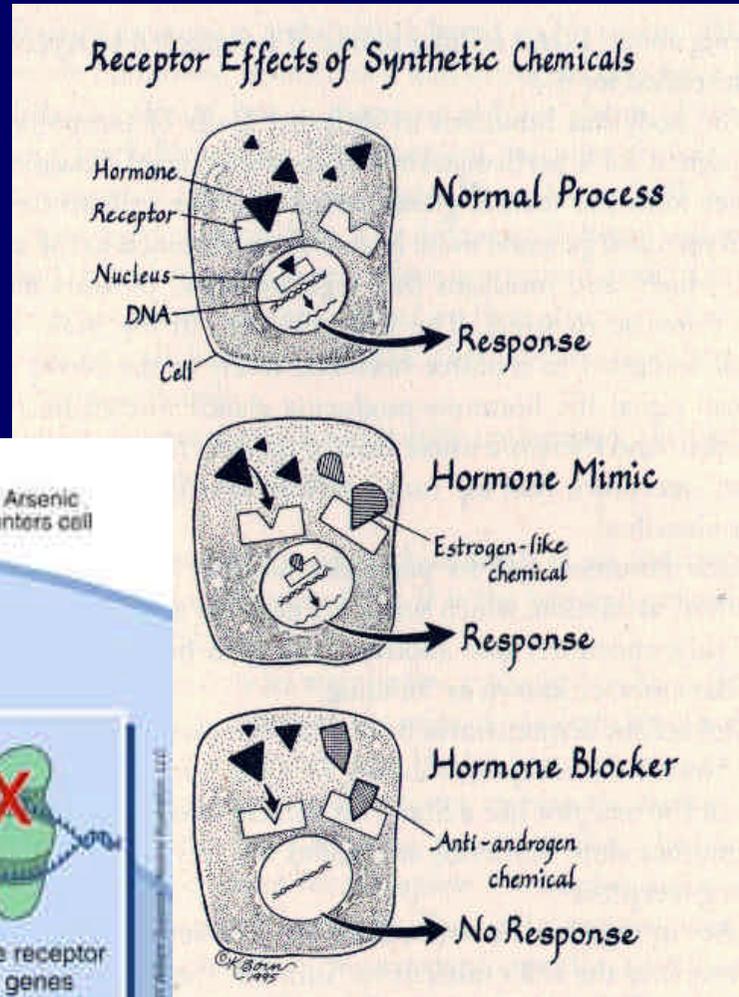
**Contaminants that interfere with the body's natural signalling system**

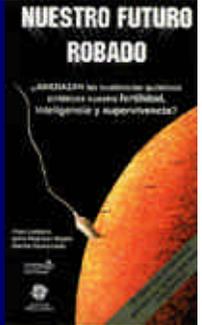
**Affect the rates of synthesis or breakdown of hormones**

**Block or mimic hormone messages**

**Alter sensitivity to hormonal stimulation**

# DISRUPTING HORMONE SIGNALS

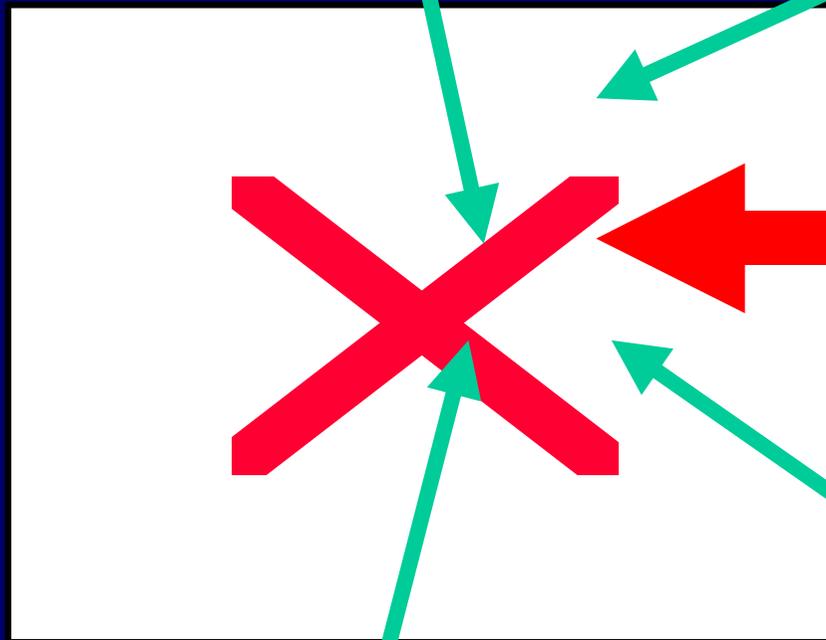




# FETAL DEVELOPMENT IS ESPECIALLY VULNERABLE

**Hormones**

**Growth factors**



**Hormone disruptors**

**Cytokines**

**Neurotransmitters**

[www.OurStolenFuture.org](http://www.OurStolenFuture.org)

# WHAT IS THE EVIDENCE?

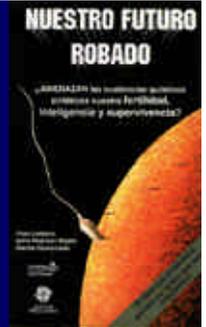
**Laboratory experiments**

**Wildlife observations**

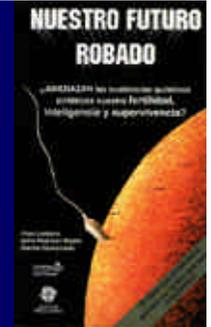
**Well-studied human exposures**

**Epidemiology of people.**

[www.OurStolenFuture.org](http://www.OurStolenFuture.org)



# THE CASE OF THE ATLANTIC SALMON

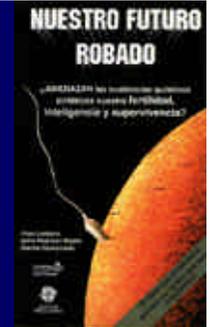


**Decline attributed to traditional causes...**

**overfishing  
habitat destruction  
dams**

**Now, osmoregulatory failure likely involved**

# LAB STUDIES SHOW REPRODUCIBLE EFFECTS



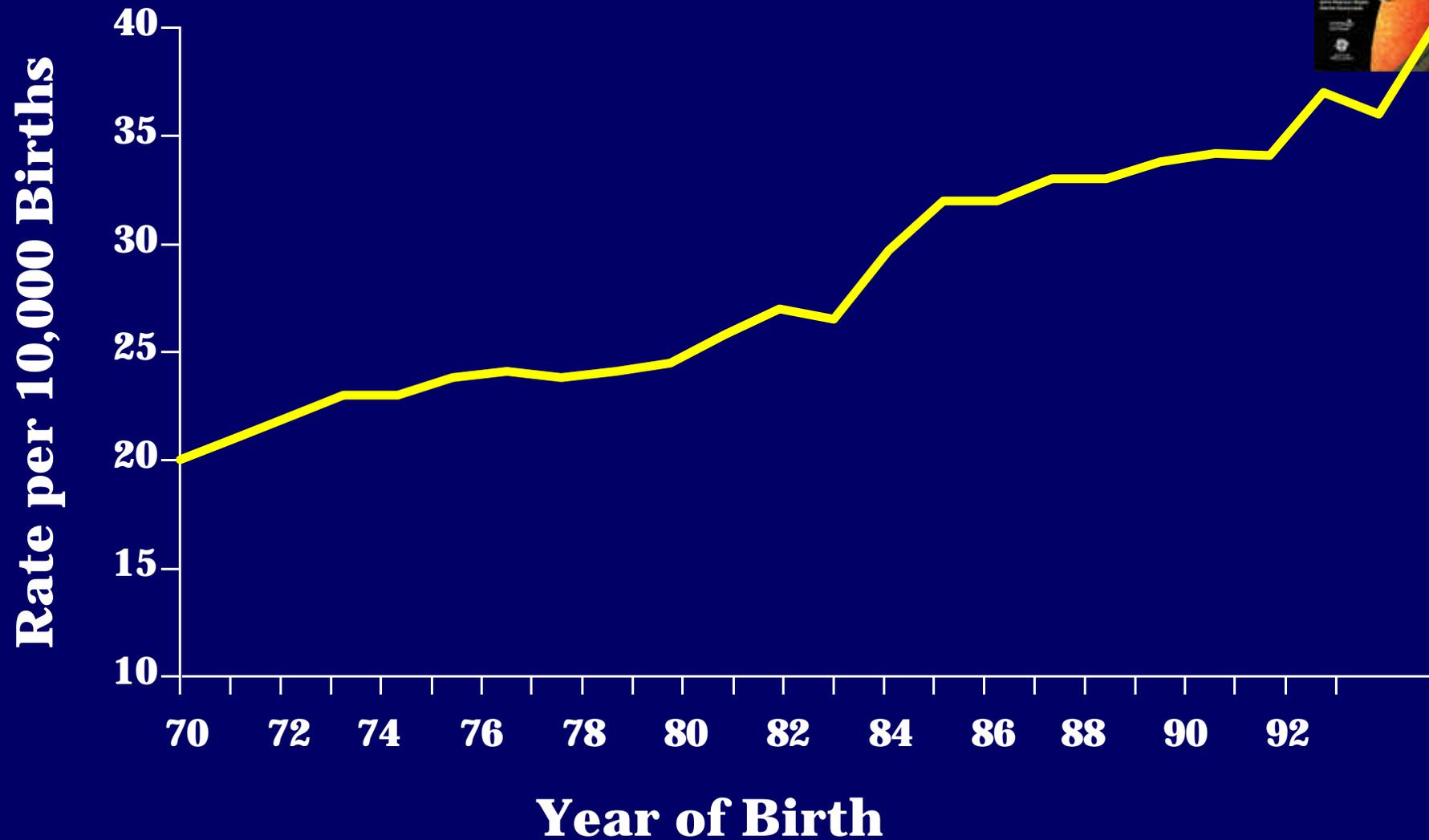
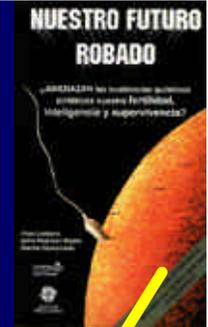
## On many endpoints

**Reproductive birth defects and  
reduced fertility**

**Behavioral disorders**

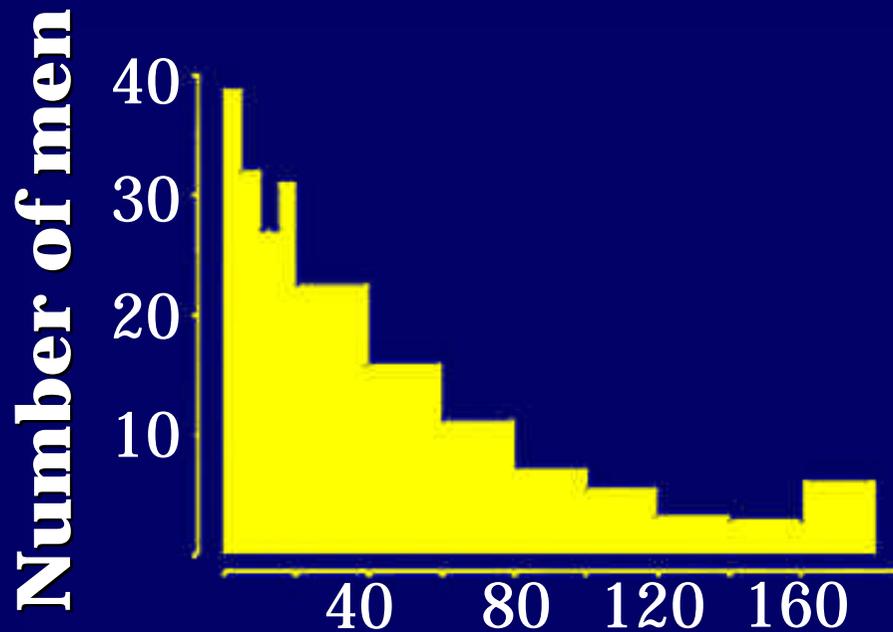
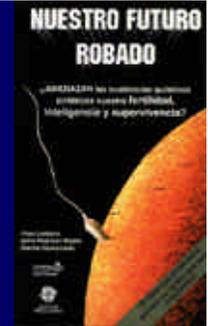
**Immune system impacts**

# HYPOSPADIAS in the US



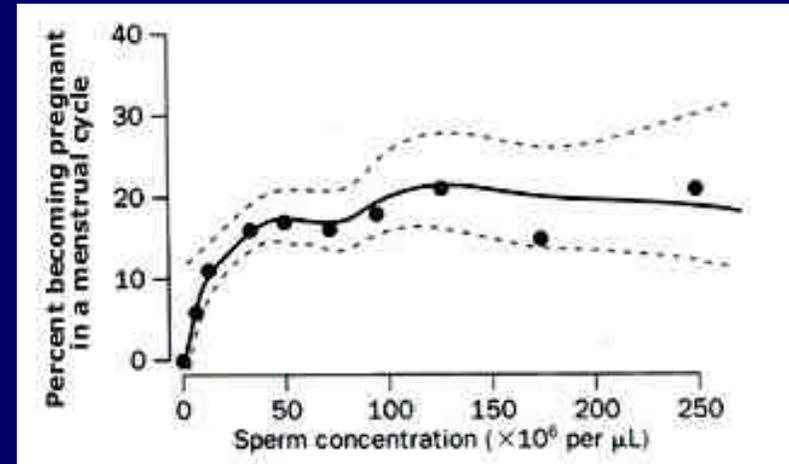


# SPERM OF DANISH MEN



**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**

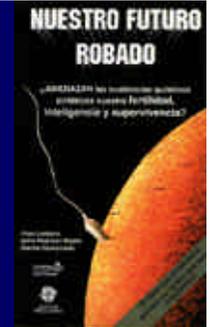


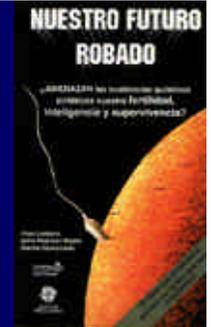


# **SOME OBSERVED EFFECTS**

**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 :**

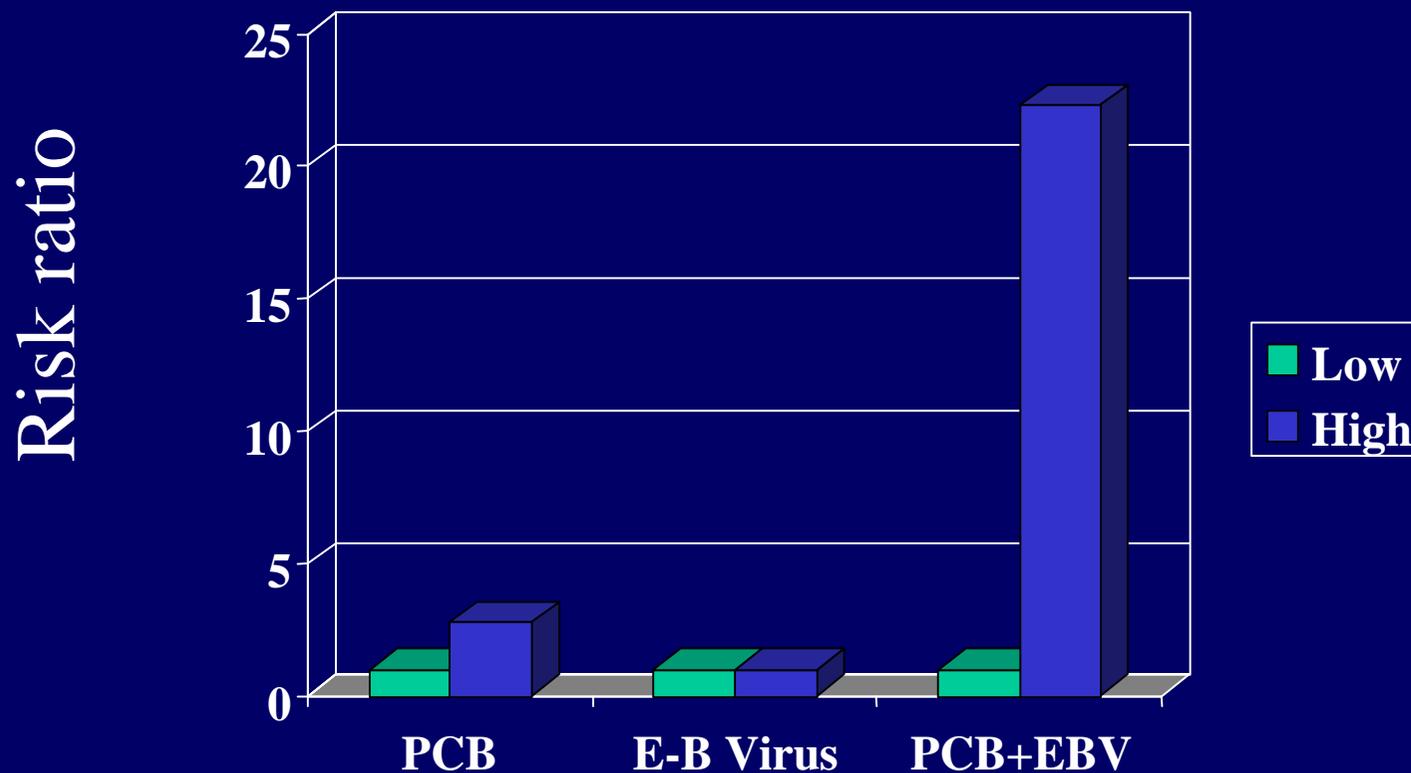
**8 times more likely to have had chicken pox**

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



# NON-HODGKINS LYMPHOMA

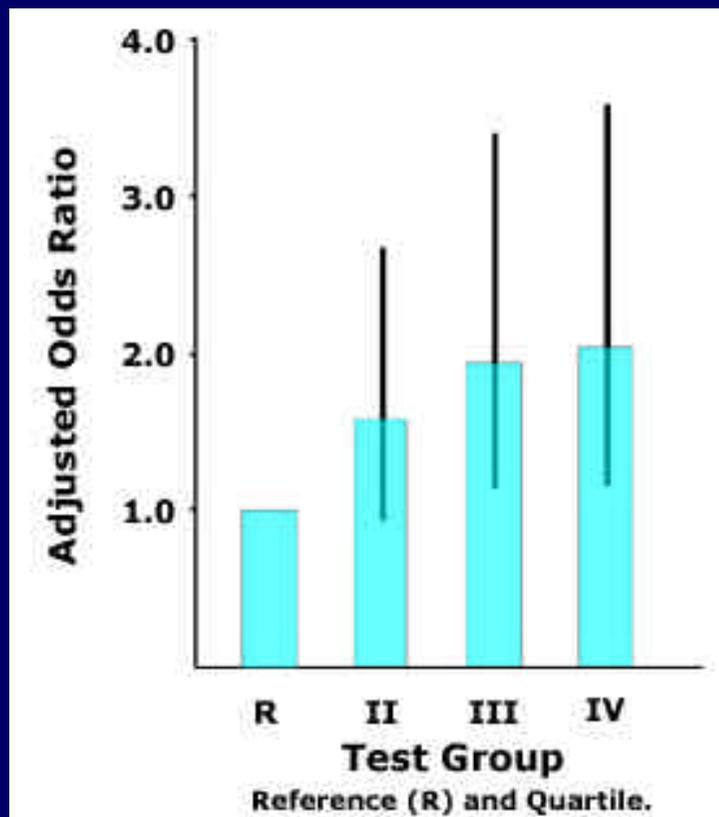
## Interaction between contaminant and virus



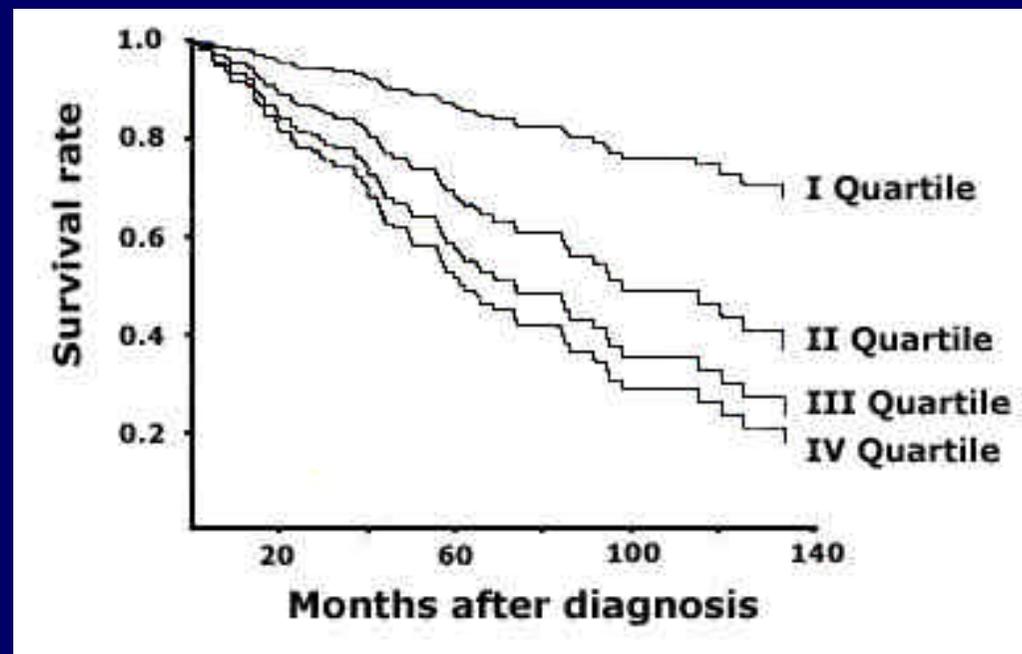
Rothman *et al.* 1997



# CANCER ENDPOINTS ALSO RELEVANT

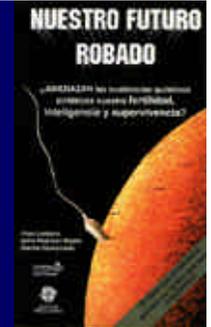


*Hoyer et al. 1998*



*Hoyer et al. 2000*

# **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](http://www.OurStolenFuture.org)**

[www.OurStolenFuture.org](http://www.OurStolenFuture.org)

# MAJOR TRENDS...

## 1. The geography of contamination has become global.



### *An Arctic Meal: Seal Meat, Corn Chips and PCB's*

By ANTHONY DePALMA

IGLOOLIK, Northwest Territories — It was early on a Monday morning, another gray start to a gray day in the Canadian Arctic. But thinking ahead to providing a hot, nutritious meal for his family later that day and through the week, Serapio Ittusardjuat was already defrosting a seal.

It was an entire ringed seal about three feet long that the Inuit hunter had caught in the fertile waters around the island of Igloolik and then allowed to freeze in the 30-below temperatures until he needed it.

But Mr. Ittusardjuat (pronounced ee-too-sar-dzoo-wat) was only dimly aware that the seal was probably contaminated with dangerous substances like the pesticide DDT and industrial compounds like PCB's, which are released into the air all over the earth and drift north.

Once they hit the cold polar regions, the contaminants settle like dirty water swirling down the drain of a kitchen sink. They easily seep into the Arctic food chain, and are especially concentrated in sea mammals like seals that have a thick layer of fat that stores the dangerous compounds. Scientists have known about the contaminants for some time, and are most concerned about the effects on babies and the unborn in the north. But they have not advised the Inuit to change their diet.



Deporah Attagutalukutuk cleans Arctic char on North Baffin Island. Researchers say dangerous compounds emitted around the world reach the polar regions and contaminate the traditional Inuit diet.

New York Times, 6 February 1999

[www.OurStolenFuture.org](http://www.OurStolenFuture.org)





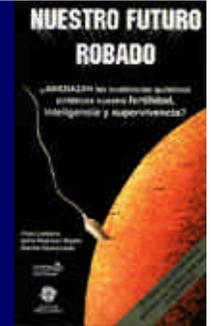
# **EDCs ARE EVERYWHERE**

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

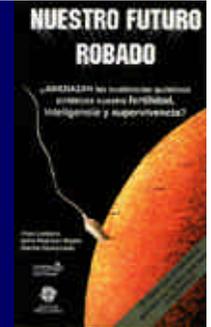
**They are being remobilized by  
global warming**

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

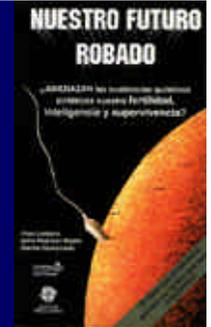
[www.OurStolenFuture.org](http://www.OurStolenFuture.org)



# WE UNKNOWINGLY PUT THEM ON OURSELVES...



# EDCs ARE EVERYWHERE



**As a result...**

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

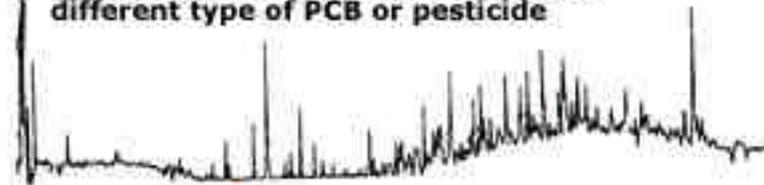
# AND THEY DON'T OCCUR AS SINGLE CHEMICALS

**Always mixtures...**

**Gas chromatographs of human baby urine**

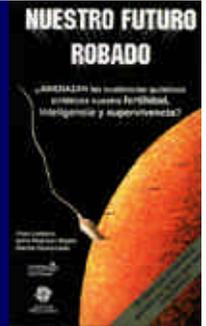
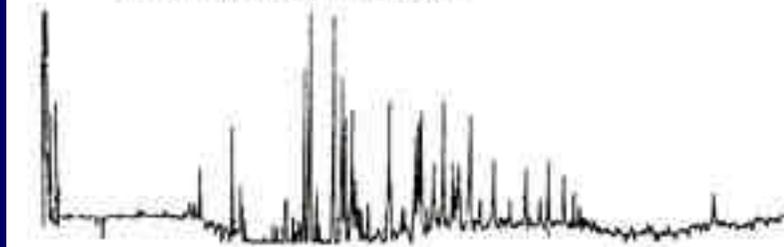
**Breast fed**

each peak reflects the presence of a different type of PCB or pesticide



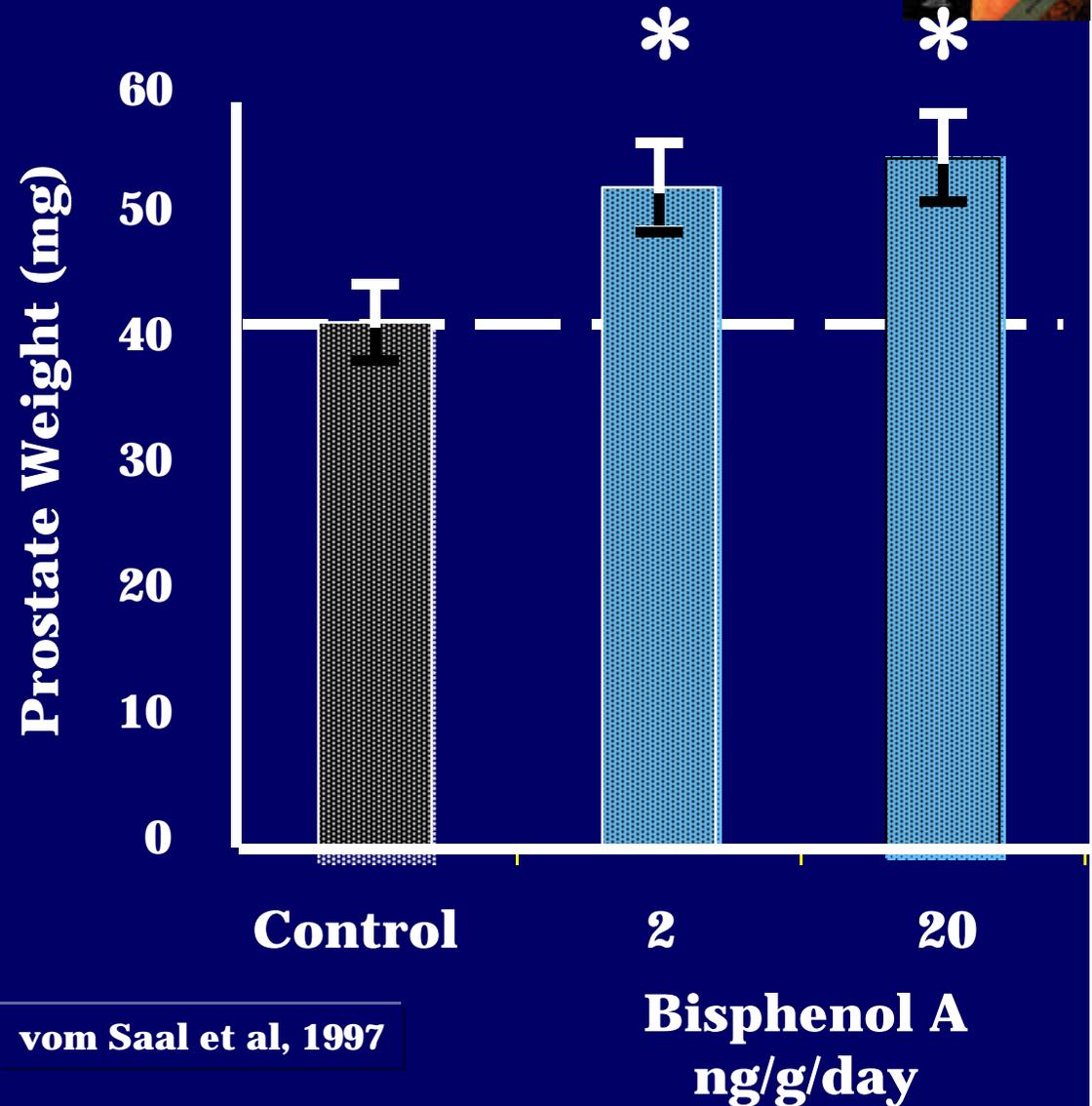
the amount is proportional to the height of the peak

**Bottle fed**



# MAJOR TRENDS...

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



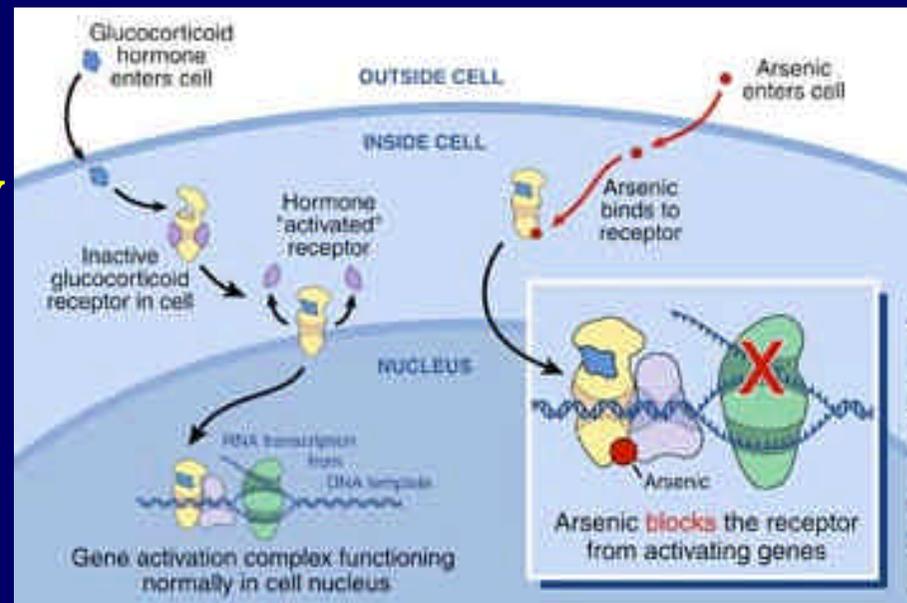


# ARSENIC: a glucocorticoid disruptor

ED<sub>01</sub> 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.”

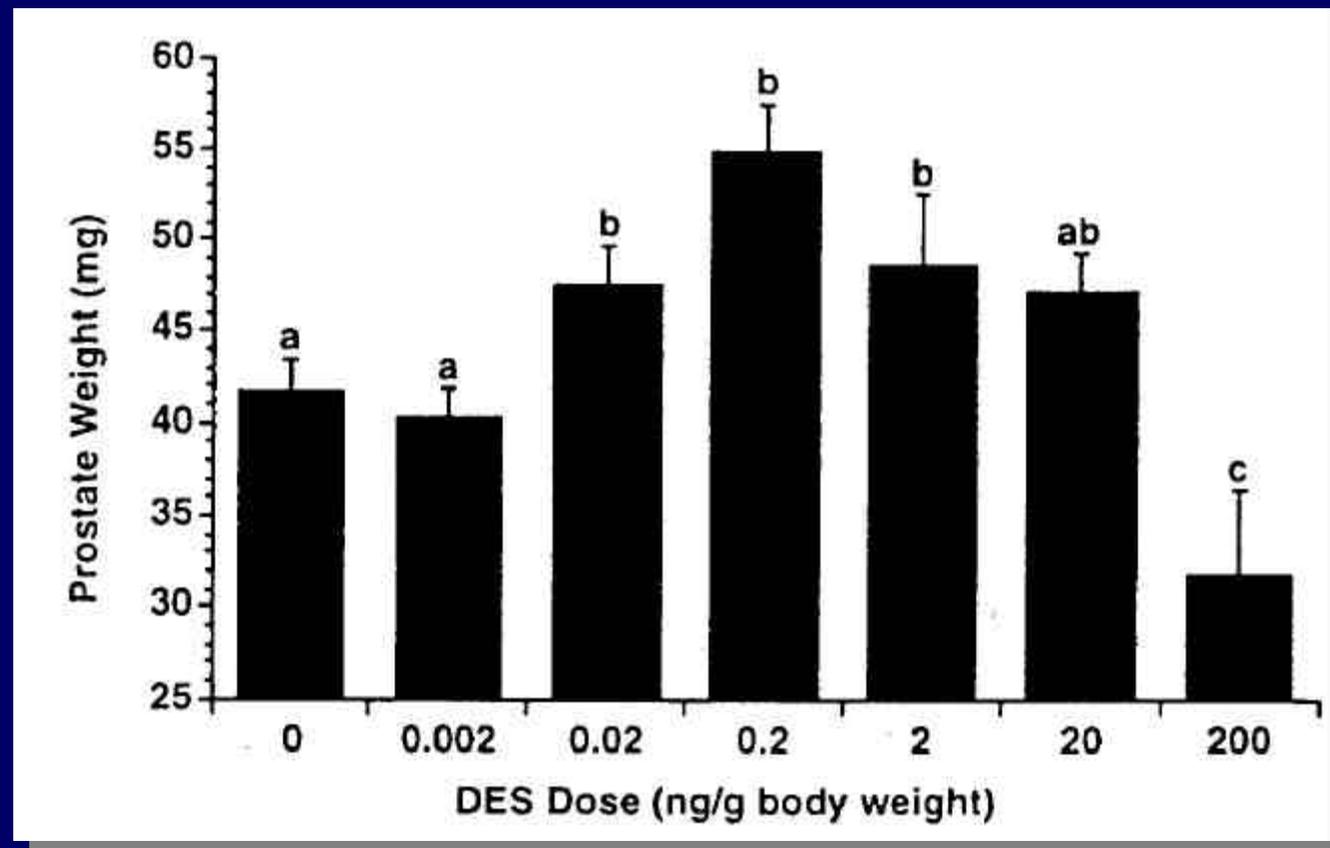
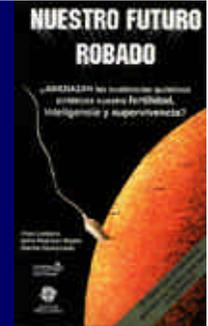


[www.OurStolenFuture.org](http://www.OurStolenFuture.org)

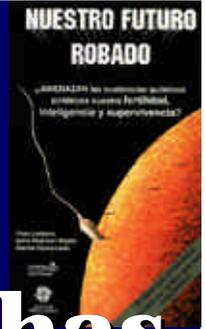
GR activates PEPCK gene

# 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...



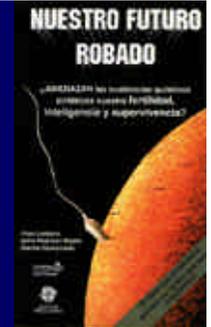
**3. The message systems affected has been found to be much broader.**

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

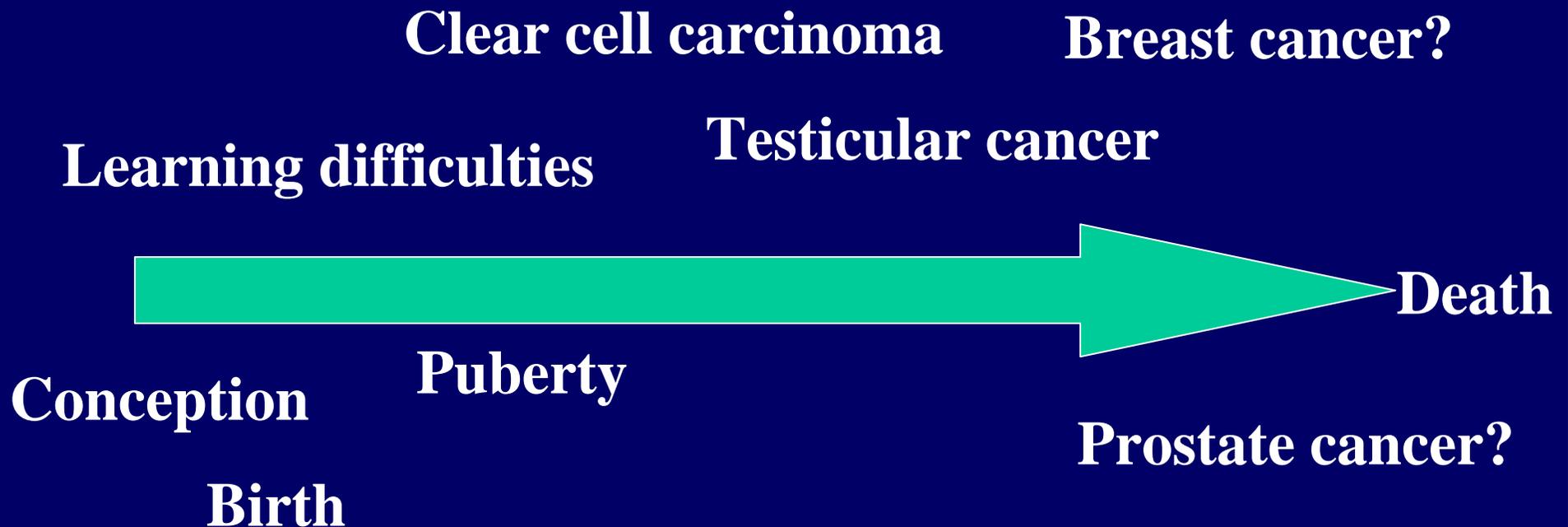
**We must be looking for new endpoints**

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

# MAJOR TRENDS...

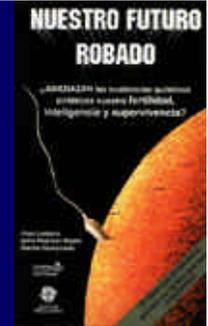
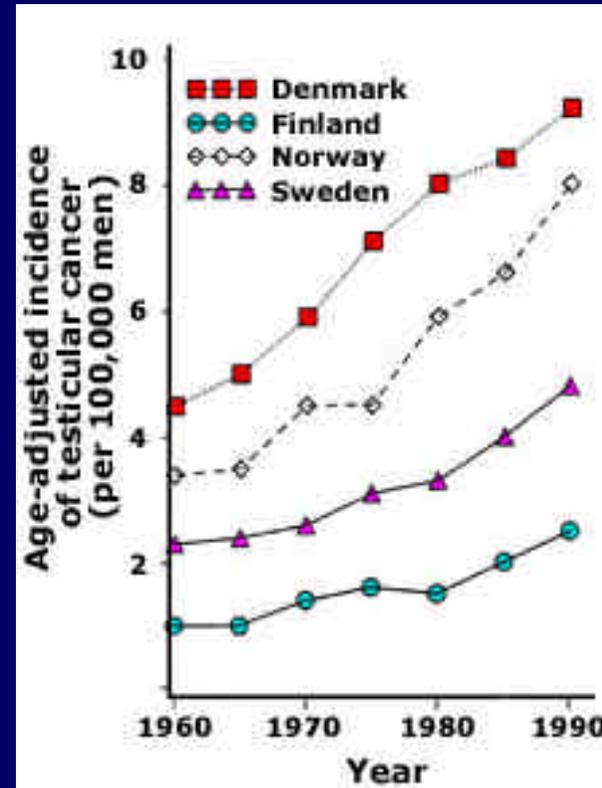


**4. The time frame for concern has been extended to life-long impacts caused by fetal exposures.**



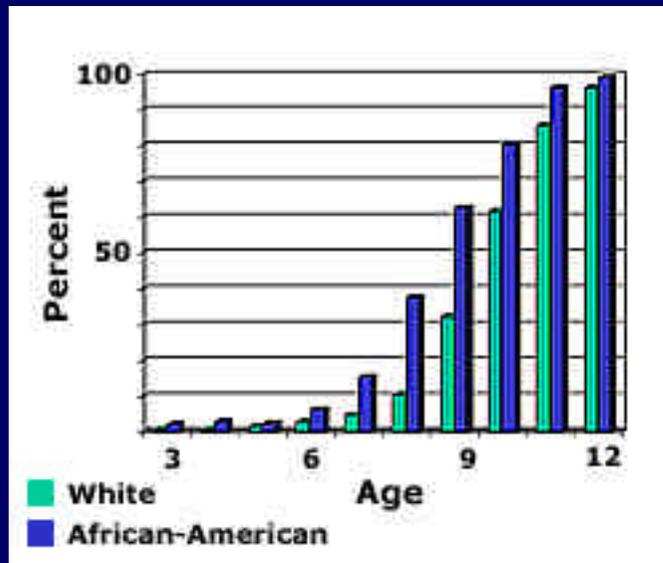
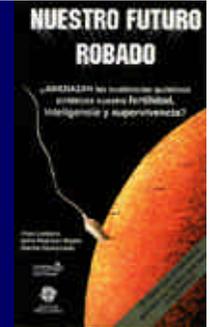
# TESTICULAR CANCER

**Disrupted  
development  
of the fetal  
testes**

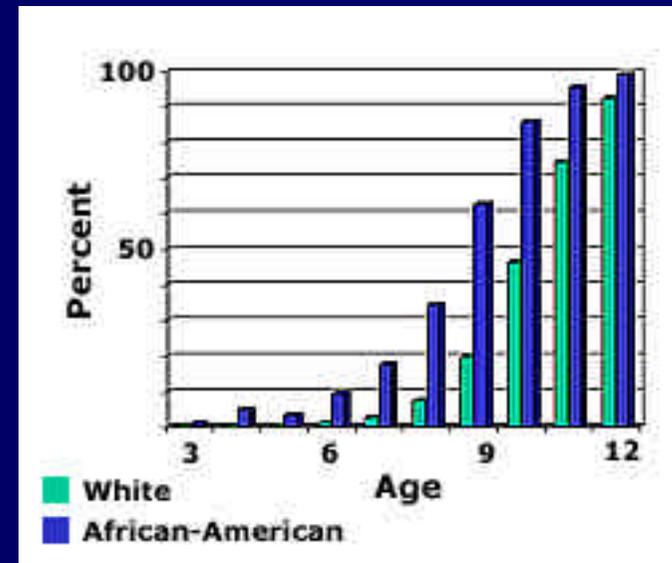




# SEXUAL MATURATION IN AMERICAN GIRLS



**Breast development**



**Pubic hair**



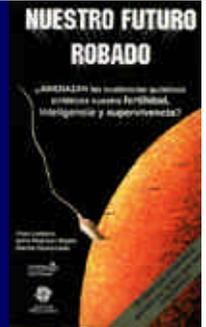
# FIVE CONCEPTUAL SHIFTS

- 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**

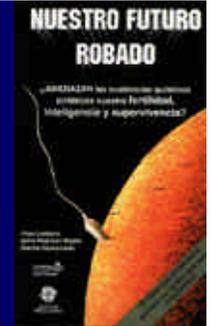
# CONCEPTUAL SHIFTS

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

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



# CONCEPTUAL SHIFTS

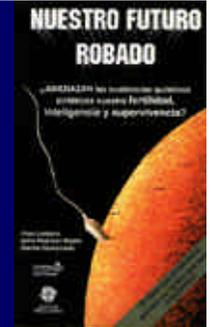


**Old...**only high levels matter

**New...**impacts at everyday levels...

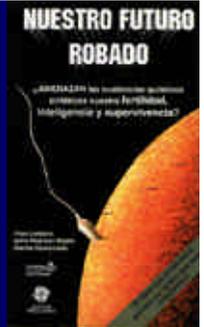
levels people had become accustomed to calling “normal,” background levels.

# 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

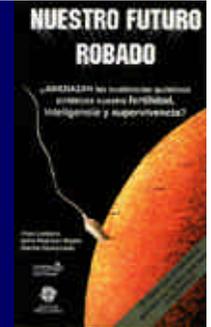
**New** ...long latencies following developmental exposure.

# CONCEPTUAL SHIFTS



**Old...**take chemicals one at a time  
**a time**

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



# CONCEPTUAL SHIFTS

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

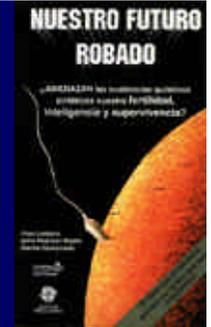
**New...** epidemiology may be incapable of confirming real impacts for a very long time



# EPIDEMIOLOGY IS A BLUNT INSTRUMENT

**In general... relatively good at rare events,**

**Less powerful for risk factors affecting more common endpoints.**



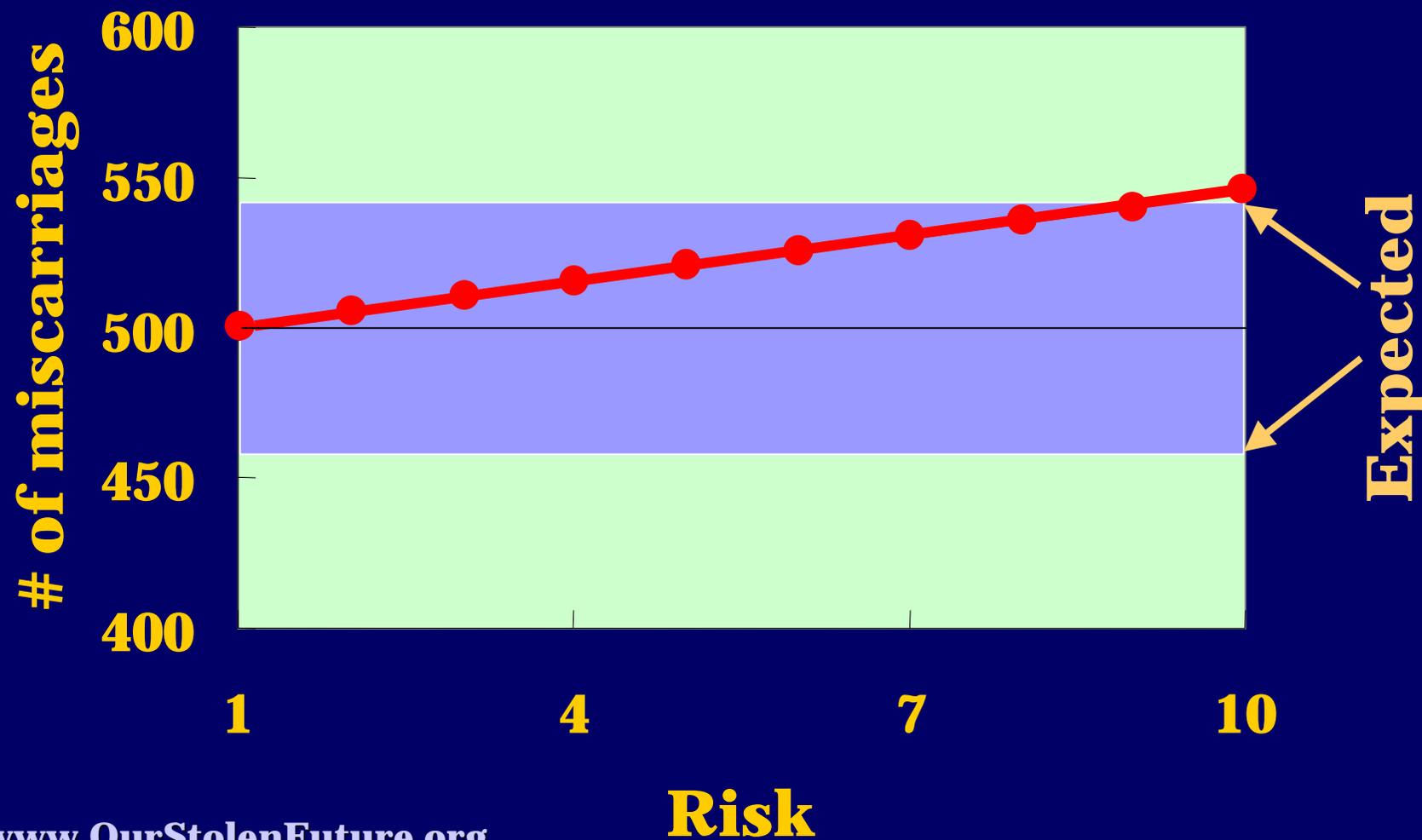
# EPIDEMIOLOGY IS A BLUNT INSTRUMENT

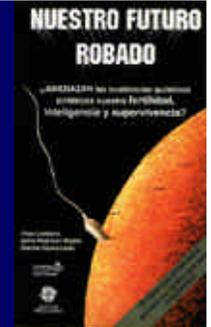
## *A thought experiment*

- \* **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

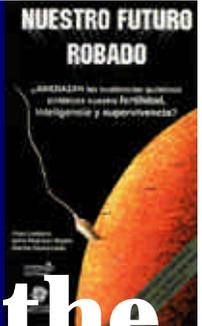
**Low dose, non-monotonic D-R curves**

**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**

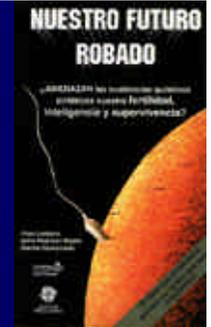


# **EDC CHARACTERISTICS**

**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**

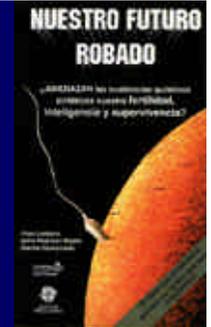


# **EVEN WITH THESE CHALLENGES**

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

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

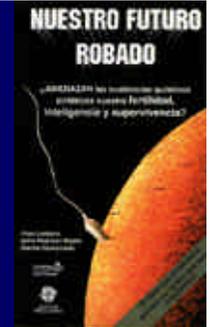
*Bell et al. 2001 Epidemiology 12:148-156*



# **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.**

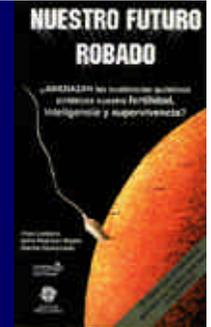


# **EVEN WITH THESE CHALLENGES**

**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*



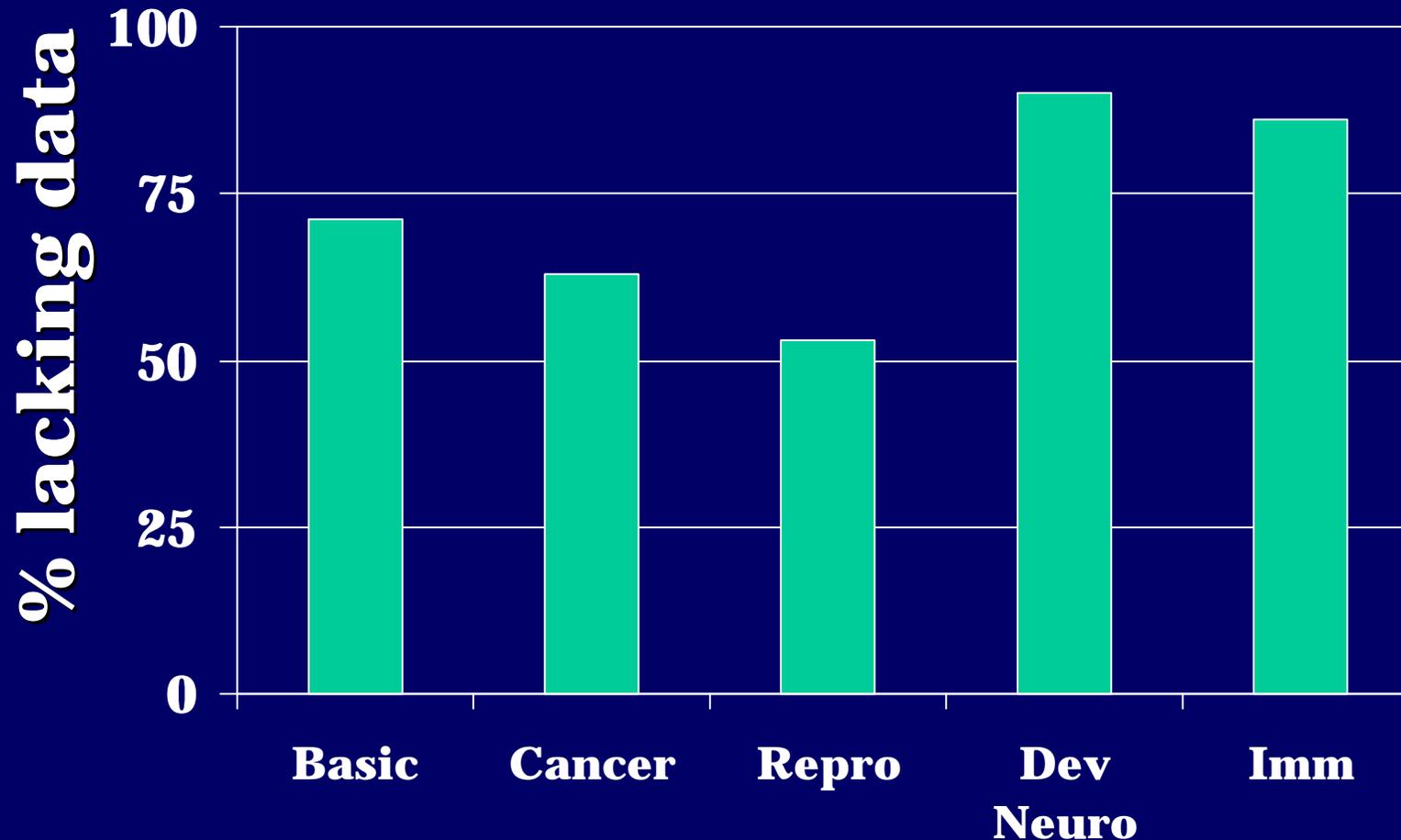
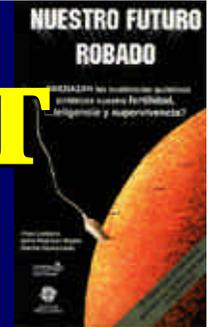
# **EVEN WITH THESE CHALLENGES**

**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.**

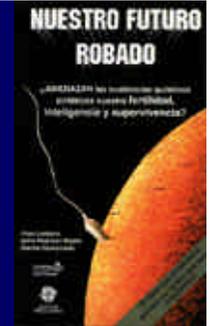
**Blanck *et al.* 2000 Obstetrics & Gynecology 96**

# BUT WE REMAIN IGNORANT



**3000 high volume chemicals lack data**

[www.OurStolenFuture.org](http://www.OurStolenFuture.org)



# 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**

[www.OurStolenFuture.org](http://www.OurStolenFuture.org)



# **POLYBROMINATED FLAME RETARDANTS**

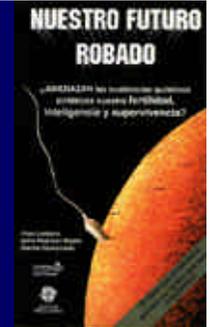
**Used in many consumer  
products, industrial processes**

**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**



# 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**