HORMONE MIMICKING CHEMICALS

- *Are sperm counts falling?*
- *Could chemicals be to blame?*

Some synthetic and natural chemicals can mimic natural hormones, and there are questions whether there are sufficient amounts of such chemicals in the diet or the environment to cause adverse effects on human health (e.g. on sperm counts) or to affect wildlife.

This note looks at the scientific evidence on this subject and the policy issues arising.

POST **108**
TECHNICAL REPORT
January 1998

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HORMONES AND THEIR ROLE

Many functions of the body - from maintaining body heat, to growing and reproducing - are controlled by hormones acting within the **endocrine system**. For instance, the pituitary and other glands each secrete a number of hormones. Once released, the hormones travel to target cells in other organs, where they 'lock on' to receptors, triggering specific responses in the cell. Some examples of hormones and their effects are in **Table 1**.

Table 1 SOME HORMONES AND THEIR EFFECTS

Hormone	*Produced by*	*Role / Effect*
Oestradiol	ovaries	controls egg production
Testosterone	testes	controls sperm production
Adrenalin	adrenal glands	increases heart beat
Thyroxin	thyroid gland	controls metabolic rate
Human growth factor	pituitary gland	controls growth
Insulin	pancreas	controls blood sugar levels

Hormones are large and complex chemical molecules, but they still interact with their target cells in a relatively simple way, which it is possible for simpler chemicals to emulate or disrupt. The first such chemicals identified tended to interfere with oestrogen, and were called environmental oestrogens. However, it is now realised that this is just one example of a more general effect of endocrine disrupting chemicals (EDCs). These act in a number of ways, including:

- blocking the receptors so that the chemical message carried by the hormones cannot be delivered; or
- latching onto hormone receptors and causing a spurious response.

RESEARCH INTO EDCs

Research into hormone mimics can be traced back to 1938, when it was found that certain chemicals (substituted phenols) could work in a similar way to oestrogen. Much of the subsequent research focused on the potential pharmaceutical uses of synthetic oestrogen mimics, but by the late 1960s, evidence was emerging that low levels of certain chemicals in the environment could upset hormone balances in some species of marine organisms. In particular, the Plymouth Marine Laboratory found that female dog whelks had developed male characteristics - a condition known as 'imposex', especially in marinas contaminated with tributyl tin (TBT), used as an antifouling agent on boats. This led during the 1980s to restrictions on the use of such paints[1], but it also helped turn the spotlight on to other endocrine disrupting effects elsewhere.

During the early 1980s, scientists found an unusually high incidence of fish exhibiting both male and female reproductive organs (hermaphrodites) downstream of sewage works on the River Lea in Hertfordshire, and similar effects were observed in rivers in Florida, and in the American Great Lakes. Furthermore, a decline in the population of alligators in central Florida was associated, *inter alia*, with male alligators exhibiting levels of testosterone similar to those found in females. Observations like this suggested that environmental levels of certain chemicals were high enough to affect the reproductive systems of aquatic species, and led to further research on which chemicals might be responsible, their mechanisms of action, and whether they might also affect human reproductive health.

More recent findings were reviewed by the Medical Research Council's Institute for Environment and Health (IEH) in 1995. The IEH's report found that much of the work on human reproductive health had focused on sperm counts and quality, but research had also been carried out into the possible effects of EDCs on other biological functions, such as the development of the nervous system. In addition, there was a growing

1. Regulations introduced in 1987 banned the use of TBT antifouling paints on vessels less than 25m in length, under the Control of Pesticides Regulations 1986 (SI 1986/1510).

Table 2 POSSIBLE EFFECTS OF EDCS

Males	*Female*	*Wildlife*
Decreased sperm counts or quality	breast cancer	infertility
testicular cancer	cardiovascular effects	sex-changes (imposex)
undescended testes		developmental abnormalities
malformed penis		thyroid dysfunction
intelligence deficit	intelligence deficit	behavioural abnormalities
neurological problems	neurological problems	dysfunctional immune system

Source: IEH, WWF

Table 3 TRENDS IN SPERM COUNTS

Research Location	*Study location*	*Period Studied*	*Annual Trend*
Denmark	worldwide	1938-1990	0.8% fall
UK	Scotland	men born 1951-1973	1.7% fall
France	Paris	1973-1992	2.6% fall
USA	(re-analysis of Danish study)	1938-1990	1.5% fall (USA) 3.1% fall (Europe)
USA	Wisconsin	1978-1987	no change
USA	Seattle	1972-1993	no change
Finland	Finland	1968-1996	no change
USA	New York	1970-1994	0.6% rise

Source: IEH, NIH

literature on possible wider impacts on wildlife. **Table 2** outlines the main areas of concern, and we look at the evidence in each of these areas below.

Sperm Counts and Quality

Over the last 25 years, many studies have assessed trends in sperm counts and quality, but the results have been somewhat inconclusive (**Table 3**). Some show decreases in sperm counts, others have found little change, while some have even recorded a slight increase. Making sense of these results is difficult because the reasons for variations are not fully understood. For instance, earlier sperm counts may not have been as accurate as modern ones; most studies rely on volunteers from fertility clinics who may not be representative of the wider population (what statisticians call 'selection bias'); lifestyle factors (e.g. smoking, testicular temperature, age and ethnicity) may be confusing the picture; and sperm counts may fluctuate normally geographically, over time or in an individual.

Recent evidence in Table 3 however, supports the view that sperm counts may have fallen slightly. Thus the US National Academy of Sciences reanalysed the results from a 1992 Danish study, and agreed with its findings of a fall, while a US National Institutes of Health (NIH) survey found that sperm counts in the USA have declined by around 1.5% per year between 1938 and 1990. In the UK, work by the MRC Reproductive Biology Unit (RBU) looked at the quality of semen from 577 men in Scotland born between 1951 to 1973, and found decreasing sperm counts and concentrations, and decreasing numbers of motile sperm.

With the role of geographical variations and other factors still poorly understood, it would be premature to conclude that sperm counts are falling significantly in all men. Moreover, any such trends do not translate automatically to a decline in male fertility, as research suggests the quality of sperm (e.g. their motility and stamina) is very important. Research is underway to try and reduce remaining uncertainties over the real direction of trends, to examine the potential contribution of chemicals, and how far any trends are due to lifestyle aspects (e.g. diet, smoking and the effects of clothing). For instance, in the UK, the Department of Health (DH), the Health and Safety Executive (HSE), and the Department of the Environment, Transport and the Regions (DETR) are sponsoring research to investigate trends in male fertility across the country, and to look for evidence of any links with occupational and environmental exposures to suspected EDCs, and the influence of other factors such as lifestyle and diet. A clearer picture may emerge over the next 2-3 years.

Table 4 TRENDS IN TESTICULAR CANCER

Country	*Period Studied*	*% Change*	*Annual % Change*
USA	1935-1979	205%*	4.7%
Denmark	1945-1990	197%	4.4%
England and Wales	1979-1987	35%	4.4%

* for 25-34 year-olds

Source: IEH

Other Effects

Among other parts of the male reproductive system, the incidence of **testicular cancer** has certainly increased over the past 50 years - particularly among young white men in westernised countries (**Table 4**). There has also been some concern over the rates of congenital malformations of the penis and undescended testes, although questions over the quality of the data in the little research involved, makes it difficult to establish trends. There is however, evidence that cases of undescended testes carry a higher risk of testicular cancer.

Similarly, there is clear evidence that the incidence of **breast cancer** in women has been increasing steadily. Thus, breast cancer mortality in Finland rose from 25 per 100,000 in 1953 to more than 40 per 100,000 in 1980. In Denmark, the increase in cancer rate was from 40 per 100,000 in 1945 to about 60 per 100,000 in 1980. In the USA between 1973 and 1980, the incidence rose by 8% in women less than 50 years old, and by 32% in those 50 years old or more. Some of this is through improved detection, but the underlying real increase is estimated at around 1% each year since the 1940s. In the UK, between 1970 and 1989, breast cancer mortality rose by 13%, although it has now returned to 1970 levels due to improved screening and treatment (the current level is 50 deaths annually per 100,000 women).

Much work has gone into assessing the risk factors and underlying causes of breast cancer. One key factor is the woman's total lifetime exposure to reproductive

hormones, which is influenced by age at the onset of menstruation, first full-term pregnancy and menopause, as well as her use of oral contraceptives. Other key factors are diet and overall calorie and alcohol intake; family history of breast cancer; and any exposure to radiation. Because of the link with hormone exposure, a suggestion is that EDCs could play a role.

There has also been increasing concern over possible effects of EDCs on **non-reproductive systems** - e.g. the immune, neurological and other endocrine systems (Table 1). For instance, it is known that the thyroid gland secretes hormones that are essential in helping the brain and nerves to develop. There is thus the possibility that chemicals capable of mimicking the hormones involved might interfere with this process, with effects on neurological and behavioural development and possibly intelligence. Indeed a small number of studies have found a link between levels of PCBs in children's bodies and their intelligence - although it has not been established whether the effect was actually caused by PCBs, or if so, whether it was because the PCBs were acting as EDCs or via another mechanism.

In contrast to the somewhat limited evidence of trends in human reproductive health, field studies on wildlife and experiments on laboratory animals show clearer evidence of effects on reproductive systems as well as changes in other biological functions, such as depressed immune systems, thyroid dysfunction and abnormal behaviour. Principal examples are masculinisation in marine gastropods and feminisation of male fish. Similar effects have also been found in birds, with some male herring gulls showing signs of feminisation, thyroid dysfunction and abnormal behaviour.

POSSIBLE CHEMICAL MECHANISMS

The above analyses of trends, even if more conclusive in recent work, gives little **direct** clue as to cause. However, as understanding of the way our bodies develop under the continual influence of hormones improves, the potential mechanisms through which chemicals might exert various effects are becoming better understood.

The role of the key hormones is outlined in **Box 1** where, in the reproductive system for example, the influence of the balance between testosterone and oestradiol remains from the developing foetus into adulthood. Where chemicals are capable of shifting this balance, a number of consequences can be foreseen:

- Sperm production is influenced by the balance between testosterone produced by the testes and oestrogens, produced by its breakdown in the body. Consequently, chemicals capable of mimicking the function of oestrogens could inhibit the production (or reduce the quality) of sperm produced.
- Hormone receptors are also found in many different types of cells in the reproductive system, and the balance between hormones such as testosterone and oestrogen appears to help determine the number and function of these cells. EDCs disrupting this balance in a foetus or developing child could interfere with these processes, causing irreversible changes in masculinisation, sperm production and possibly cancer.

Recent research , however, points to oestrogens having a wider role in the body than just the reproductive system. For instance, a new type of oestrogen receptor has been discovered in many organs, including the heart, the vascular system and bones. With oestrogen acting at so many sites in the body, it has now been postulated that testosterone may act as a 'carrier' for a chemical message, and that it is converted to oestrogen in the target cells when the message is 'delivered'. For example, at the start of puberty in boys, testosterone levels in the body increase, but the message to start the pubertal growth 'spurt' is actually delivered via the conversion of testosterone to oestrogen in localised target cells at the ends of the bones. The signal for the bones to stop growing also comes from oestrogen converted locally from testosterone. Such insights into the

Box 1 HORMONES AND MAMMALIAN REPRODUCTION

The sex of a developing foetus is not determined until either a gene on the Y chromosome stimulates the development of testes or (in the absence of such a signal), the foetus continues to develop to form ovaries. Once formed, the testes secrete testosterone which stimulates the formation of the male reproductive tract. Spermatozoa formation within the testes is primarily regulated by two key hormones - testosterone and follicle stimulating hormone (FSH). In addition, Sertoli cells (which line the seminiferous tubules within the testes) produce various agents that regulate sperm formation. A key regulatory function of the Sertoli cells is to transform testosterone to an oestrogen (oestradiol) which, through a 'negative feedback' effect, controls the production of testosterone by inhibiting the production of the Sertoli and their associated Leydig cells. Because of the role of oestradiol in the function of these groups of cells in the developing male and its role in increasing the concentration of sperm, it has been htpothesised that exposure to EDCs from outside the body may reduce their numbers and function especially in early life, and also disrupt functions dependent on them, such as masculinisation and sperm-formation, or even lead to the proliferation of cell tissues - resulting in testicular cancers.

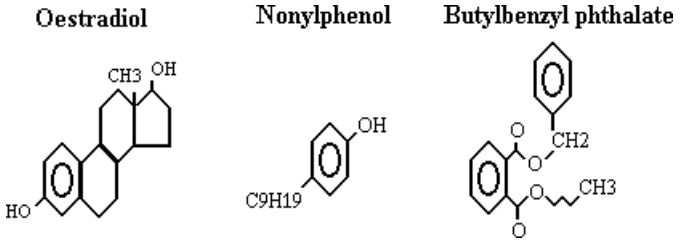
In females, oestradiol is the main oestrogen secreted by the ovaries during the menstrual cycle. It has important roles in maintaining the workings of the female reproductive tract, and is vital in the production of eggs (ova), increasing the ability of ova to move from the follicles to the uterus, and in helping fertilisation. In addition, oestradiol also stimulates the growth of breast ducts, and in adulthood is important for the maintenance of bone structure, by stimulating calcium deposition, and the health of the blood circulatory system. Abnormally high levels of oestrogen may thus affect the working of ovaries and fertility, and may lead to the proliferation of uterine and breast tissue leading to cancers.

Box 2 CHEMICAL CANDIDATES

There are essentially two ways of determining whether a chemical is an endocrine disrupter - either by carrying out tests *in vivo* (i.e. in whole, living organisms) or *in vitro* (i.e. on cells and tissues outside the body). While *in vitro* tests can determine whether a substance has the **potential** to be an EDC, *in vivo* tests are necessary to **confirm** the ability of a substance to disrupt an endocrine system. Internationally agreed and validated tests are not yet available.

Some EDCs have structural similarities to parts of the hormone molecules they are mimicking (see Figure), and thus it may be possible to infer whether a substance is likely to be an EDC by deriving general relationships between the structure of the chemical and its activity (so-called structure activity relationships, SARs). If clear SARs could be identified, it would be possible to screen many chemicals, without having to test them. However, while a factor in some cases, it is not the only one, and cannot yet give reliable predictions

Figure OESTROGEN AND SOME MIMICS



On current evidence, important groups of suspected EDCs are:

- **Natural and synthetic hormones** - Mammals excrete oestradiol and oestrogens and these, together with the breakdown products of oral contraceptives, may enter the environment via sewage effluents. In addition, synthetic growth-promoting hormones have also been detected in the environment.
- **Phyto-oestrogens** are naturally present in many foods (particularly in soyabeans, beans, peas, cabbage, spinach, and grains), but (in *in vitro* tests) are generally 500-1000 times less potent than the naturally-occurring 17beta-oestradiol. Some exhibit anti-oestrogenic properties.
- **Alkylphenol polyethoxylates (APEs)** are industrial non-ionic surfactants, used in detergents, paints, herbicides, pesticides, plastics and in textile and pulp and paper manufacturing.
- **Phthalates** are used extensively in industry, in plastic packaging, inks, paint and vinyl products. Some have oestrogenic properties, and they can leach out from plastic, paper and board packaging into foodstuffs.
- **Bisphenol-A** is used in the production of epoxy resins for lacquers to coat metal products such as food cans, bottle tops and water supply pipes, and polycarbonate plastics (often used in food packaging).
- **Organochlorine pesticides** such as DDT, dieldrin and lindane are no longer used in developed countries, but their residues can persist for a long time in biological tissues.
- **Polychlorinated biphenyls (PCBs)** had been widely used in industry since the 1930s, but their use has now ceased. They persist for a long time, and are now widely distributed throughout the environment.
- **Dioxins** which are formed during incineration and industrial processes that involve chlorine (e.g. paper manufacture).

subtleties of hormonal responses complicate rather than simplify the task of identifying the nature of EDCs' effects in humans.

The main types of chemical molecule which can mimic oestrogen or 'male' hormones (androgens) such as testosterone, and have other endocrine disrupting effects, are described in **Box 2**. The range of EDC candidates is wide. Some EDCs are found naturally in food (particularly vegetables - the so-called phyto-oestrogens), or food moulds. Clearly exposure to natural hormones, such as (synthetic) oestrogen in the contraceptive pill, provides a source of EDCs, and work has shown that sewage effluent discharges which cause feminisation of fish in some rivers contain women's excretions of natural and synthetic oestrogens as well as other possible EDCs such as detergents. The relative importance of these is still unclear, and it is also possible that oestrogen mimics may be formed from biochemical reactions within the sewage itself - e.g. through the metabolism of cholesterol by sewage bacteria.

Among the synthetic chemicals which have been highlighted to date are alkylphenol ethoxylates (APEs), PCBs, DDT, dioxins, phthalates and bisphenol A (Box 2). Some (e.g. nonylphenol - see figure in Box 2) have been shown to cause changes in aquatic species when present as environmental contaminants (e.g. in rivers receiving sewage effluent such as the River Aire in Yorkshire where effluent containing APEs comes from the wool-scouring industry). There is also concern that parallel effects could be occurring in humans through food contamination, traces in drinking water, etc., where phthalates and bisphenol A (used in packaging) could also be a factor.

As far as regulatory responses are concerned, some EDCs are already banned and phased out (e.g. DDT, PCBs) or subject to tight emission controls (e.g. dioxins) on the grounds of their toxicity and persistence in the environment. The position with the other chemicals in common use is less clearcut. Some precautionary measures have been taken in some countries (**Table 5**) - both regulatory and voluntary- but the main thrust is on the need for more research (see later). Meanwhile attention is turning to the question of how many other chemicals (of the many thousands in common use) could exhibit endocrine-disrupting properties.

NARROWING THE UNCERTAINTIES

As described above, some EDCs such as DDT have long been known to affect reproductive processes ever since their role in the decline of birds of prey during the 1950s

Table 5 EXAMPLES OF PRECAUTIONARY ACTION

Organisation	*Action*
Danish Ministry of the Environment	phasing out pesticides containing NP
Swiss government	banned all APEs
UK soap and detergent industry	recommended phase-out of APEs
UK speciality cleaning industry	recommended phase-out of APEs
UK food packaging industry	removed phthalates from plastics
Belgian toy retailers (and some UK firms)	removed phthalates from PVC
Danish cosmetics and soaps industry	removed all APEs
Italian Government	encouraging phase out of PVC in toys

Box 3 PRIORITIES FOR RESEARCH

In December 1996, an international workshop of experts on EDCs considered all major assessments (including IEH's 1995 review) and recommended:

- **Basic scientific requirements** - improving understanding of the endocrine and reproductive systems, and the detailed mechanisms of action, including the role of hormones at key stages of life cycles.
- **Human health investigations** - epidemiological studies on links between abnormalities and their effects on biological functions; investigations of maternal/offspring effects, and the role of other factors (e.g. diet, location, ethnic origin, etc.) on human reproductive health.
- **Ecological investigations** - epidemiological studies in different environments and geographical areas for reproductive effects, including surveys of reproductive and behavioural effects at different levels within ecosystems.
- **Improving test methods** - including enhancing routine test protocols, developing test systems and biomarkers, and identifying and using indicator species.
- **Risk models and risk assessment** - developing and maintaining a list of priority chemicals for study; enhancing risk assessment methodologies to cope with EDCs (especially those affecting reproductive systems); and establishing a

was first established. The case that some EDCs are capable of disrupting aquatic wildlife is also generally accepted as proven. There remains considerable uncertainty however over how extensive are the effects, how significant they are in ecological terms, and which chemicals are most important - as illustrated by the difficulty of disentangling the relative importance in sewage effluent of natural hormones (especially from pregnant women), synthetic hormones (e.g. from the contraceptive pill), industrial contaminants, and chemicals produced in the sewage treatment process itself.

Furthermore, the effects of some EDCs may be reversible and disappear once exposure has ceased or been sufficiently reduced. For instance, in the example of the Florida alligators cited earlier, the effects resulted initially from a chronic spillage of a pesticide (rather than a general increase in the background levels of EDCs) and once the spill was cleaned up, the effects in the alligators began to diminish (although the population remains low).

With people, the trends in some aspects of male and female reproductive health, together with biologically plausible theories of how EDCs in the environment could contribute to the observed changes, do not comprise proof of such a link in themselves. However, the firmer evidence for effects in wildlife leads the IEH to note that this "*increases the concern that a link may indeed exist*" between exposure and falling sperm counts etc. Reducing these uncertainties is the goal of the research aimed at targets outlined in **Box 3**.

Many of the chemicals involved are manufactured in different countries, used across the world and, in the case of persistent chemicals such as PCBs and DDT, can spread far beyond the point of manufacture or use to even the remotest parts of the planet. The question of EDCs is thus **increasingly seen as a global issue** and one that has to be tackled by international as well as national measures.

At the national level, the most substantial activities are underway in the USA. There:

- In 1996, Congress legislated to require the US Environmental Protection Agency (US EPA) to develop (before 2000) a screening programme to determine whether substances can mimic natural hormones, and to take appropriate action necessary to protect public health.
- The EPA has since established an Endocrine Disrupters Screening and Testing Advisory Committee (EDSTAC), which plans to decide which of the 80,000 commercial chemicals should be tested. So far, EDSTAC has proposed high-throughput screening,followed by a more detailed prioritisation, screening and testing programme in partnership with industry. So far, Congress has not appropriated any funds for the programme, and no cost estimates have been produced.
- The US NIH and other research centres are examining the levels of exposure in humans of 50 suspected EDCs (from the categories in Box 2).

In the UK, the main initiatives are:

- DETR has recently established an Interdepartmental Group on Endocrine Disrupters (IGED) to coordinate a publicly-funded research programme planned to total £5M. This and other Government action is outlined in **Box 4**.
- The Environment Agency is due to issue its strategy for dealing with EDCs in relation to water quality and impacts on aquatic species by end January 98.

At the European level,

- The chemical industry, through the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), is to research the mechanisms of endocrine disruption.
- The EC is preparing a strategy on EDCs that will

Box 4 UK GOVERNMENT ACTION ON EDCs

The Interdepartmental Group on Endocrine Disrupters (IGED) is focusing on coordinating research into:

Risk Assessment of Chemicals

- Of the 78 priority chemicals under the EU Existing Substances Directive, the UK is assessing the risks associated with 13 (including 2 EDCs nonylphenol and bisphenol A). Results will be available by mid-1998.

Prioritising and Testing

- IEH is identifying and prioritising sex hormone disrupting chemicals.
- DETR is taking part in OECD discussions on test methods.

Human Health Effects

- Research on exposure and effects of EDCs on male reproductive health (e.g. trends within the UK, and the role of lifestyle factors and chemical exposure) - DETR/DH/HSE.
- DH's Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) has reviewed the toxicity of phyto-oestrogens (e.g. soya-based infant formulae).
- MAFF research on phyto-oestrogens and possible EDCs in food and food packaging, guidance on phthalates in food.

Wildlife Effects

- DETR, MAFF, and the Scottish and Northern Ireland Offices are reviewing the inputs and fate of potential EDCs in the marine environment; and effects on wildlife.
- The Environment Agency is undertaking research in conjunction with the Natural Environment Research Council to examine the incidence of reproductive effects in aquatic species (particularly fish), and to investigate whether these are caused by discharges of EDCs to the environment.

Regulatory Action

- The Scottish Environmental Protection Agency (SEPA) is surveying specific industrial discharges and receiving waters to identify sources of EDCs, and has set an environmental quality standard (EQS) for nonylphenol.
- The Environment Agency is considering the significance of oestrogenic chemicals in sewage effluents and water courses.

Consultation

- The Government Panel on Sustainable Development is examining the issues and is expected to report by January 1998.

cover research needs, and how existing and new EU legislation may influence the use of EDCs in products and their release to the environment.

Internationally, :

- The Intergovernmental Forum on Chemical Safety (IFCS) between the USA and the EU has formed a joint Working Group to co-ordinate research.
- The North Sea Conference, Oslo and Paris Commissions and the UNECE have called for improved knowledge of the consequences of suspected EDCs in the marine environment.
- The G8 Environment Ministers pledged to cooperate in developing risk management or pollution prevention strategies for EDCs; and agreed to prepare an assessment of the science. These are being taken forward by IFCS and OECD.
- Unified test guidelines are being developed within the OECD.
- Environmental groups (chiefly WWF, Greenpeace and FoE) are undertaking their own research.

ISSUES

Regulating EDCs

With thousands of chemicals in everyday use, there is no single 'policy' on EDCs which can be appropriate for all, and it may be helpful to consider five broad groupings. These are:

- the 'old' EDCs such as PCBs and DDT, where regulatory action has already been taken;
- chemicals which are the centre of current debate over the level of restriction (NPE, phthalates etc.);
- the 'unknown' EDC properties of many other existing chemicals;
- new chemicals entering use where they may enter the environment or diet;
- 'natural' oestrogens such as the phyto-oestrogens (found in foodstuffs).

We discuss these in turn.

Already banned substances. There is little argument that substances such as DDT and PCBs should remain banned, and equally there is little more that can be done other than to wait for these substances to degrade in the environment and for the risks to fade slowly.

Chemicals where the potential for endocrine disruption is established. These provide the main focus for debate over what measures should be taken, but policy formulation is complicated by the scientific uncertainty over the degree of actual effects in humans and wildlife. Here (and similarly with existing untested chemicals) the debate is over where the **burden of proof** should lie for regulation and over the role of the **precautionary principle**[2].

Environmental and other groups argue that sufficient evidence already exists to justify phasing out some suspected EDCs (e.g. APEs and phthalates). They see the combination of animal test data[3] and suggestions of falling sperm counts as sufficient under the precautionary principle to take action. Furthermore, some (e.g. WWF) argue that where chemicals (both existing and new ones) enter the environment in significant quantities, a 'precautionary' approach should assume that chemicals are 'guilty' of endocrine disruption until proven 'innocent'. In view of their global use, there have also been calls for a world-wide convention to reduce and eliminate these chemicals.

2. Defined at the 1992 Earth Summit as "*Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.*"

3. For example, it has been found that pregnant rats exposed to octylphenol or octylphenol penta-ethoxylate produced offspring with testes significantly smaller, and with lower sperm counts than the control animals.

The chemical industry argues however that to take action without a sufficient body of scientific evidence would be premature and disproportionately expensive. The industry sees no definitive proof that EDCs are responsible for the observed trends in reproductive health in people, and that any effects of chemicals have yet to be disentangled from lifestyle, diet and other environmental factors. Moreover, alternatives may not work as well as the chemicals they are replacing. For instance, the CIA has pointed out that sales of nonylphenol (NP) in some sectors (such as detergents) did fall when the risks of endocrine disruption first became apparent. However, customers found that the alternatives did not work as well, and sales of NP have begun to increase again. Meanwhile, the use of NP has been increasing in some areas, such as in printing ink resins and in the oil industry. Controversy exists over whether difficulties in finding effective replacements for NP and other EDC candidate chemicals comprises an argument for regulatory caution (because of the potential disruption to industry) or early regulatory action (to speed up the search for replacements which are both safer and more efficacious).

The industry does accept however that steps to reduce risks (up to and including the phasing out of specific chemicals) will be necessary where a sufficient body of peer reviewed scientific evidence indicates that a precautionary approach should be used. The Government's view is that (at present) "*there are insufficient grounds for additional controls on chemicals, beyond those which already exist, based on current knowledge.*"[4] The current position is, therefore, that while some examples exist (Table 5) of where some precautionary action is being taken on EDCs internationally and nationally, there is no coordinated international **regulatory** action.

Third and fourth categories (the 'don't knows' and the new chemicals). Environmental groups remain concerned that many existing chemicals are as yet untested; and that many novel chemicals are produced each year which are not tested for endocrine-disrupting properties. Consequently, they have called on governments to require more testing of chemicals and for industry to provide more information about its releases of EDCs to the environment and their presence in products. Such calls reinforce measures flowing from the Agenda 21 document signed at the 1992 'Earth Summit' at Rio de Janeiro which required governments to draw up inventories of chemicals produced and released in their countries.

These inventories are being discussed internationally within the OECD which is producing guidance on compiling what are termed 'Pollutant Release and Transfer Registers'. These PRTRs are being developed in the EU through the recently-introduced Integrated Pollution Prevention and Control (IPPC) regime, which requires an EU-wide Polluting Emissions Register (PER) to be compiled (expected to be complete shortly after 2000). UK Environment Agencies have maintained Chemical Release Inventories (CRIs) since 1990, and these will have to be incorporated into the EU PER. To date, however, the CRIs have not included specific mention EDCs, and **questions remain over whether they, or the PER will do so (when reliable tests become available)**.

Policies and regulatory controls on chemicals have evolved considerably over the years as scientific knowledge of particular hazards has increased. Thus the early tests for explosivity or flammability and lethal toxicity have already been extended to screen for non-lethal toxicity and the potential to cause cancer or mutations. One could thus see concerns over endocrine disruption as just the latest potential hazard it is necessary to consider, and allow the regulatory system to evolve accordingly to incorporate appropriate testing procedures. This suggests a middle way between the environmental groups' calls for the 'precautionary' banning or phasing-out of many chemicals without robust and comprehensive testing for endocrine disruption, and the *status quo* where chemicals are allowed onto the market without being tested for these effects.

One obstacle to allowing existing systems to evolve in this way is, however, that while existing regulations specify tests for 'reproductive effects', some non-reproductive (e.g. behavioural) effects remain outside the regulatory regime, and amendments to national and international regulations would be needed to require such testing. Another barrier is that, as discussed earlier, there are as yet no internationally agreed definitions of (or test protocols for) endocrine disruption , although OECD is working to produce these within the next few years. Action now depends on testing existing and new chemicals against end-points that merely **indicate** a broad range of endocrine disrupting effects. This is the approach taken by IEH, which is compiling a database to assist the DETR to produce a list of priority chemicals based on *in vitro* screening tests, after which more definitive tests will be applied. **While uncertainties remain over what tests to use and the significance of the results, substantial barriers remain to adapting the existing regulatory system to accomodate non-reproductive effects of EDCs**.

Natural phyto-oestrogens. These include foods such as soya where there is no evidence of adverse effects in populations which have traditionally eaten large quantities of soya (e.g. Japan and China). However, these societies have traditionally had high-soya diets so may

4. DETR submission to the Government Panel on Sustainable Development, May 1997.

well have built up resistance to any adverse effects which could affect those (such as in the West) unused to large intakes. In the UK, DH has recommended that the 1% of babies who are fed soya-based infant formula on medical advice should continue to be so fed, but other cases require medical advice. At the same time, manufacturers of soya-based formula are considering ways to reduce phyto-oestrogen levels.

On the positive side, it has been alleged that phyto-oestrogens can alleviate menopausal symptoms in post-menopausal women, and such claimed benefits are being used increasingly in marketing some foods and food supplements aimed at older women - e.g. a bread with added soya flour and linseeds (both higher in phyto-oestrogens). As with vitamin B6 (POSTnote 107), this raises the question of whether such functional foods should fall under food or medicines law.

Research Needs

As described above, there is already considerable activity (particularly in the USA) looking at screening a large number of potential chemical candidates. There are, however, substantial problems still to be overcome, since the range of chemicals with demonstrated effects in the laboratory so far does not suggest a single simple way of predicting a chemical's ED effects 'from scratch'. Some EDCs have been surmised to operate by having parts which are similar in shape to the hormone 'key' which can fit the target cell receptor 'lock', and some progress is being made on predicting which chemical structures will do this, but understanding of these 'structure-activity relationships (SARs)' is still insufficient to dispense with the need for a battery of tests to evaluate a chemical's real activity.

Another complication arises from the suggestion that EDCs do not exhibit the simple 'dose-response' relationship of traditional toxins where, the greater the dose, the greater the toxic effect. Thus some EDCs (e.g. bisphenol-A and the bioflavonoids in food) may cause little endocrine disruption at low and high doses, but significant effects at moderate doses. In addition, the timing of exposure to an EDC may be as important as the dose received; especially at critical stages of development, such as before or soon after birth, and around puberty. Thus exposure of trout to oestrogens can cause feminisation, but only 10 days either side of egg-hatching. Similarly, there is as yet no single agreed definition of 'endocrine disruption', and hence, of the many different kinds of reproductive, behavioural and neurological effects that could be observed, none has yet emerged as being a key indicator that identifies a substance as an EDC.

Some indication of the difficulties facing screening programmes comes from recent experience where widely-publicised results from a 1996 study showed that various combinations of chemicals could produce much greater *in vitro* effects than would be expected from the sum of each individual chemical's effect (a so-called 'synergistic effect'). Since then, however, other researchers have not been able to reproduce the observations, and the original researchers took the uncommon step of withdrawing the findings from the scientific literature, leaving open the question of whether EDCs can act in synergy. Despite this, concern remains that effects of EDCs may be additive and that where mixtures are concerned some means is needed to measure the total effect as well as that of that of individual chemicals. Current screening and testing methods do not allow such assessments to be made.

With these substantial areas of uncertainty still existing, some are concerned that until a clear consensus emerges on the definition of EDC, the test designs and their significance, the type of 'crash' programme being considered in the USA may be an ineffective use of public funds and lead to results which are open to much dispute over their validity and significance. There is thus support for the staged strategy described earlier where research is focused on making progress (in the areas in Box 3) on defining the basic science of endocrine disruption, whether there is a problem and developing robust test methods **before** considering a blanket screening programme. Clearly, however, the US Congress was sufficiently convinced of the need to take some action for it to legislate for such a screening programme, that also requires the EPA to take the necessary actions to protect public health from EDCs, and there remains pressure to mount similar action in the UK and EU.

Irrespective of the pace of future research etc., the question whether adequate coordination is taking place is an important one. Extensive arrangements are already underway internationally, at a European level and nationally, but there is a danger that, should the US programme gain significant momentum before the OECD has developed robust tests, then some of the US screening tests could become the *de facto* standards within the OECD. If these are not properly validated, this could lead to inappropriate testing, and inaccurate or misleading identification of some chemicals as EDCs.

Chemicals policies across the EU are being revised, and in the UK a consultation paper on chemicals policy is expected by Autumn 1998. One option may be, therefore, for **the forthcoming consultation paper to address these questions and include specific policies on the role of the precautionary principle and the production, use, release and monitoring of EDCs in products and the environment**.