

ENDOCRINE DISRUPTORS AND HUMAN HEALTH:

An Overview of the Current State of Knowledge and Regulatory Action

***Tuesday, 19th October 2010,
Food Standards Agency, London***

**Dr Mike Roberts,
Defra Chemicals & Nanotechnologies Division**



defra

Department for Environment
Food and Rural Affairs

**Chemical cocktail
risk to fertility**

STOLEN FUTURE

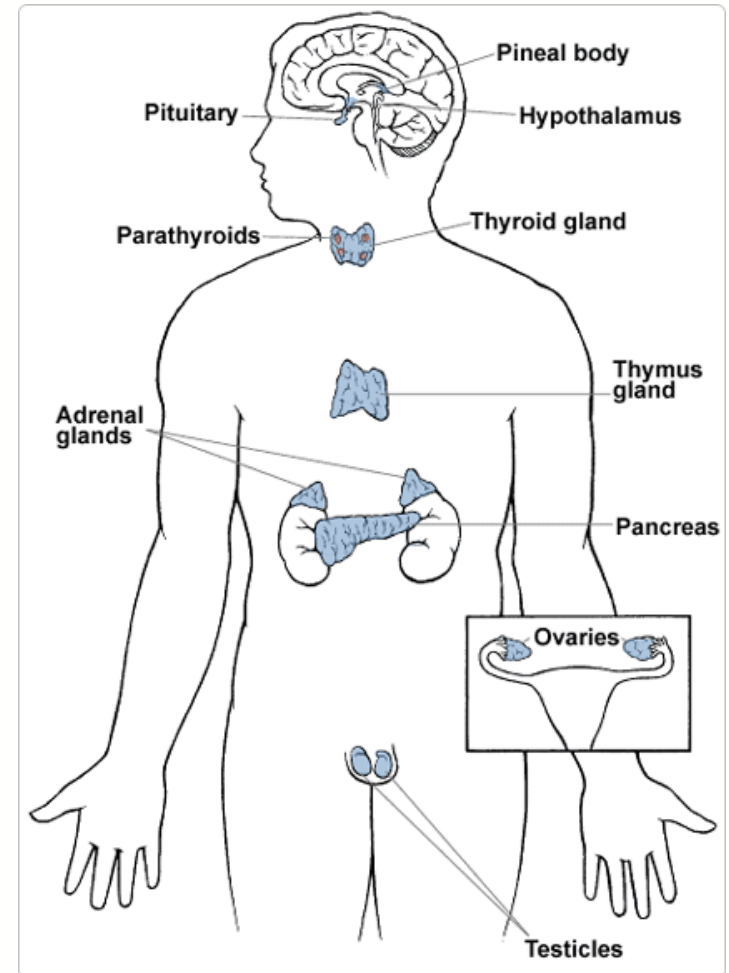
**Are chemicals
behind drop in
boys' birth rate?**

GENDER BENDERS

ENDOCRINE (HORMONE) SYSTEM

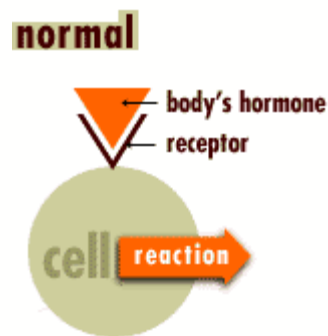
Produces hormones,
chemical messengers:

- released from a gland to a target organ;
- regulate metabolism, growth, development and reproduction.



Some examples in the human body:

<i>Hormone</i>	<i>Produced by</i>	<i>Effect</i>
Oestradiol	Ovaries	Feminising
Testosterone	Testes	Masculinising
Adrenalin	Adrenal Glands	Increases heart beat
Insulin	Pancreas	Controls blood sugar



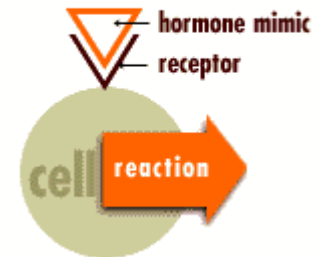
Hormones: large and complex molecules;

Interact with target cells relatively simply - 'lock on' to receptors and trigger specific responses.

Other chemicals can disrupt hormone functions.

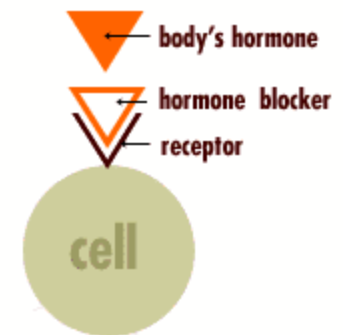
Mimicking the action of a hormone - *agonistic effect*:

excessive



Blocking the action of a hormone – *antagonistic effect*:

blocked



Chemicals which either mimic or block the feminising effects of natural female sex hormones are often referred to as ***oestrogenic*** or ***anti-oestrogenic*** substances.

Chemicals which mimic or block the masculinising effects of natural male sex hormones are referred to as ***androgenic*** or ***anti-androgenic*** substances.

In addition, chemicals might interfere with the production/removal of hormones or their receptors.

Or they may also interfere with neurotransmission and affect neural and neuro-endocrine control of the endocrine system.

Weybridge definition, 1996

“An endocrine disrupter is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary (or consequent) to changes in endocrine function.”

“ A potential endocrine disrupter is a substance that possesses properties that might be expected to lead to endocrine disruption in an intact organism.”

European Commission:

...."endocrine disruption" is not a toxicological endpoint *per se*, but it is a class of many mechanisms of action that may lead in different species to various types of effects which may result in adverse consequences on humans and ecosystems....

Concerns:

Exposure to endocrine disrupting chemicals (EDCs) may have different effects at different times of an animals life - in the embryo, permanent structural modifications might be caused.

Theory posits that low-dose exposures to EDCs can cause effects not seen at higher doses.

Endocrines typically found across wide animal groups – ‘*canaries in coalmines*’?

Examples of EDCs:

Naturally occurring chemicals:*

- **Phytoestrogens** - isoflavones, lignans and coumestans, in e.g. soya, beans, peas, cabbage.
- **Mammals** - excrete oestradiol and oestrogens.

Synthetic chemicals:

- **Diethylstilbestrol (DES);**
- **Dioxin* and dioxin-like compounds;**
- **PCBs, DDT and some pesticides;**
- **Plasticisers** - phthalates, bisphenol-A.

Male Reproductive Health Concerns

Increased incidence of testicular cancer;

Declining semen quality;

**Increased incidence of hypospadias and
cryptorchidism;**

***Sharpe-Skakkebæk Hypothesis of Testicular
Dysgenesis Syndrome.***

Trends in Female Breast Cancer:

<i>Country</i>	<i>Period</i>	<i>Change</i>
Finland	1953-80	from 25 to >40 per 100,000
Denmark	1945-80	from 40 to 60 per 100,000
USA	1973-80	8% rise in women <50 32% rise in women >50.

Wildlife Concerns:

Declines in eggshell thickness in some birds – e.g. Peregrine falcon;

Declines in Baltic Sea grey seals – uterine stenosis;

Pseudo-hermaphroditism reported in female polar bears ;

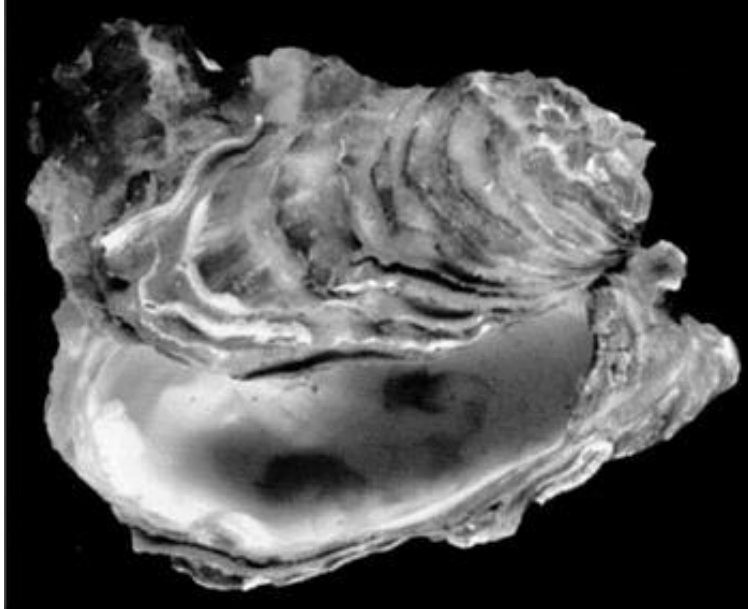
Contaminant-related impacts on alligators in Lake Apopka, Florida.

Environment Agency

2002/3 fish survey

- 46 sites; 38 (80%) had feminised male fish;
- 40% of males intersex;
- most sites had greater than 30% incidence of intersex;
- intersex measurable effect in many English Rivers;
- risk of reproductive impacts.



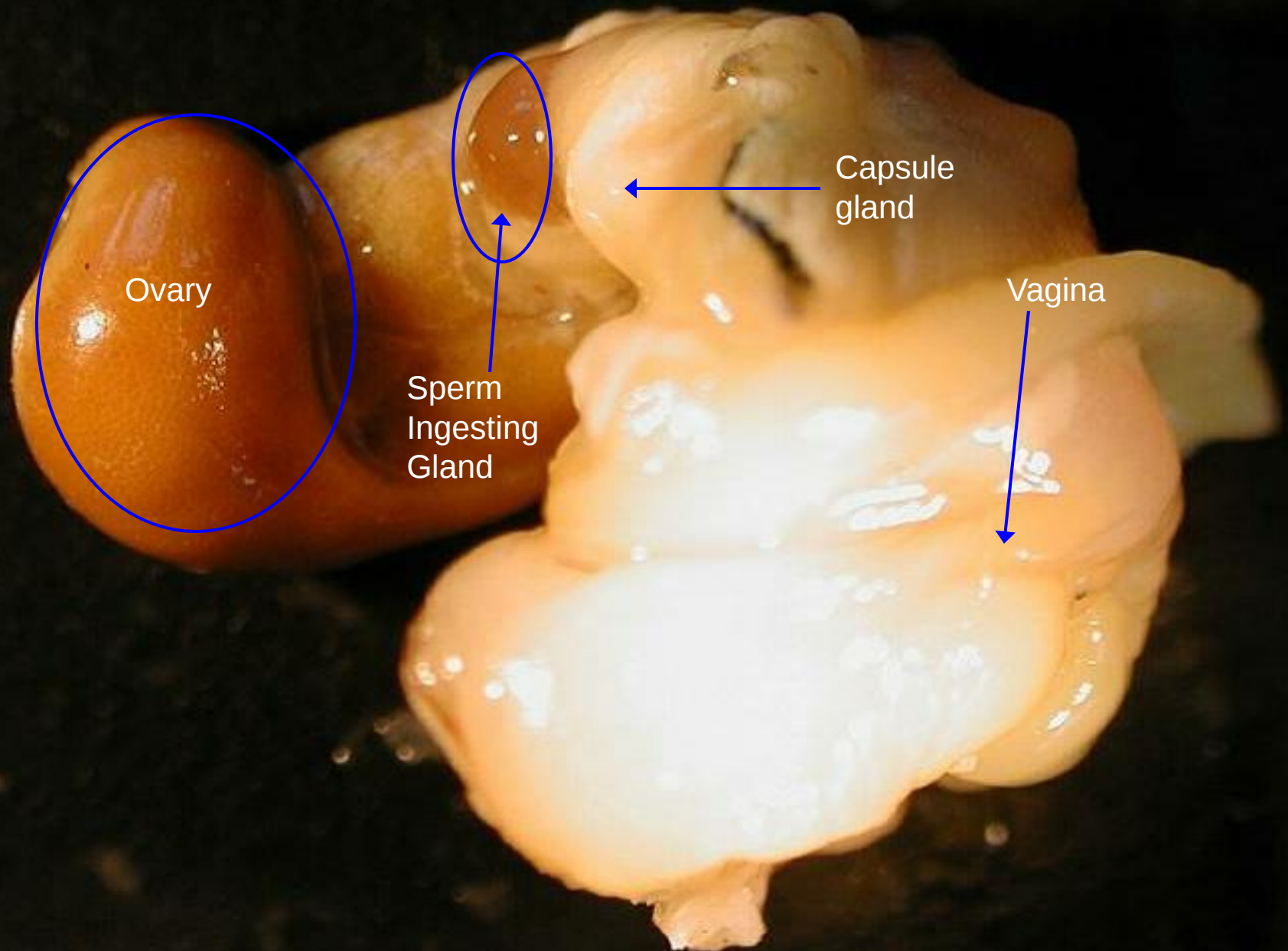


**Shell deformation of
Pacific oysters
(*Crassostrea gigas*)**

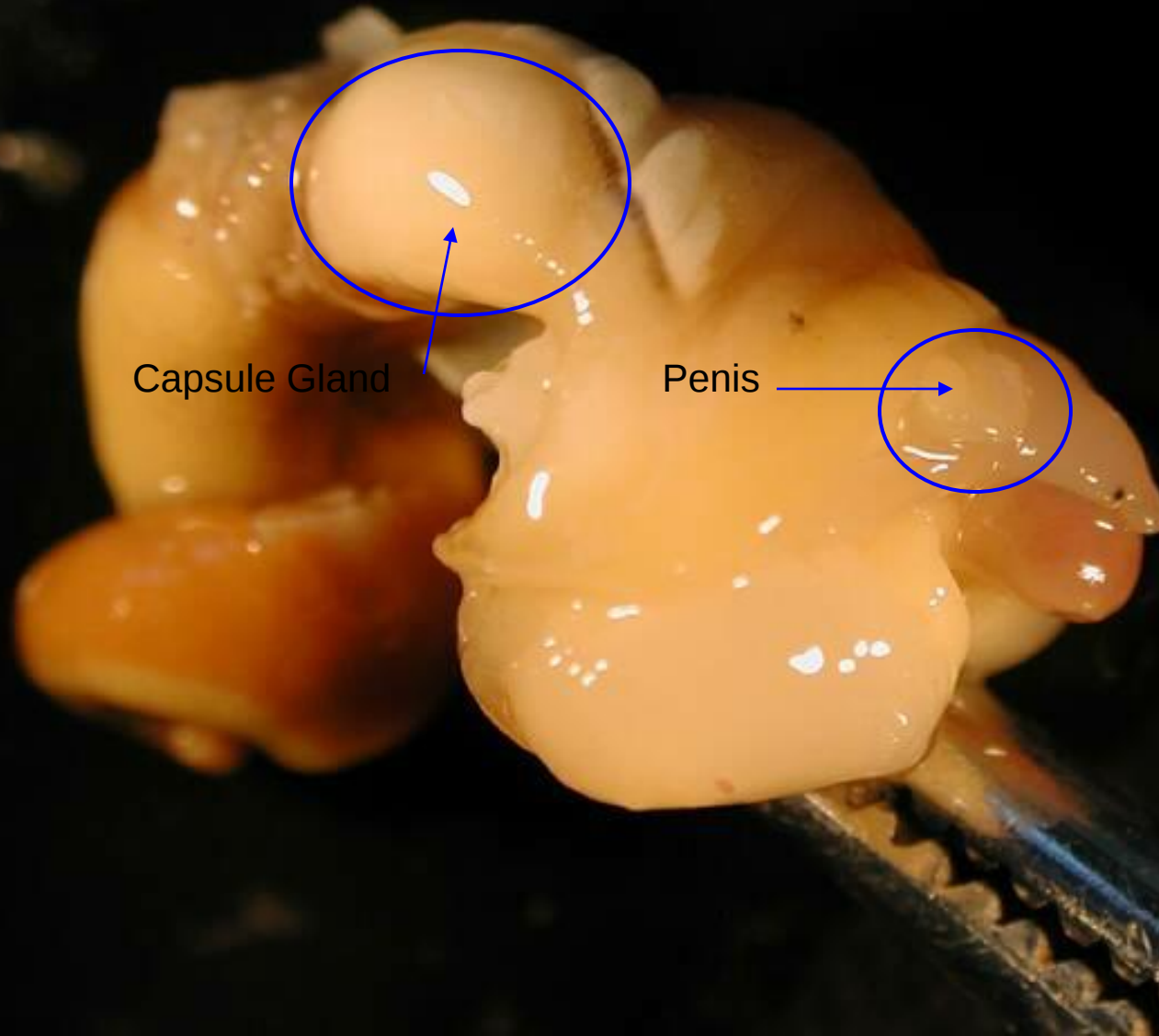
**Imposex in Dog Whelk
(*Nucella lapillus*)**



Female Nucella



Female Nucella with advanced imposex



Imposex in *Nucella*

Stage 0: Normal female

Stage 1: Small lump at penis site

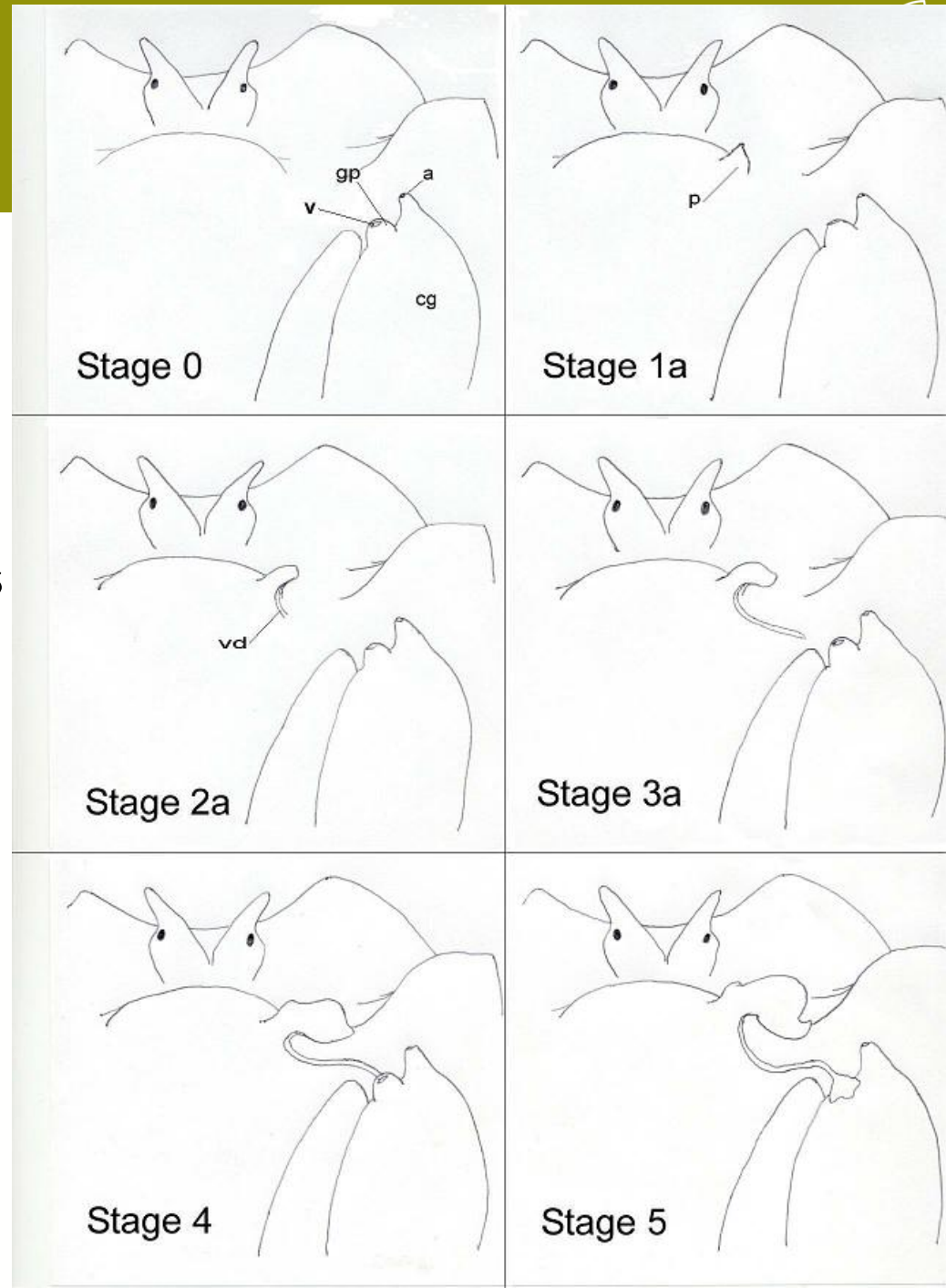
Stage 2: Small penis with vas deferens starting

Stage 3: Penis with substantial vas deferens

Stage 4: Penis with complete vas deferens reaching vaginal pore

Stage 5: Vaginal pore blocked with vas deferens **STERILE**

Stage 6: Capsule gland blocked with aborted eggs **STERILE**



Importance of Imposex in Nucella:

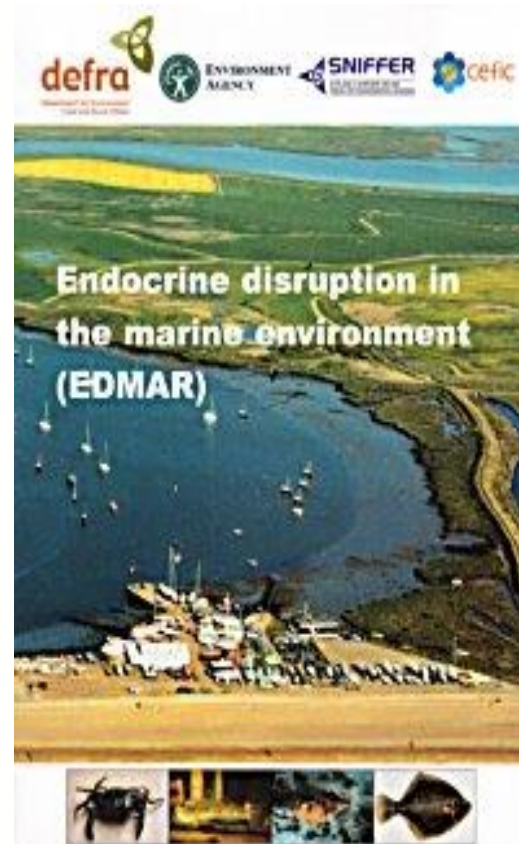
- **Reproductive failure prevents local recruitment;**
- **Populations can become composed of ageing males and masculinised females;**
- **Species lacking motile larval stage can become locally extinct;**
- **Widespread – extensively observed around UK and North Sea coastlines;**
- **Identified in 45 marine gastropod species worldwide.**

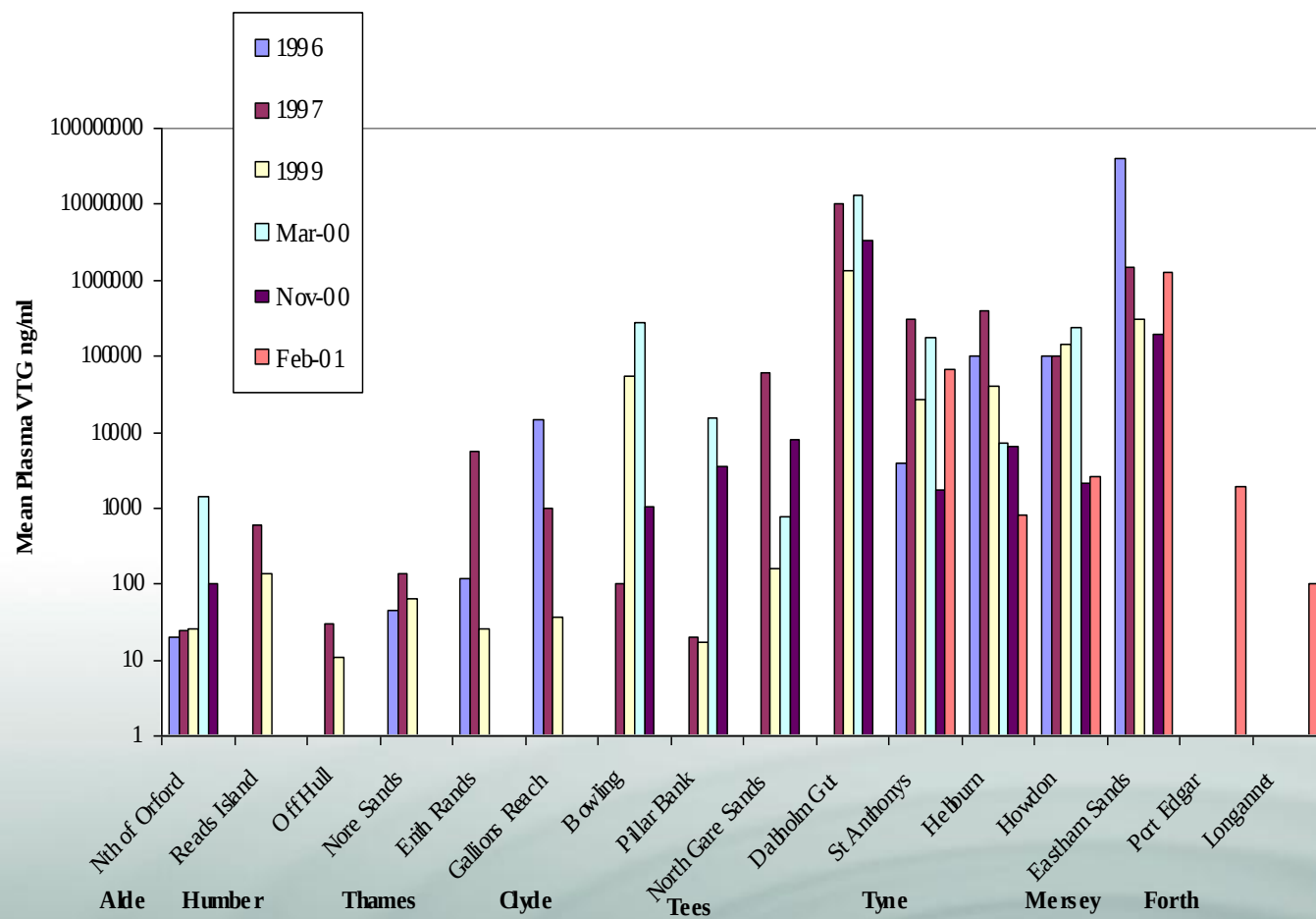
Causal substance

- **Tributyltin – a constituent part of molecules in a class of organotin compounds;**
- **Widely used as a constituent of marine anti-fouling paints.**



The Endocrine Disruption in the Marine Environment Programme (EDMAR)





EDMAR KEY RESULTS:

- **continued feminisation of flounder, but declining in some areas;**
- **feminisation in sand goby and blenny fish in some estuaries;**
- **slight feminisation of migratory salmon and trout, but not a problem;**
- **no evidence of effects on crabs and shrimps when exposed to chemicals causing feminisation in vertebrates.**

- research to address gaps in knowledge, in UK and with Japan;**
- chemicals strongly implicated as endocrine disrupters proposed for full risk assessment under European Regulations - e.g. nonylphenol, bisphenol-A, PDBE flame retardants.**

Community Strategy on EDCs* ***Short Term Actions -***

Focused on up-to-date scientific information on effects and on the extent to which EDCs were affecting people and wildlife;

establishment of a priority list of substances for further evaluation of their endocrine disrupting effects:

* http://ec.europa.eu/enviromnet/endocrine/index_en.htm

Priority List 2002- 2006:

- 575 substances investigated;
- 320 showed evidence or potential evidence for ED effects;
- 109 were not retained, either insufficient data on ED effects or insufficient scientific evidence;
- 147 excluded as double entries, mixtures or of doubtful relevance;
- majority with evidence for ED already covered by EU legislation.

Other Responses:

Legislation at global levels - TBT;

**UK Demonstration Programme –
evaluation of effectiveness of improved
wastewater treatment;**

**Development of test guidelines under
OECD auspices.**

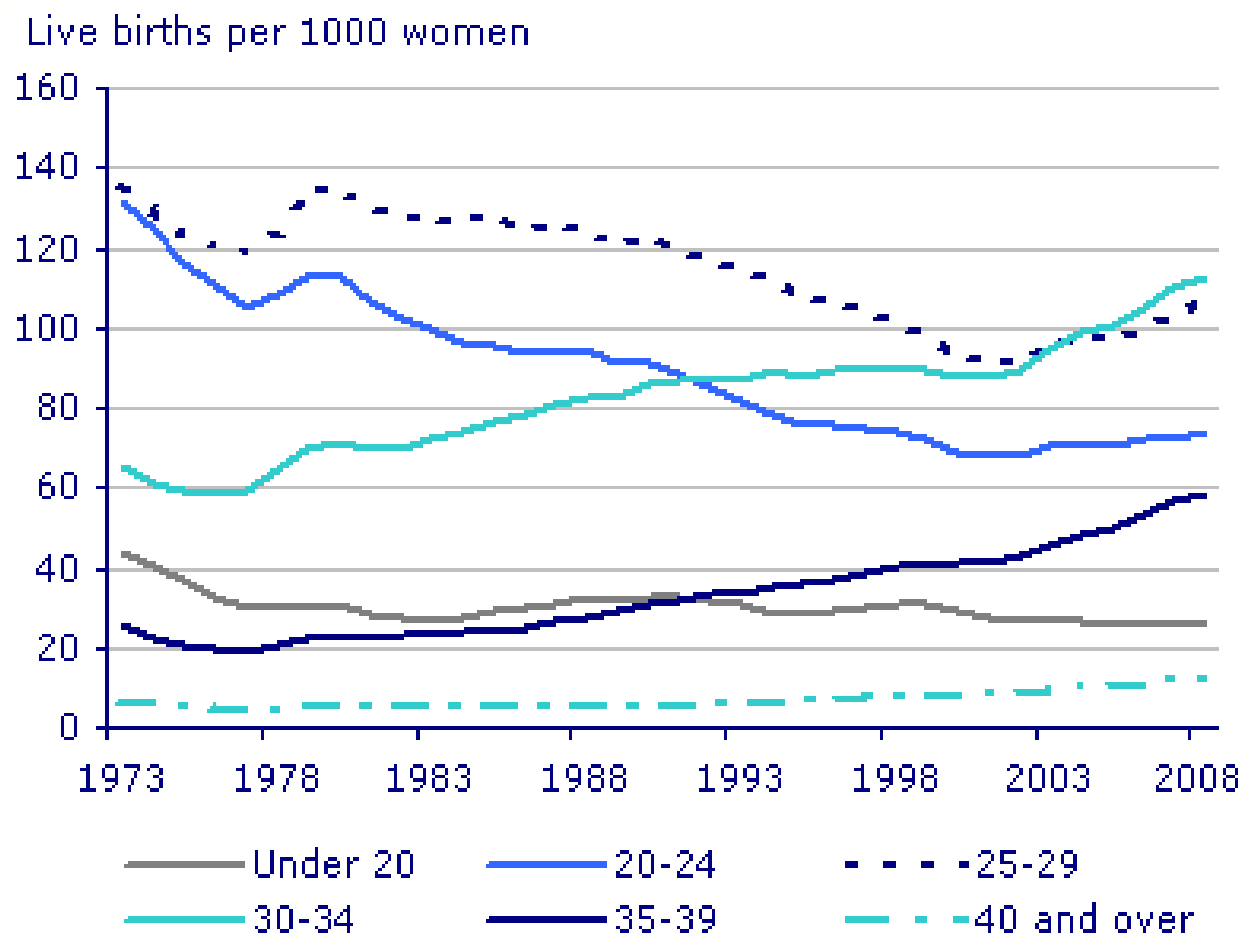
Miyamoto and Burger (2003):

‘... after substantial research ... no conclusive findings of low level environmental exposures to Endocrine Active Substances causing human disease’.

‘... global effects attributed to [endocrine disruption] not as all-pervading or fearsome as some have asserted, nor as trivial as others would wish’.

Miyamoto J and Burger J (2003) *Implications of Endocrine Active Substances for Humans and Wildlife: Executive Summary (SCOPE/IUPAC Project on Endocrine Active Substances Symposium 2002 Report)*, Pure Appl. Chem, Vol 75, xv-xxii.

UK Fertility Rates:



UK Office of National Statistics

Total Fertility Rate (TFR) in the UK reached 1.96 children per woman in 2008, the highest since 1973.

The UK TFR has increased each year since 2001, when it hit a record low of 1.63.

Fertility has been increasing in all four UK countries since 2002.

Demonstration Programme - improved treatment processes can reduce the risks from endocrine disrupting substances.



Roach breeding experiments show mildly intersex fish can breed as successfully as normal ones.

Enter the REACH Regulation:

**Registration, Evaluation, Authorisation and
Restriction of Chemical substances (EC 1907/2006);**

**Endocrine disrupting chemicals (EDCs) proposed for
authorisation as:**

- **carcinogens, mutagens, repro-toxins (CMRs); or**
- **persistent, bio-accumulative and toxic (PBTs); or**
- **very persistent and very bio-accumulative (vPvBs).**

Plant protection products (pesticides):

New Regulation to replace Directive 91/414/EEC in 2011: Move from risk to hazard-based authorisation.

- **EDCs which may cause adverse effects in humans excluded unless exposure negligible;**
- **Potential legal implications, endocrine disruption already in legal contexts in some Member States – new need for a definition.**

Outstanding Issues:

- development and implementation of a strategy for dealing with EDCs under REACH;
- review by 2013 under REACH with regard to the authorisation process as applied to EDCs;
- new research: e.g. anti-androgens, thyroid hormones, interpreting results of OECD test methods, new tests (molluscs);
- low-dose effects, bisphenol-A.

- Study by Danish EPA on children's simultaneous exposure to several EDCs and an expert workshop in Denmark in January 2009;**
- Recent 'state of the art' review by European Commission;**
- Conclusions adopted at Environment Council, December 2009 - need for further work to assess combination effects of individual chemicals.**

**‘As usual, far from closing
mysteries, science opens new
ones.’**

Human Recipes.

Matt Ridley in *Prospect*, July 2004

‘There is something fascinating about science. One gets such wholesale returns of conjecture from such a trifling investment of fact.’

Mark Twain *Life on the Mississippi*, 1883