In the light of the Pesticides Legislation, how effective are the current EDCs criteria?

How to ensure Healthy Food for our Children
Brussels, European Parliament,
30th of September 2013

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Regulation 1107/2009

- *..pesticides with endocrine disrupting properties that may cause adverse effects cannot be approved..*
- Article 4 of the Regulation obliges SANCO to evaluate pesticides "*in the light of current scientific and technological knowledge*"

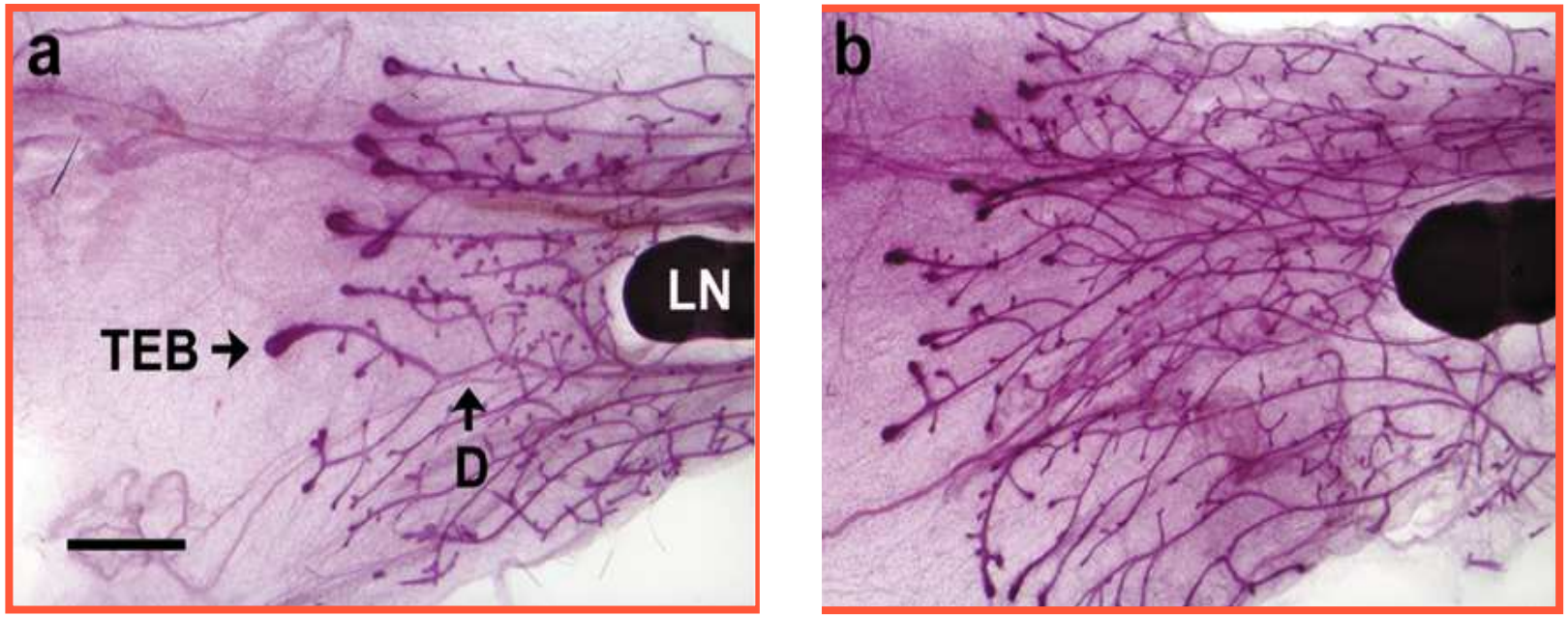
Breast Cancer

- An example to emphasise the vulnerability of the fetus
- At a 1/1000th of the dose required to affect adults
- From one chemical, Bisphenol A, which acts in the environment in a complex mixture of > 1000 other xenochemicals

Diamanti-Kandarakis E *et al. 2009 Endocrine-Disrupting* Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews 30(4):293-342*

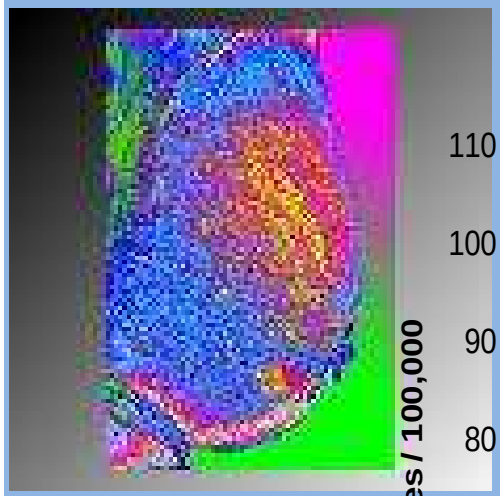
- When considering the role played by EDS in the etiology of breast cancer the report concludes that
- "*Collectively, these data support the notion that endocrine disruptors alter mammary gland morphogenesis and that the resulting dysgenic gland becomes more prone to neoplastic development*."

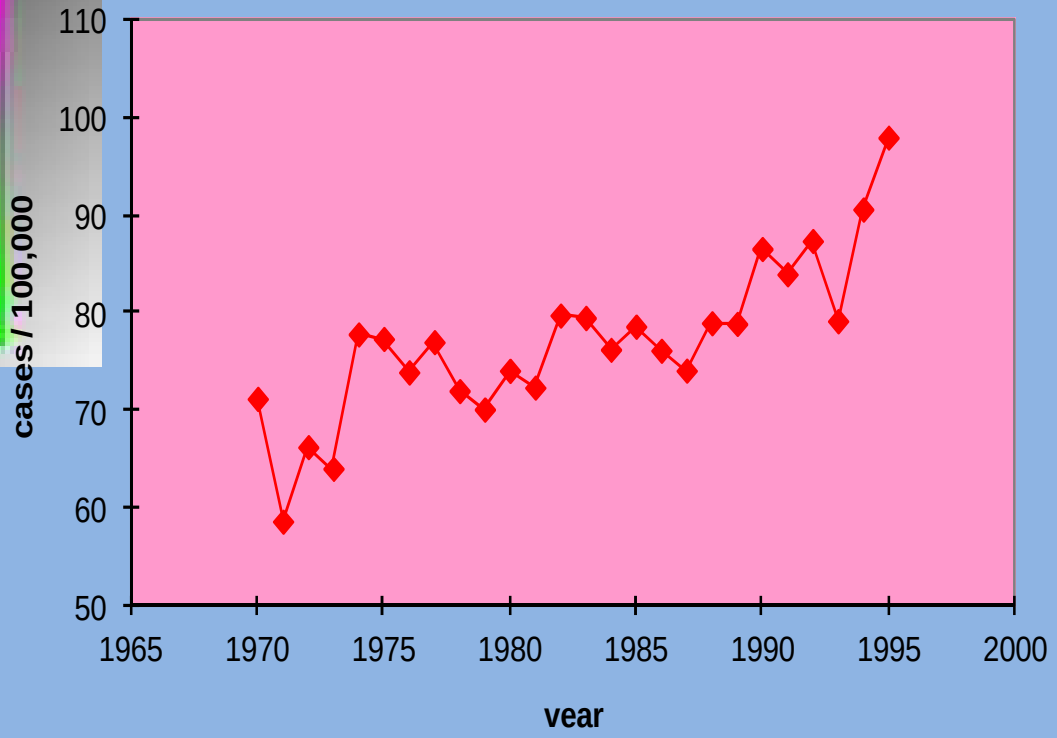
Prenatal bisphenol A increases mammary gland duct size and number of terminal end buds in CD-1 mice 200,000-times below the current No Effect Dose



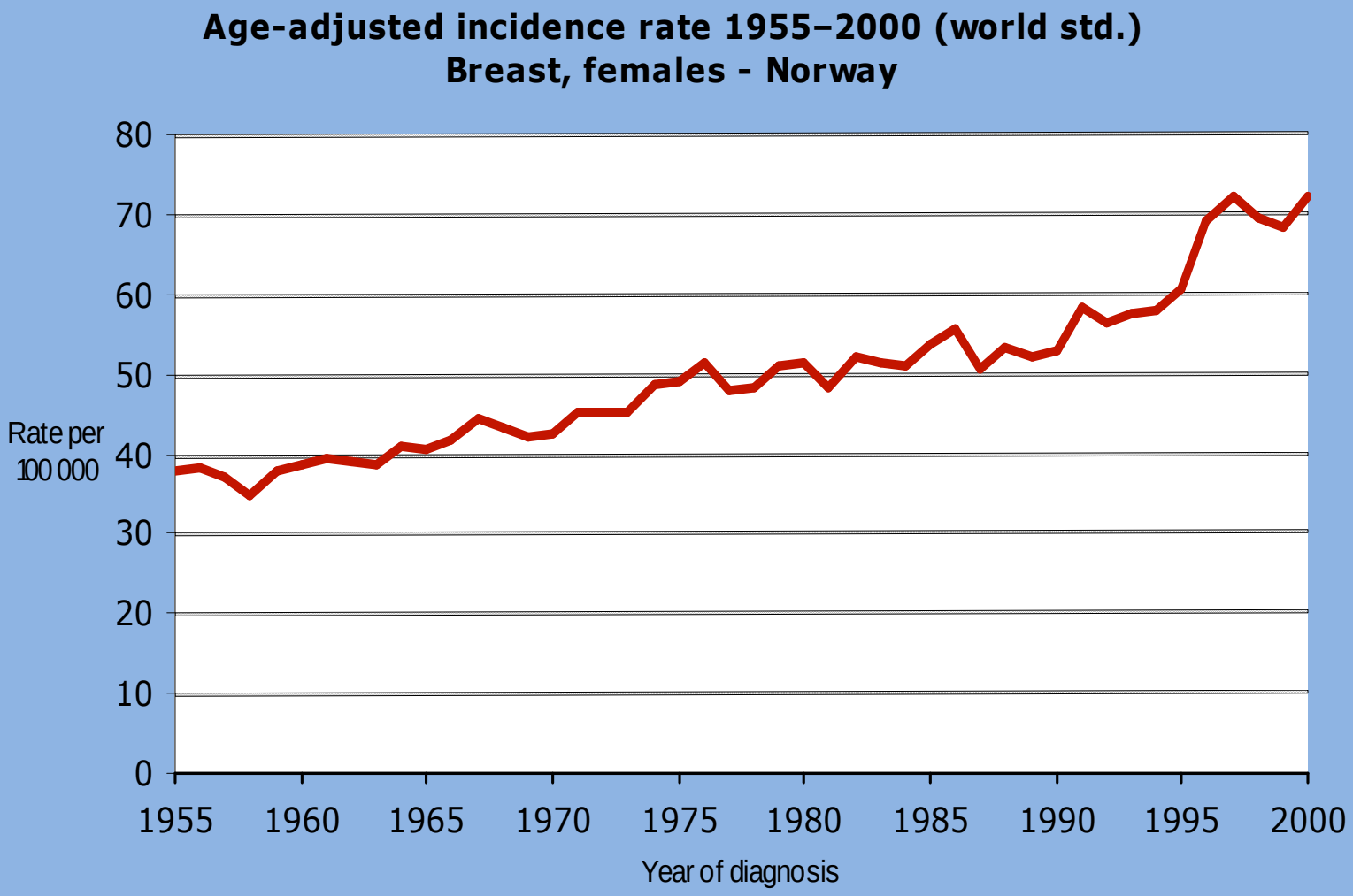
Markey et al., 2001
Biol. Reprod.

Temporal Trend in the Incidence of Female Breast Cancer





age standardised
Germany- Saarland


Age-adjusted incidence rate 1955–2000 (world std.)
Breast, females - Norway
Rate per 100 000
80
70
60
50
40
30
20
10
0
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
Year of diagnosis

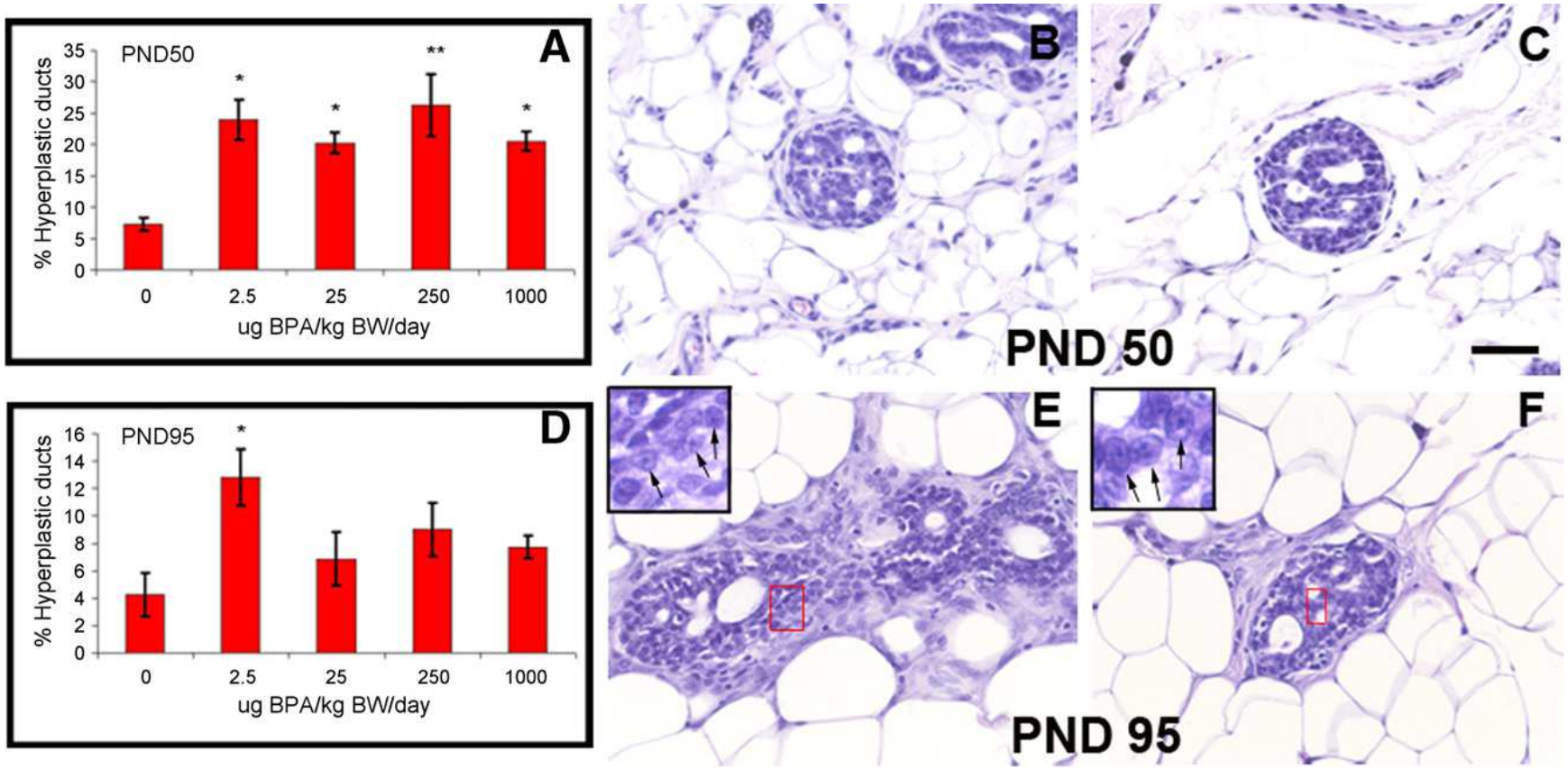
Available online at www.sciencedirect.com
ScienceDirect
Biomedicine & Pharmacotherapy 61 (2007) 623–630
BIOMEDICINE & PHARMACOTHERAPY
www.elsevier.com/locate/biopha

Dossier : Cancer : Influence of environment

The cancer incidence temporality index: An index to show temporal changes in the age of onset of overall and specific cancer (England and Wales, 1971–1999)

J.A. Newby [a,*], C.C. Busby [b], C.V. Howard [c], M.J. Platt [d]

Murray, T. J., Maffini, M. V., Ucci, A. A., Sonnenschein, C. & Soto, A. M. (2006) Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol A exposure. *Reproductive Toxicology* **23**, 383–390.



Current regulatory toxicology

- Predicated on adult toxicology
- One compound at a time
- Requires the assumption that there are ‘no effect’ levels from the interpolation of linear dose response curves
- Does not acknowledge that development can be ‘hijacked’ at low dose by many chemicals previously assumed to be biologically inert

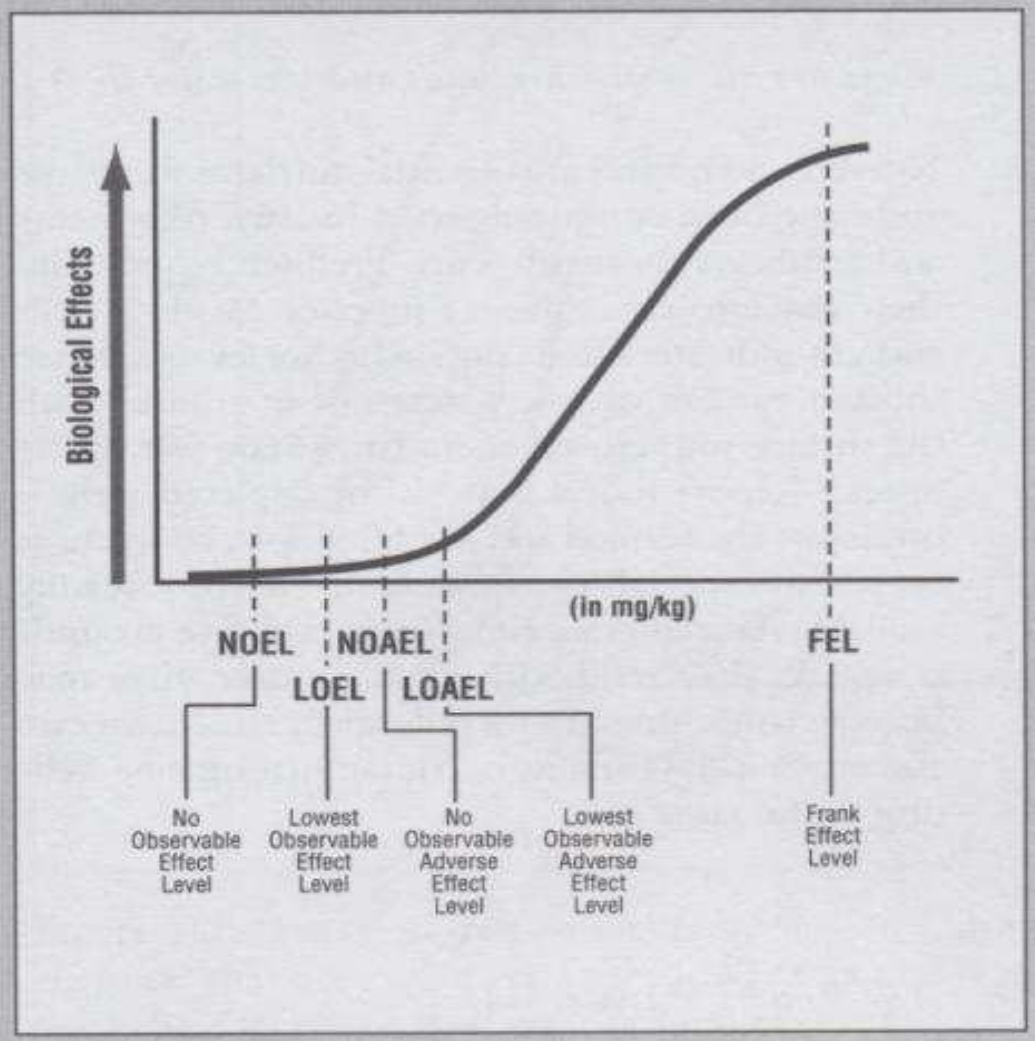
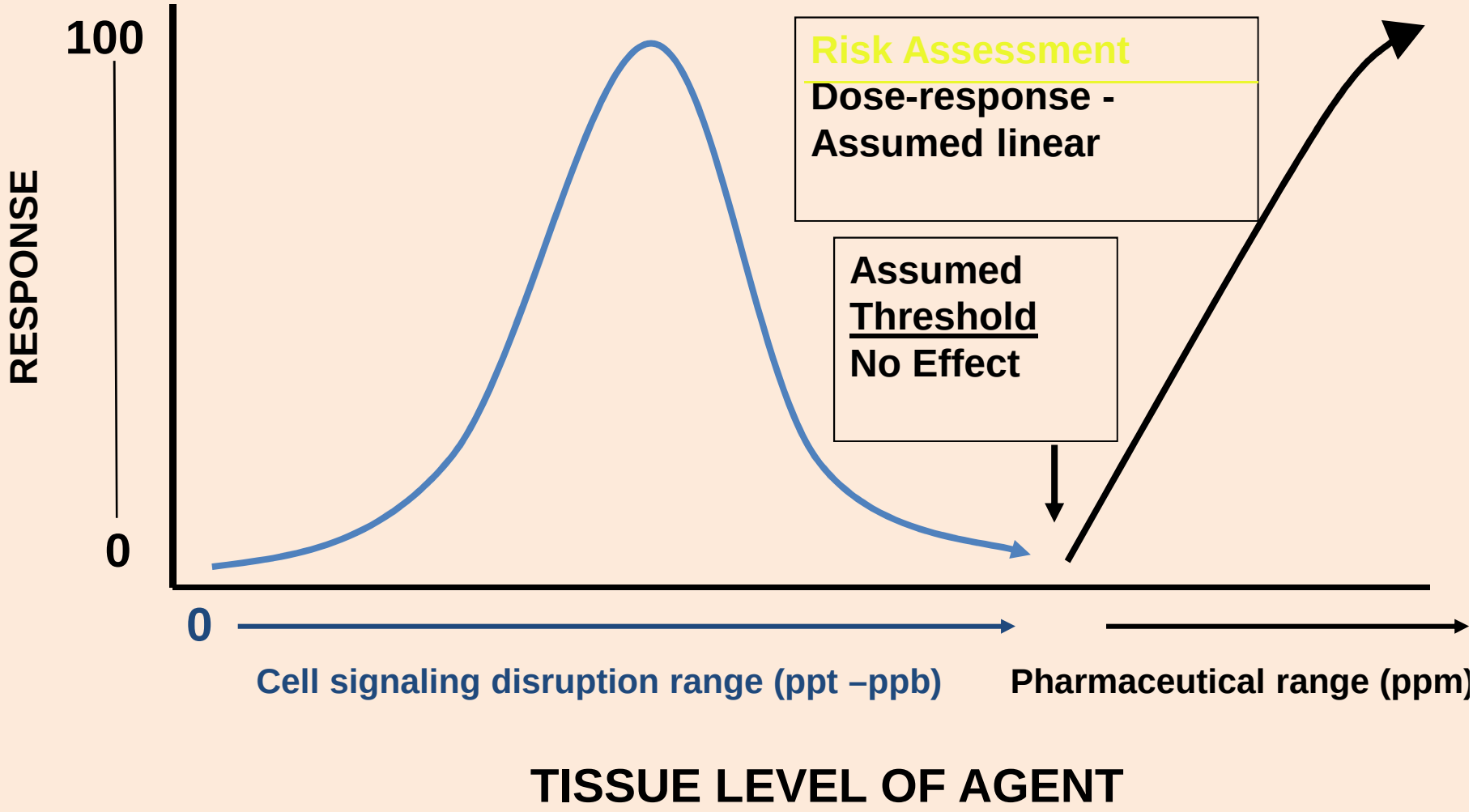
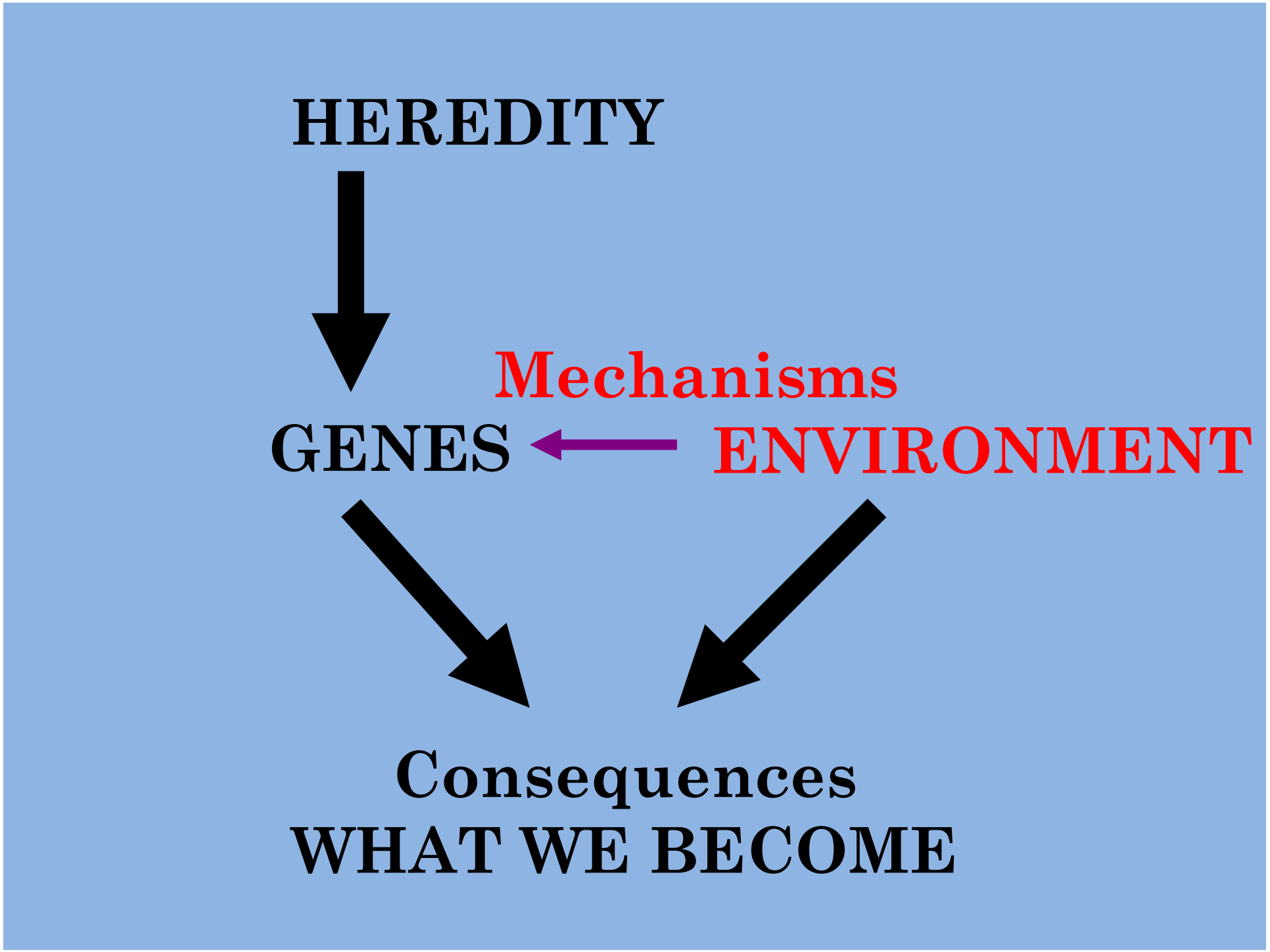


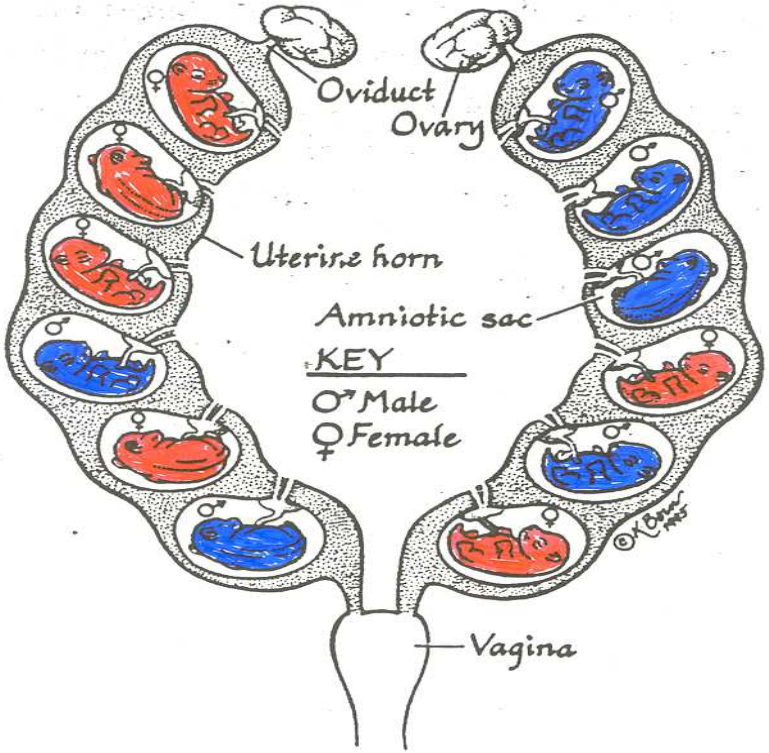
Illustration of the locations of various effect-no effect levels on a dose-response curve. *Reprinted with permission from Ecobiochen D.*, The Basis of Toxicity Testing, *Copyright CRC Press, Boca Raton, FLA 1990/1992.*

INVERTED-U DOSE-RESPONSE CURVE FOR CELL SIGNALLING DISRUPTORS




HEREDITY
Mechanisms
GENES
ENVIRONMENT
Consequences
WHAT WE BECOME

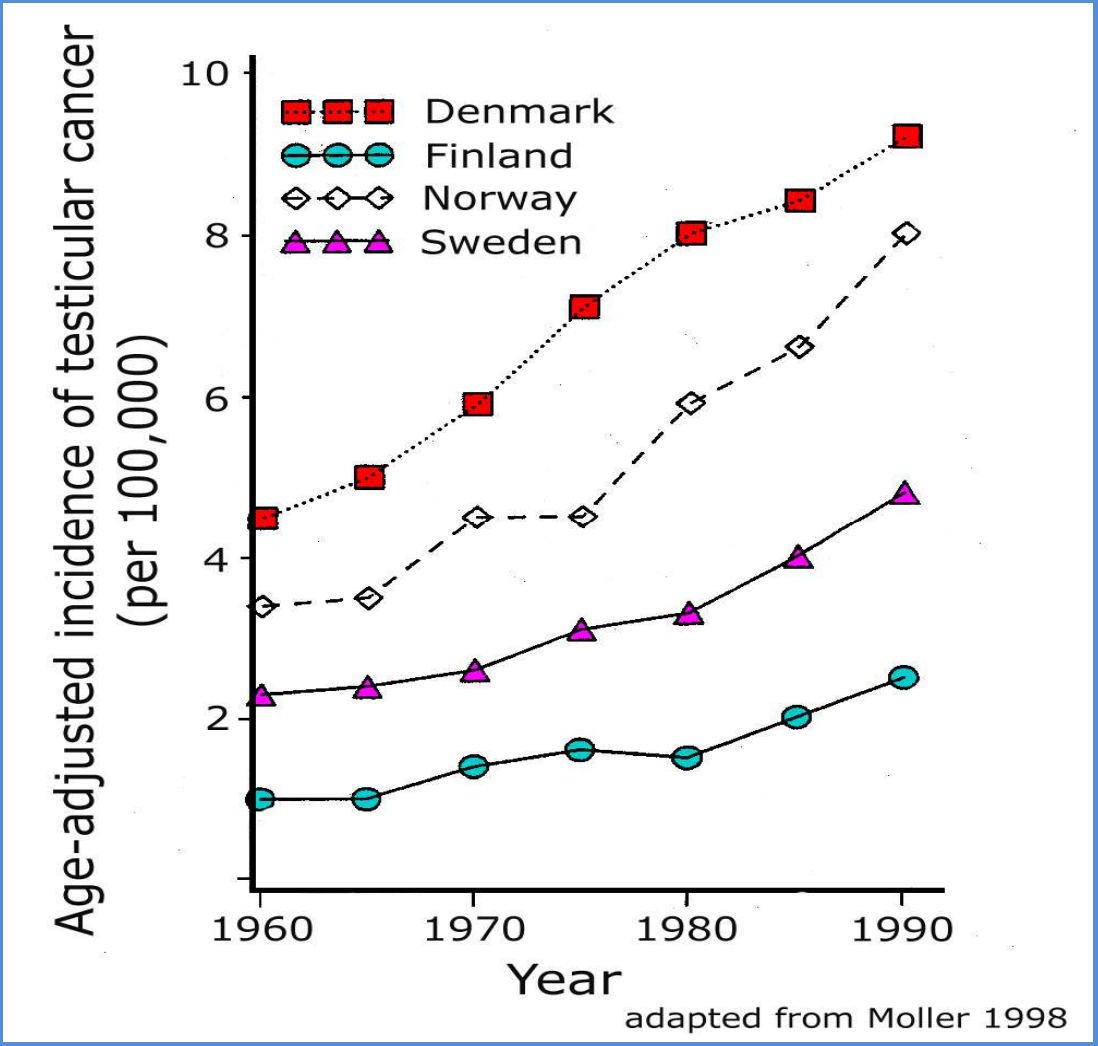
The developmental process is both sensitive and vulnerable



Behavioral and reproductive differences in mice can be predicted to a remarkable degree by their position, which is related to hormone exposure, in the womb. (Adapted from vom Saal and Dhar, 1992)

FETAL ORIGIN OF ADULT DISEASE HYPOTHESIS: TESTICULAR CANCER

Dr. N.E. Skakkebaek Copenhagen



Human Reproduction VoLl6, No.5 pp. 972-978, 2001

OPINION

Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects

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Numerous reports have recently focused on various aspects of adverse trends in male reproductive health, such as the rising incidence of testicular cancer; low and probably declining semen quality; high and possibly increasing frequencies of undescended testis and hypospadias; and an apparently growing demand for assisted reproduction. Due to specialization in medicine and different ages at presentation of symptoms, reproductive problems used to be analysed separately by various professional groups, e.g. paediatric endocrinologists, urologists, andrologists and oncologists. This article summarizes existing evidence supporting a new concept that poor semen quality, testis cancer, undescended testis and hypospadias are symptoms of one underlying entity, the testicular dysgenesis syndrome (TDS), which may be increasingly common due to adverse environmental influences. Experimental and epidemiological studies suggest that TDS is a result of disruption of embryonal programming and gonadal development during fetal life. Therefore, we recommend that future epidemiological studies on trends in male reproductive health should not focus on one symptom only, but be more comprehensive and take all aspects of ms into account. Otherwise, important biological information may be lost.

Keywords: environmental disrupters/inferti1ity/male reproduction/testicular cancer/ testicular development

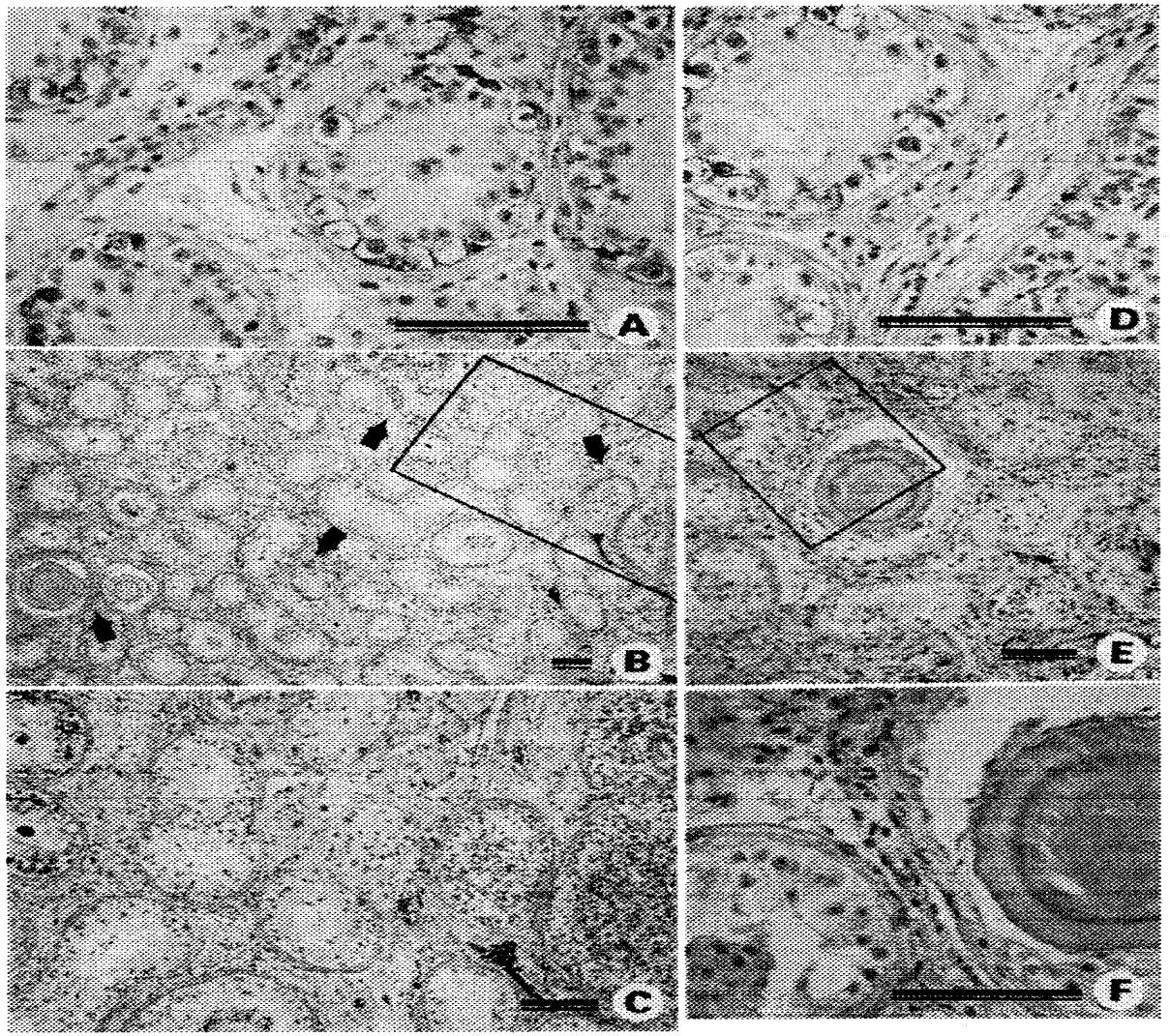


Figure 2. Examples of testicular dysgenesis in two contralateral biopsies of patients with unilateral testicular tumours. Both biopses contain carcinoma in-situ (CIS) cells, which are visualized by immunohistochemical staining for placental-like alkaline phosphatase (dark brown colour). Morphology of CIS cells is shown in detail in (**A**) and (**D**); the latter showing two CIS tubules side by side with a tubule with undifferentiated Sertoli cells and microcalcifications. (**B**) General overview of a biopsy with three dysgenetic features (indicated by arrows): CIS tubules, microliths (hyaline bodies) and undifferentiated Sertoli cells. The marked field contains CIS tubules and dysgenetic tubules resembling gonadoblastoma nests and is shown in higher magnification in (**C**). (**E**) Another biopsy with CIS, a large hyaline body and Sertoli cell-only tubules. The marked field is shown in detail in (**F**). Note poorly differentiated Sertoli cells in a tubule adjacent to the microlith. Scale bar = 100 μm.

It is not only about cancer

- Subtle functional deficits predominate
- Reproductive function compromised
- Neuro behavioural deficits

- Such end points are not routinely tested for in current regulatory toxicology
- However methods for their detection have been published

N.E.Skakkebæk, E.Rajpert-De Meyts and K.M.Main

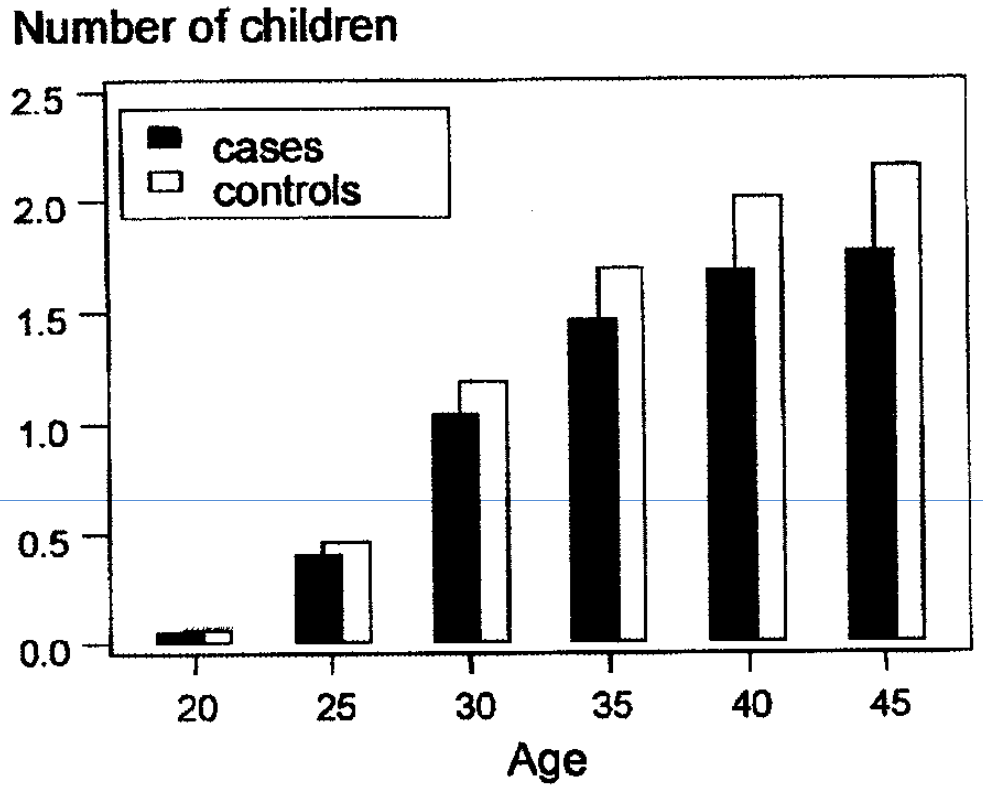
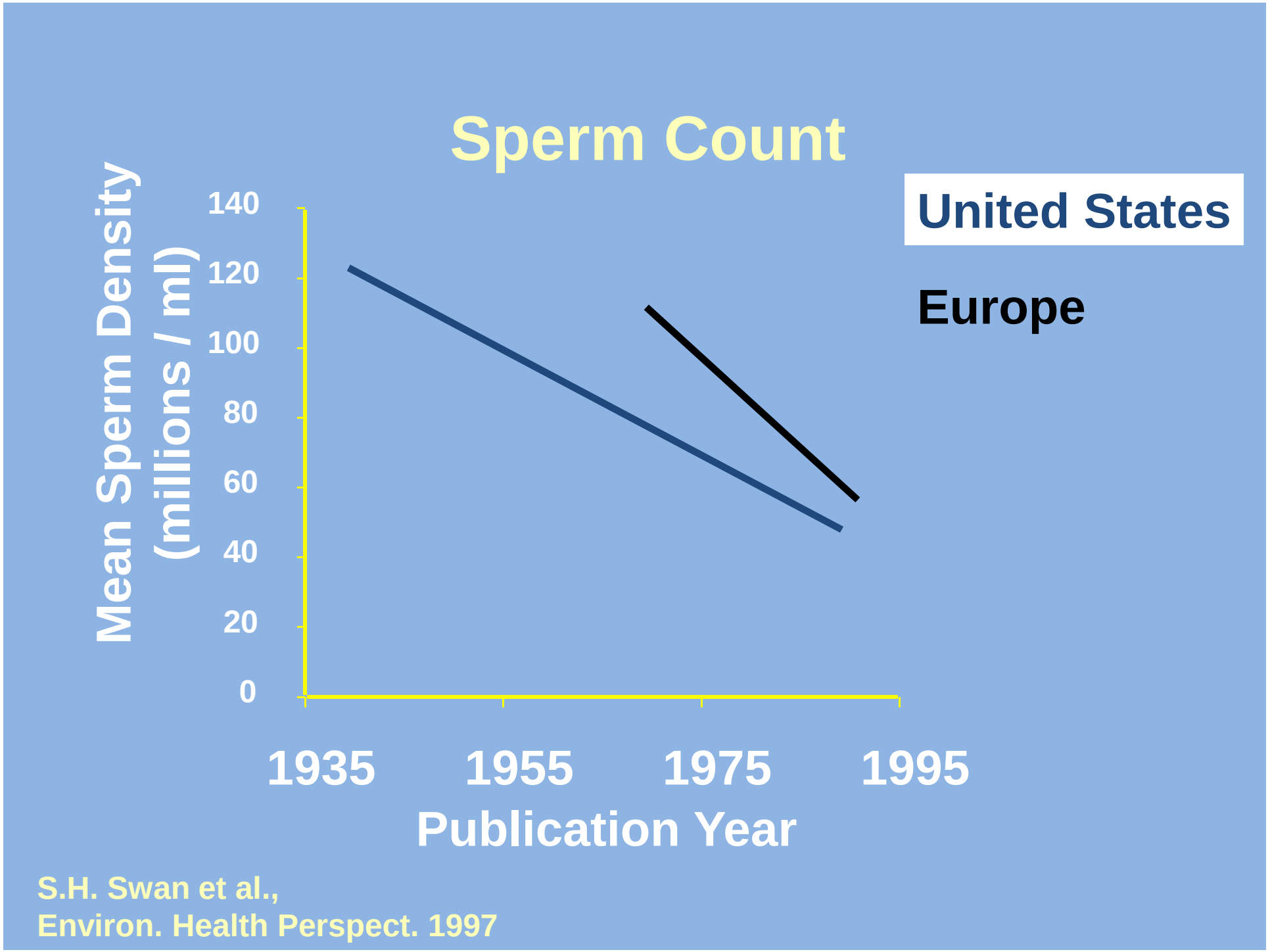
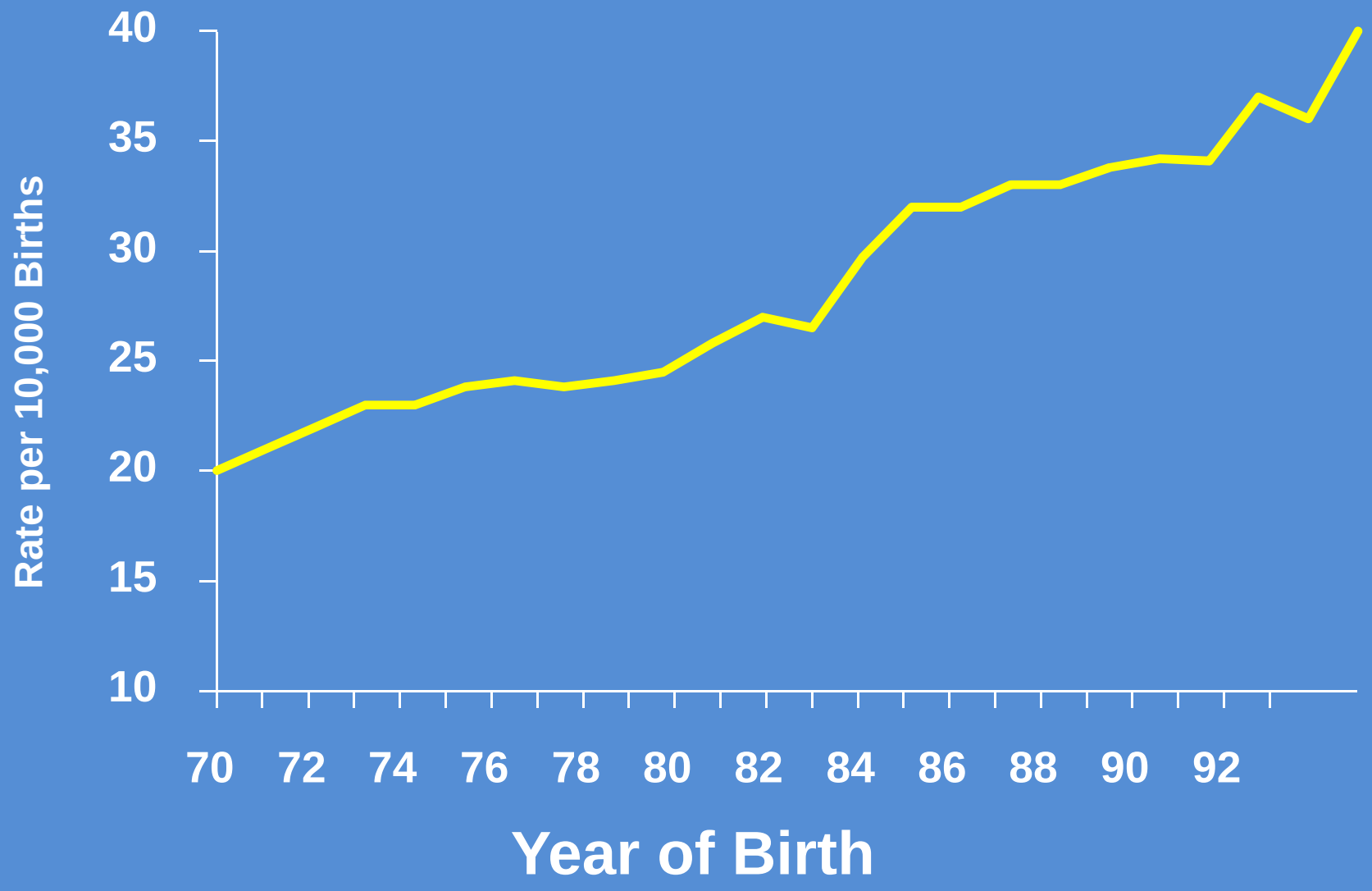


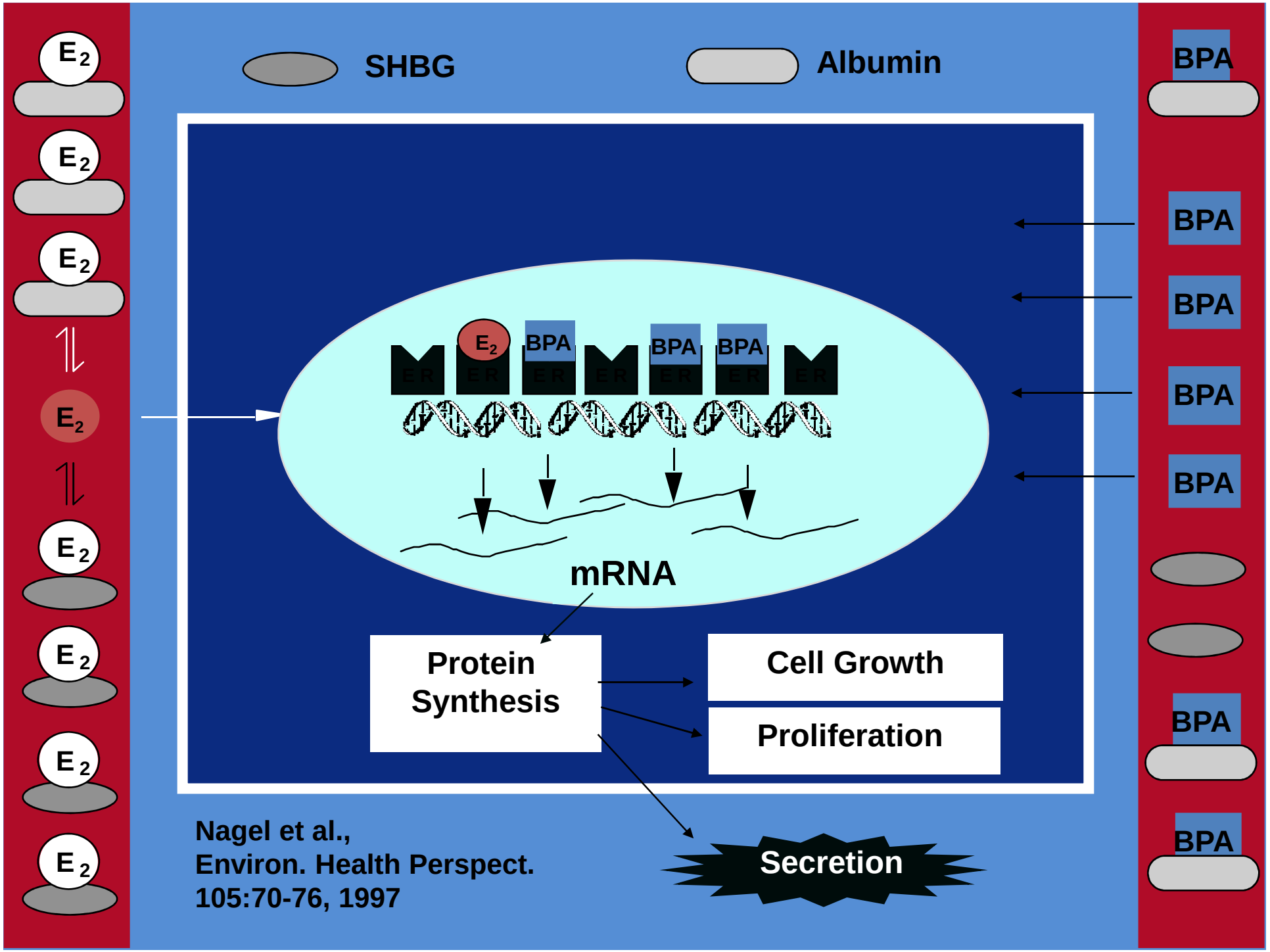
Figure 3. Epidemiological evidence of decreased fertility in men who later developed testicular tumours. The bars represent mean cumulative age-specific fertilities of men with testicular cancer and of control men. [Reprinted with permission from Møller and Skakkebæk, *Br. Med. J.* (1999) **318**, 559–562.]


Sperm Count
Mean Sperm Density
(millions / ml)
140
120
100
80
60
40
20
0
1935
1955
1975
1995
Publication Year
United States
Europe
S.H. Swan et al.,
Environ. Health Perspect. 1997

HYPOSPADIAS RATES: 1970 - 1993

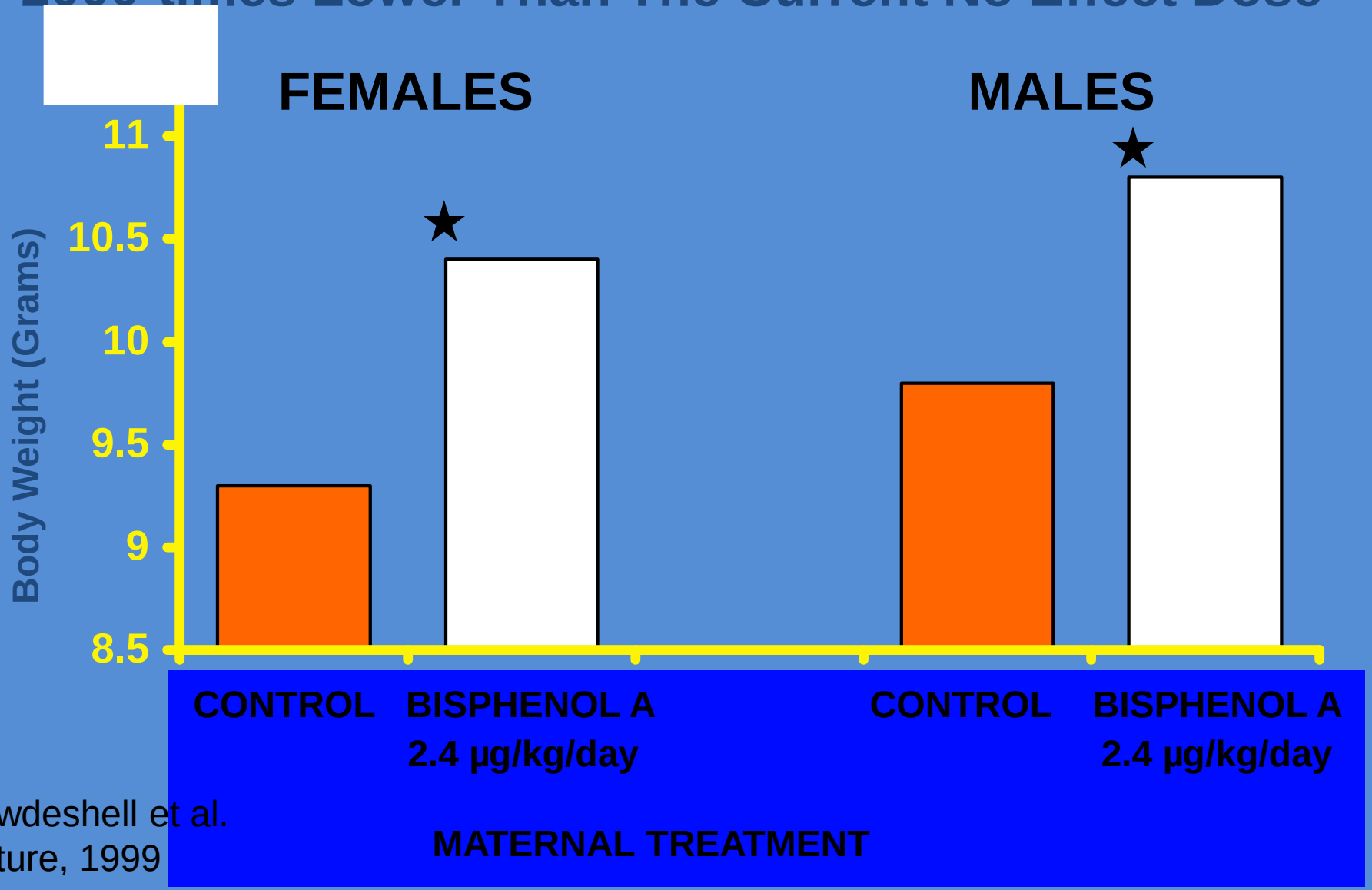


Paulozzi et al., 1997


SHBG
Albumin
E2
BPA
ER
mRNA
Protein Synthesis
Cell Growth
Proliferation
Secretion
Nagel et al.,
Environ. Health Perspect.
105:70-76, 1997

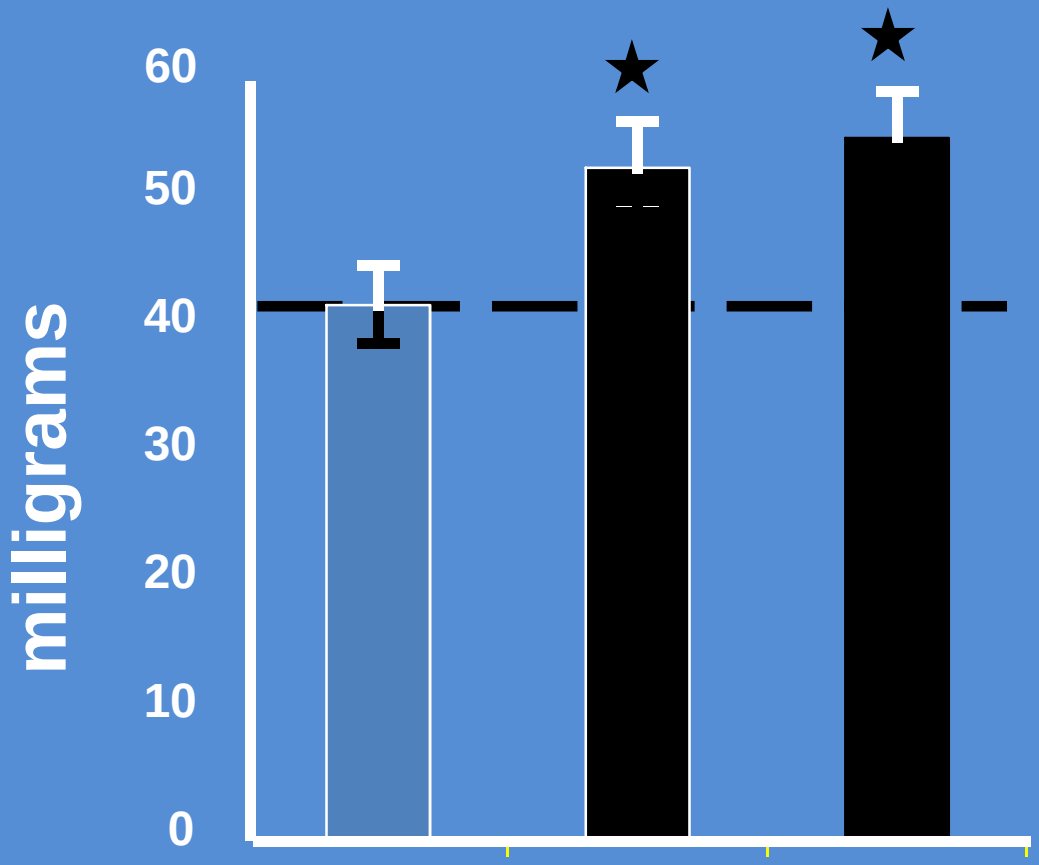
EFFECT OF PRENATAL BISPHENOL A ON BODY WEIGHT AT WEANING IN CF-1 MICE

2000-times Lower Than The Current No Effect Dose



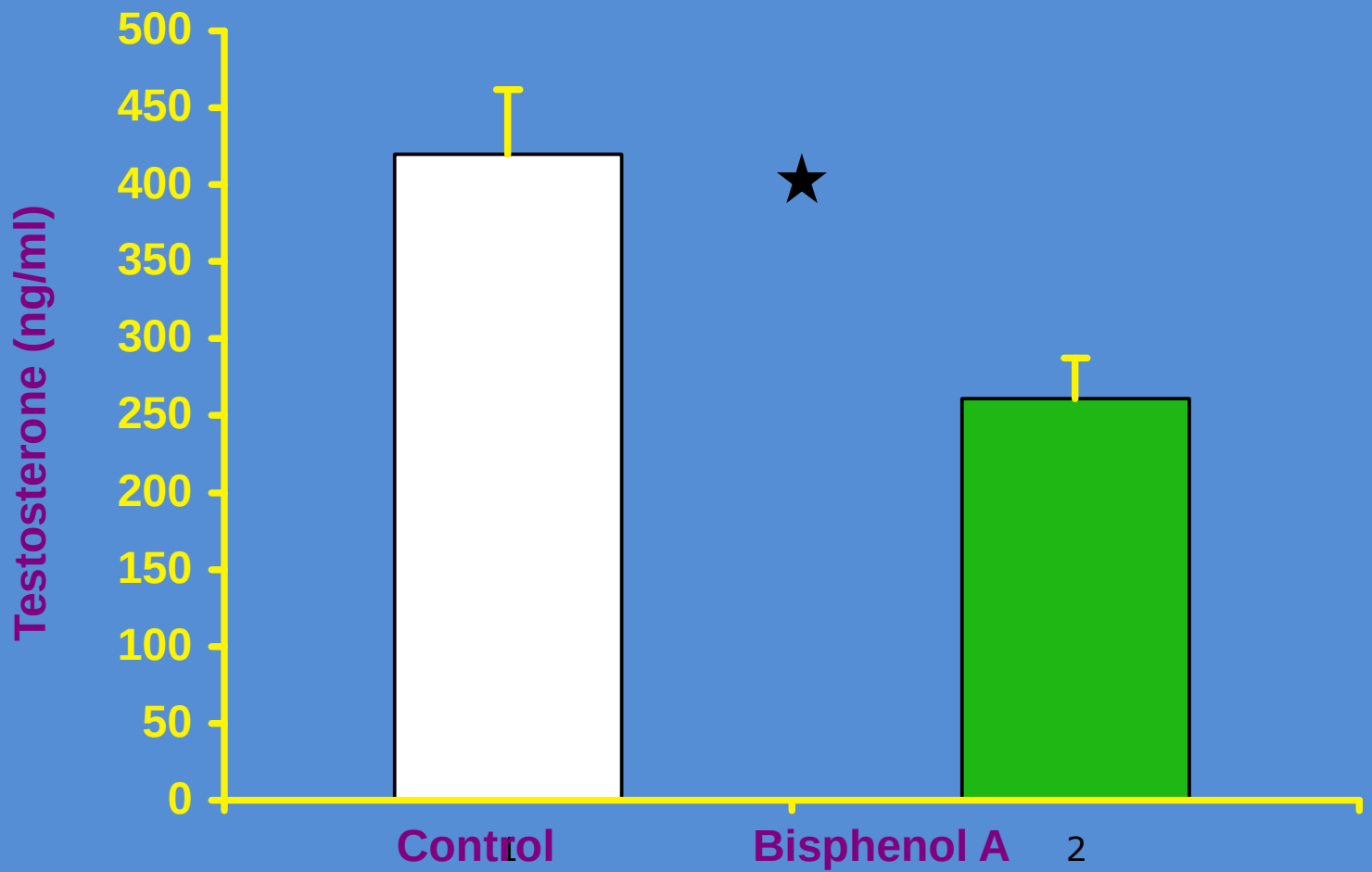
Howdeshell et al.
Nature, 1999

EFFECT OF PRENATAL BISPHENOL A ON ADULT PROSTATE WEIGHT IN CF-1 MICE



vom Saal et al.
Tox. Ind. Health
14:239-260, 1998

PERINATAL BISPHENOL A EXPOSURE DECREASES TESTICULAR INTERSTITIAL FLUID TESTOSTERONE LEVELS IN RATS



Akingbemi et el.
Endocrinol. 2004

Risk Assessment – 4 phases

- **Hazard identification** – requires insight and understanding of the system in question
- **Hazard assessment** – costs time and money for hard science – positive findings require action
- **Exposure assessment** – can be very expensive and, for human exposure, complex
- **Risk assessment** – depends totally on the 1st three steps

What is the PP for?

Precautionary principle stifles discovery

Sir — The so-called 'precautionary principle' (PP) has gained currency in discussions about environmental protection and genetic manipulation, but it should be treated with caution.

The principle has been endorsed in international treaties, including the consolidated version of the treaty establishing the European Union. In many of these documents the PP has not been explicitly defined, but the Wingspread conference attempted to define it[1]. We believe the following definition would be accepted by most proponents:

"When an activity raises threats of serious or irreversible harm to human health or the environment, precautionary measures that prevent the possibility of harm (for example, moratorium, prohibition) shall be taken even if the causal link between the activity and the possible harm has not been proven or the causal link is weak and the harm is unlikely to occur."

In our view, there are problems with the PP as so defined. The PP tells us to balance evidence in a specific way. The weight given to evidence is ordinarily thought to be a function of its epistemic warrant (the degree to which we have reasons for believing the evidence). The PP instructs us to change this normal balancing by giving evidence pointing in one direction more importance than evidence pointing in the other direction, even in cases where the evidence has the same epistemic warrant. Such discounting will distort our beliefs about the world, and will lead us to hold false beliefs. The PP cannot therefore be a valid principle for evaluating evidence.

As a principle of rational choice, the PP will leave us paralysed. In the case of genetically modified (GM) plants, for example, the greatest uncertainty about their possible harmfulness existed before anybody had yet produced one. The PP would have instructed us not to proceed any further, and the data to show whether there are real risks would never have been produced. The same is true for every subsequent step in the process of introducing GM plants. The PP will tell us not to proceed, because there is some threat of harm that cannot be conclusively ruled out, based on evidence from the preceding step. The PP will block the development of any technology if there is the slightest theoretical possibility of harm. So it cannot be a valid rule for rational decisions.

This fatal weakness of the PP illustrates a common problem in attempting to convert moral choices into legislation. The temptation is great to try to find one absolute and easily applicable principle, but such a principle will often be simplistic and will, when applied, lead to unjustifiable conclusions. Many moral choices are complex, and in making political decisions we should not lose sight of this complexity.

Søren Holm, John Harris
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1. http://www.wajones.org/wingcons.html

correspondence

Sensible precautions make good science...

Sir— Søren Holm and John Harris strongly criticize the precautionary principle but they seem not to understand it (*Nature* **400**, 398; 1999). They complain that it is not valid for evaluating evidence, when that is not what it is for. It is a tool for decision-making, and, like many such tools, deals in expectations rather than probabilities.

The point is that it requires us to take into account not just the probability that a technology will be hazardous, but also the benefits if it succeeds and the costs if things go wrong. There may have been a very small probability that a large ship travelling at high speed in the North Atlantic would hit an iceberg, but the captain of the *Titanic* should have thought more about what could happen if it did — and all the more so because it didn't really matter if the voyage lasted a few hours more.

Holm and Harris argue that the precautionary principle would have stopped us developing genetically modified organisms (GMOs) because the greatest uncertainty about their possible harmfulness existed before anybody had produced one. But the principle does not demand that we halt research if we cannot be certain the end result will be safe (though common sense suggests it is unwise to make large investments if the end result is likely to be dangerous). It is to be applied at each stage in the process, weighing the risks in going one step further against the likely benefits if the project is successful.

That is why we and many others are arguing not for a complete ban on research into GMOs but for a five-year moratorium on field trials and commercial planting. There is a lot more research to be carried out in the relative safety of a closed laboratory first. This is always good practice, but it is especially important in the case of GMOs because of the irreversibility that is inherent in the technology. If a new drug proves to be harmful we can withdraw it, but once genes have left the laboratory there is no calling them back. The experiments in which GM milkweed was found to harm the monarch butterfly were performed in contained conditions; had this been discovered in field trials, the gene might already be spreading through the environment.

Our objection to the current field trials of GM crops is based not on whether commercial planting would be safe (though we are concerned about that), but on whether the trials themselves are safe — and whether they are well enough designed to be worth the risk. Neither has been shown to be the case. At the end of a moratorium, a much better-informed risk assessment should be possible.

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Suggestions for DG SANCO

- Please return to closely examining the text of the Regulation (eg *pesticides with endocrine disrupting properties that may cause adverse effects cannot be approved).*
- This will automatically lead to the adoption of strict criteria for pesticides in the forthcoming impact assessment

Where are the tests for EDs?

- The mandatory tests published in the revised data requirements of DG SANCO do not contain ANY tests for endocrine disruption.
- DG SANCO should require all 400 pesticides currently on the market to be subjected to endocrine disruption testing, based on current scientific knowledge.
- This should be delivered by the end of 2015.

Article 4 of Regulation 1107/2009 obliges SANCO to evaluate pesticides "*in the light of current and technological knowledge*"

- Therefore the use of obsolete protocols is not legally justified
- DG SANCO should revise data requirements to include current scientific knowledge and base testing upon that, including ED effects