THE ROYAL SOCIETY

Endocrine disrupting chemicals (EDCs)

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Contents

Summary

1 Environmental pollution has been the source of much public discussion and media attention. Endocrine disrupting chemicals (EDCs) have caused particular concern because they may interfere with the normal function of the hormonal systems of humans and animals. Endocrine disrupting properties are found in several classes of chemicals released into the environment such as some insecticides and fungicides, some phthalate plasticizers, dioxins and anti-fouling paints. Speculation has linked exposure to EDCs to a range of effects in humans and animals, from falling sperm counts and increases in testicular cancer to feminisation of fish, all of which has fuelled public concern.

2 The Royal Society convened a Working Group, chaired by Professor Patrick Bateson (Vice-President and Biological Secretary), to consider the scientific evidence for a number of reproductive and developmental irregularities in humans and animals that have been associated with EDCs. The group examined the evidence and the useful future areas of research that would help address the current lack of knowledge. In addition the difficulties of carrying out risk assessment of EDCs were discussed. Finally, the current legislation governing EDCs was reviewed. The report emphasises the difficulties of making generalised assumptions based on isolated experiments and the problems of developing policy in areas in which scientific understanding is still being developed.

3 Humans are exposed daily to chemicals that have been shown, or suggested, to have hormone-disrupting properties. Speculation has linked this to a range of disorders. Whilst high levels of exposure to some EDCs could theoretically increase the risk of such disorders, no direct evidence is available at present. Trends in the incidence of some of these disorders are difficult to discern and, when they are found, are difficult to interpret because of inconsistencies in method. EDCs are but one of a variety of potential risk factors, both environmental and genetic. Despite the uncertainty, it is prudent to minimise exposure of humans, especially pregnant women, to EDCs.

4 With regard to EDCs in the environment, firm assessment of the risk to humans is not possible because of a lack of relevant data about the effects of EDC exposure. On the basis of limited animal data, identified environmental EDCs appear to pose minimal risk to humans on their own, but the risk from mixtures of compounds is unknown. In order to improve our understanding of the relationships of EDCs to health and disease further investigation is needed.

5 Despite the lack of information on the effect on humans of EDCs in the environment, strong evidence links EDC exposure to effects on some organisms in the environment, most notably the effect of tributyl tin on molluscs. The action of EDCs has resulted in the localised destruction of certain species and is a cause for grave concern. The case of intersex (having the characteristics of both sexes) fish in the UK has highlighted that a wide range of chemicals in the environment may exert an effect. Isolating any one chemical of concern is particularly difficult.

6 Increased effort should be focused on the identification of potential EDCs and the assessment of the risk posed by individual chemicals or by combinations of chemicals, supported by vigorous epidemiological studies. Further research in this area must provide evidence on the following key issues:

- the chemicals with endocrine disrupting properties
- the interaction between chemicals
- the longevity and action of these chemicals in the environment
- the levels of exposure of humans and wildlife to these chemicals
- the levels at which the chemicals are likely to cause adverse effects

7 Many regulations govern the use, manufacture and disposal of all chemicals, with specific regulations for chemicals such as pesticides. In the UK, such regulations are the responsibility of a number of different government departments. While the issue of EDCs is confused by serious gaps in our knowledge, policies to deal with the current concerns must be developed. Regulations cannot be 'put on hold' until all the evidence has been collected. Development of policies and regulations must go hand in hand with ongoing research and any legislation must be able to adapt rapidly to advances in scientific knowledge. Above all, there must be a co-ordination of both research funding and policy development between the different bodies responsible.

8 Many questions about EDCs cannot be answered yet. Continued research, with the results made openly available, is essential if the uncertainties are to be properly addressed and the risks understood. Even though new evidence will affect government policy on EDCs, policy makers must appreciate that the concerns of the public already have some foundation.

Endocrine Disrupting Chemicals (EDCs)

The following statement was prepared by a working group chaired by Professor Patrick Bateson FRS (Biological Secretary and Vice-President, Royal Society). The other members were Professor Ray Baker FRS (BBSRC); Professor Eric Keverne FRS (Sub Department of Animal Behaviour, University of Cambridge); Professor Anne McLaren FRS (Wellcome/CRC Institute, University of Cambridge); Professor Tom Meade FRS (MRC Epidemiology and Medical Care Unit); Dr Richard Sharpe (MRC Human Reproductive Sciences Unit); Professor John Sumpter (Department of Biological Science, Brunel University); Ms Sarah Wright (Secretary); Dr Rebecca Bowden (Secretary). [It has been endorsed by the Council of the Royal Society.]

Introduction

There has been recent public concern over the potential adverse effects of environmental pollutants, including those termed endocrine disrupting chemicals (EDCs). The subject has also been the focus of much media attention. EDCs are substances which may interfere with normal function of the endocrine (hormone) system of humans and animals, since many of them mimic the structure of natural hormones produced in the body e.g. oestrogens, androgens.

Although much research has already been carried out on the possible effects of EDCs (see Appendix 1 for some examples of recent/ongoing research) there is still a need for further basic research, in addition to research designed to inform policy decisions in this area. The list of possible EDCs and their effects is extensive and this statement aims only to highlight a few examples of concerns which have been raised. Strong claims have been made about the possible adverse effects of EDCs on growth, reproduction and development in both humans and animals. Each example given in this statement highlights the complexity of the issues involved and the difficulties of interpretation of data. The statement is intended for consideration by policy advisors as well as for general readership. It considers the scientific evidence available, identifies areas in which further research is needed and advises on how such concerns may best be addressed by policy makers.

There are many extensive reviews and reports on the subject of EDCs which cover the subject in much greater detail than this statement. In particular, the recent report by the National Academy of Sciences [Ref 1], a special edition of the Journal of Pure and Applied Chemistry published by the IUPAC [Ref 2], a report by the Parliamentary Office of Science and Technology [Ref 3], the IEH report [Ref 23], and the DETR 'Government Interdepartmental Group on Endocrine Disrupters - Report of activities between November 1995 and May 1999 [Ref 24].

Outline

This document addresses existing scientific evidence for a number of reproductive and developmental irregularities in humans which have been associated with EDCs (Section 1) and for two well studied examples of inter-sexuality in wildlife (Section 2). Section 3 highlights the difficulties of carrying out risk assessments for EDCs and Section 4 summarises the current legislation. Section 5 recommends further areas of research.

Particular attention is drawn to the difficulties of making generalised assumptions based on isolated experiments and the resultant difficulty of developing policy in areas in which scientific understanding is still being developed.

Recommendations for future research

- Many UK Government Departments and Research Councils have an interest in research on Endocrine Disruptive Chemicals. A meeting of these bodies to consider pooling of resources and division of labour should be encouraged.

- Co-operation between the United States and Europe should be expanded so that the time-consuming process of analysis may be accelerated.

- The Government's recently established Sustainable Development Commission should take into account the possible effects of endocrine disrupting chemicals released into the environment when considering the wider issues of sustainable development.

- Many regulations govern the use, manufacture and disposal of all chemicals, with specific regulations for chemicals such as pesticides. In the UK, such regulations are the responsibility of a number of different government departments. Co-ordination between them is crucial.

- While the issue of EDCs is confused by serious gaps in knowledge, policies to deal with the current concerns must be developed. Regulations cannot be 'put on hold' until all the evidence has been collected. Development of policies and regulations must go hand in hand with ongoing research and any legislation must be able to adapt rapidly to advances in scientific knowledge.

- Continued research, with the results made openly available, is essential if the uncertainties are to be properly addressed and the risks understood. Even though new evidence will affect government policy on EDCs, policy makers must appreciate that the concerns of the public already have some foundation.

1 Human reproductive and developmental disorders

Humans are exposed daily to environmental chemicals which have potential endocrine disrupting activity (see Appendix 2 for some examples) [Ref 7], raising concerns, provided that the level of exposure is sufficient, that such chemicals might be linked with phenomena such as declining sperm counts in the adult male, testicular cancer, breast cancer, age at puberty, etc. The ability to interfere with the normal function of the endocrine system is found in several classes of environmental chemicals e.g. DDT, the fungicide vinclozolin, some phthalate plasticizers, dioxins, alkylphenolic and bisphenolic compounds. Whilst there is currently no direct evidence to support an association between exposure to EDCs and any reproductive effects in humans, few if any, studies have attempted to look for such evidence. The following examples of areas of concern highlight the difficulties in designing studies to produce data which will contribute to our wider understanding of the action of EDCs on humans. Without such data, there are obvious difficulties in formulating policy on all aspects of human exposure to EDCs.

1.1 Human Sperm Counts

A possible decline in human sperm counts has recently become an issue of concern and has received much media coverage. There are many causes of infertility in men and although sperm count does not equate by any means precisely with fertility, it is recognised that men with very low sperm counts often have fertility problems. There has been some speculation that a decrease in sperm count may be a direct result of increasing human exposure to EDCs.[Ref 15]

Sperm counts may vary considerably between different individuals within a population, and also from sample to sample in the same man. There are also likely to be differences between different populations. Such differences make selection of individuals for study very difficult. Numerous studies of sperm counts have been published in recent years and although some of these indicate that counts have declined in some countries, others suggest that no change has occurred [Ref 4; Ref5; Ref 19]. One of the possible explanations for these differences and for consequent uncertainty about whether sperm counts are declining is that all of the published studies on sperm counts have 'design' flaws, for the reasons given below.

In order to obtain definitive data on possible long-term trends in sperm counts, it is necessary to carry out monitoring over a considerable period of time. In addition the methods used to establish sperm count must be standardised so that different studies can be compared reliably. Comparison of several studies may identify global trends, but it is impossible without standardisation. The World Health Organisation addresses the issue of methodology in its Guidelines on sperm counts [Ref 16], however there may be differences in interpretation of these. Lack of effective standardisation of methodology makes interpretation of the available data at present very uncertain, so the evidence for declining sperm count is currently inconclusive.

Another difficulty in the design of effective studies on sperm count is that males born today will not have measurable sperm counts for another 20 years or more. Any cause which acted early on in development to subsequently decrease sperm counts in adulthood, would therefore be difficult to identify at a later date. As there are valid (but unproven) concerns for such a possibility, it is cautious and reasonable to consider the possibility that sperm count may have fallen despite a lack of conclusive evidence at the present time.

Although data from sperm count studies are not ideal, there is evidence that suggests that there has been a decrease in sperm count related to year of birth, (average decrease of 2-3% for each later year of birth). Other disorders of male reproduction (Section 1.4) show a similar correlation. This may be because the disorders are inter-linked and form a 'syndrome', or because the disorders have the same cause, though at present such relationships remain speculative.

In light of the lack of conclusive evidence of any trend in sperm counts, or association of a trend with exposure to EDCs, we recommend that further research is carried out, bearing in mind the following points:

- Future studies on sperm counts should endeavour to establish firm data for sperm counts now and then monitor changes in sperm counts prospectively over a period of time using standardised methodology. In order to make comparisons of studies a possibility, they need to use rigorously standardised methods and recruitment of study groups representative of all relevant age groups (preferably using random samples) and allow for differences such as ethnic group, socioeconomic group, or abstinence which are known to affect sperm counts. Co-ordination of studies in different centres and countries would give additional statistical power and enable global trends to be monitored. Such studies will be time consuming and it is important not to discount available data from earlier studies, even if their method was not standardised. Studies of sperm counts using rigorously standardised methods of subject recruitment and semen analysis are underway in Europe and affiliated studies have also commenced in the USA and Japan.

- Further investigation of the potential relationships between low sperm counts and other male reproductive disorders (see section 1.2) is warranted.

- There is a need for conclusive data on trends in sperm counts before any cause of possible trends can be evaluated. If EDCs are thought to affect sperm count it may be possible to establish sperm counts for people known to have been exposed to different levels of EDCs over the same period of time but there are many difficulties with this approach.

The example of the possible effect of EDCs on human sperm counts highlights a situation in which it is extremely difficult to compare data from studies conducted in different places at different times because of difficulties with experimental design. In addition, many factors may interact to influence sperm count, it is therefore difficult to identify any one cause of an observed effect. It is not possible, based on present evidence, either to refute or confirm the possibility of a connection between human exposure to EDCs and the disputed fall in sperm counts.

1.2 Testicular cancer and other male reproductive disorders

Testicular germ cell cancer is the commonest cancer of young men in most countries in the Western World and its incidence is increasing world-wide [Ref 15]. Information on testicular cancer incidence is based on cancer registry data, for which diagnosis and reporting have always been reasonably accurate and is therefore fairly reliable (although there are some concerns regarding the reliability of detection). It is unlikely that possible changes in death certification and cancer registration practices could explain why incidence rates have increased. Further, because of its occurrence in young men, the incidence rate has not been affected by increases in life expectancy. In general, incidence rates have tended to double almost every 30 years since the 1930s. Mortality from testicular cancer has also increased, but has declined dramatically since the 1970s, with the availability of effective treatment. As with human sperm counts, there has been speculation that observed trends might be linked in some way to human exposure to EDCs [Ref 7 & Ref15].

The epidemiology of testicular cancer has been extensively reviewed by Swerdlow (1997) [Ref 6] who found that there were considerable differences in the incidence of testicular cancer between countries (highest recorded rates are in Denmark, UK, Switzerland & Germany, with the lowest incidence in Finland,

Estonia & Japan). Differences in incidence may result from a number of interacting factors, both environmental and genetic. In many countries the increase in incidence of testicular cancer can be related in some way to year of birth, e.g. In Finland, a man born in 1965 has 10 times the overall likelihood of developing testicular cancer than a man born in 1905 (similar calculations are possible for other countries). This relationship with year of birth echoes some of the data on sperm counts (Section 1.1). It is well established that men with testicular cancer have poor semen quality and are less fertile than normal men, even prior to the development of cancer. However, there is not necessarily a link between increased incidence of testicular cancer and possible trends towards decrease in sperm counts.

Information available to date indicates that testicular germ cell cancers arise from pre-cancerous, malignant gonocytes (fetal germ cells) that develop abnormally in the testis of the male fetus whilst it is in the womb. This indicates that there may be a link with other male reproductive disorders arising during early fetal growth.

Normal masculinisation of the male fetus and the development of an appropriate male reproductive system and genitalia are all critically dependent on the production (by the fetal testis) and action of hormones. The most important of the testicular hormones are the sex steroids that are classified as androgens (e.g. testosterone). It is established that disorders of development of the male in which androgen production or action are abnormal are associated with a substantial increase in risk of developing testicular germ cell cancer (see below). There is also more limited, and less convincing, evidence that exposure of the male fetus to high levels of oestrogens may increase the risk of developing testicular cancer [Ref 15; Ref 19]. As evidence from animal studies suggests that high oestrogen exposure can reduce testosterone production and action in the fetus, it is likely that any effect of oestrogen exposure on testicular cancer risk is attributable to altered androgen production/action. Other than poor semen quality, the main risk factors for testicular cancer are disorders of reproductive development. In general, the more severe the disorder, the greater the risk of developing testicular cancer [Ref15; Ref19]. The clearest factor associated with the development of testicular cancer is failure of testicular descent into the scrotum (cryptorchidism). This common disorder confers a 4-fold greater risk of testicular cancer. What the most important risk factors for testicular cancer have in common is that they are associated with disorders of androgen production or action. Both cryptorchidism and hypospadias (an abnormality of development of the penis) occur in male infants in whom androgen production or action is abnormally low. Similarly, both conditions can be induced in animals by exposing the mother during pregnancy to chemicals which can block androgen action (i.e. are anti-androgenic). There is some indication that the incidence of cryptorchidism and hypospadias is increasing in some countries, but there are no conclusive data at present since diagnostic methods vary and incidence is not always reported.

Accepting the limitations of current data, reasonably strong evidence suggests that the incidence of cryptorchidism and hypospadias may show similar differences between countries to the incidence of testicular cancer (and may also be related to sperm counts). Such similarities have been interpreted as possible evidence that these disorders may constitute a 'syndrome'. If this is the case, cryptorchidism and hypospadias may provide early warning of a change in incidence of this 'syndrome', and thus of the future incidence of testicular cancer, as both disorders are usually diagnosed at birth. More data are required regarding the possible existence of such a syndrome before any possible causes can be investigated. In view of the serious concerns raised by such a possibility, there is an urgent need for standardisation of diagnostic methods and reporting requirements in order to gather accurate data.

How far exogenous (external) sources of EDCs contribute to the hormone levels in the fetus by comparison with endogenous (internal) oestrogen and androgen production is unclear, as it is recognised that oestrogen production during normal human pregnancy reaches extremely high levels. Against this background, the limited information available suggests that intake of exogenous oestrogenic compounds would contribute little to the total oestrogen exposure of the fetus and would thus pose little, if any risk to the developing reproductive system. However, the hormonal environment of the developing fetus is protected from endogenous steroids by conjugation to binding proteins produced by the mother and the placenta [Ref 21]. Little is known about the effects of EDCs on these proteins, or the extent to which they bind. It is therefore not possible to exclude the possibility that some chemicals, because of their particular properties, could more readily gain access to, or accumulate in, the fetus in amounts sufficient to cause effects.

In light of the concern over increased incidence of testicular cancer, and possible increased incidence of other disorders of the male reproductive system, we recommend that further research be carried out, bearing in mind the following points:

- Increased effort should be made to identify environmental chemicals with anti-androgenic activity and to evaluate their effects in animal studies.
- Human exposure to all EDCs (especially during pregnancy), and their release to the environment should be minimised on grounds of prudence.
- The incidence of human male (and female -see section 1.3) reproductive disorders should continue to be considered independently of consideration of exposure to EDCs. Both issues have a number of uncertainties and large data gaps. Though the nature of the male reproductive disorders implicates abnormalities of sex steroid production or action, causes other than environmental endocrine disrupters must be considered.
- Urgent efforts should be made to obtain accurate data regarding the possible existence of a syndrome of which sperm count, testicular cancer, and other reproductive disorders are symptoms.

1.3 Breast cancer

Breast cancer is one of the commonest cancers among women throughout the world, and is a particular problem in developed countries. Limited data are available regarding the increasing incidence of breast cancer from the 1920s to the 1960s but what is available indicates an increase in incidence. Considerably more information is available from studies in several countries started in the 1960s. In the UK, the USA, Norway, Hungary, the former Yugoslavia, Columbia, Singapore and Japan, data show increased incidence in all age groups studied (increased incidence may reflect an increase in detection rate rather than in

actual incidence) [Ref 8; Ref 22]. Only in India has this trend not been observed. The increase in incidence was accompanied by increased mortality in older women in some countries, but was offset by stable or falling mortality in younger women. As a result of the link between breast cancer and hormone activity it has been proposed that there may be a link with exposure of humans to EDCs [Ref 17; Ref 9].

Risk factors for breast cancer include increasing age, family history, early menarche (age of first menstruation), late age at first birth, nulliparity (bearing no children), late age at menopause, height, post-menopausal weight, high levels of ionising radiation and a history of benign breast disease. Reasonably clear evidence suggests that high oestrogen levels are also associated with the risk of developing breast cancer [Ref 9]. Oral contraceptives and perhaps also post-menopausal hormone replacement therapy (HRT, i.e. prescribed oestrogens), may also have an effect. There is also evidence of a dietary effect on oestrogen production (high fat diets; alcohol intake).

Recent attention has been paid to the possible role of phyto-oestrogens in breast cancer. Phyto-oestrogens are a diverse, biologically active group of compounds chemically similar to oestrogens. They are found in many edible plants (see section 3). Phyto-oestrogens have potentially anti-carcinogenic properties and growing evidence suggests that high intakes are associated with quite substantial reductions in the risk of breast cancer [Ref 10].

Breast cancer also occurs in men but there is much less information on this topic. Incidence and mortality are certainly much lower than in women but this may reflect no more than the amount of breast tissue that might be affected as well as hormonal influences.

Whether environmental oestrogens (also known as xeno-oestrogens), or EDCs in general, increase breast cancer risk and have thus contributed to the gradual and persistent rise in breast cancer incidence is a very controversial area. Although numerous studies have been published to determine whether environmental oestrogens may be involved the results are inconclusive. It is not possible, based on present evidence, to either refute or confirm the possibility of a connection between human exposure to endocrine disrupting chemicals and incidence of breast cancer. The example of breast cancer highlights a disorder which is likely to have very many causes, both genetic and environmental, possibly acting together to produce an effect. With such a variety of possible causes it is difficult to design studies to investigate any one possible cause.

1.4 Secular trends in growth and puberty in children

Growth is the result of a complex interaction of genetic, constitutional, nutritional, endocrine and socio-economic factors as well as psychosocial well-being (Ref 11; Ref 12). Over the last century, children have become progressively taller, and similar, but relatively smaller, increases in final adult height have occurred over the same time period. In addition, the age of puberty has shown similar time trends. For example, in the middle of the 19th century the age of first menstruation (menarche) in European girls averaged 16-17 years, whereas today the average is 13 years or less.
Sex steroids, including both androgens and oestrogens, have been used widely as growth promoters in farm animals and poultry since the1950s, and though this practice has been banned for some time in the EU it is still used widely in North America. This practice and related experimental studies have established that low levels of sex steroids promote growth in farm animals whereas high levels inhibit growth. This is similar to the 'growth spurt' which occurs in children at puberty (rising, but low, levels of sex hormones at the start of puberty trigger an increase in growth; attainment of higher (adult) levels of hormones results in cessation of growth later in puberty). This growth spurt is probably due to stimulation of growth hormone secretion from the pituitary gland. Similar effects may underlie the growth-stimulating effects of sex steroids in immature farm animals. Although oestrogens can promote growth they also alter skeletal maturation which effectively terminates vertical growth (height). This dichotomy makes it difficult to deduce the role, if any, of exogenous oestrogen exposure in altering growth in childhood and final height.

In laboratory animals, advancement of puberty in the immature female can be induced by exposure of the animal to both natural and synthetic oestrogens and similar changes can be triggered by administration of high doses of certain environmental oestrogens and by phyto-oestrogens [Ref 15]. These effects can be induced independently of any effect on growth though it is likely that, at low oestrogen doses, growth promoting effects may also be involved.

The possible ability of sex steroids, especially oestrogens, to advance maturation/puberty and to stimulate growth in laboratory and farm animals has raised the question of whether exposure to environmental oestrogens, or EDCs, could have caused the similar changes in humans over the past century or so. No clear evidence is available on this issue [Ref 18] and many other factors have been implicated [Ref 13]**.** Historical evidence (e.g. fossils) suggests that there may be fluctuations in height of populations rather than simply a steady increase. Such changes are most easily attributable to changes in diet/nutrition-levels (especially early in development) and there are good modern data to support this view based on studies of communities in which nutrition is sub-optimal or of individuals in which nutrition/energy balance is subnormal (eg. anorexic children or children involved in intense physical training).

Emerging evidence suggests that the trends in age at puberty, and final height, are slowing or stopping in some areas of the world (particularly developed countries), except in poorer sections of the community where they are continuing. Again, observed differences are most easily accounted for by differences in nutrition and are difficult to link to a more general exposure to EDCs. From current evidence it therefore seems most likely that trends in age at puberty and growth rates in children can be explained by nutritional changes rather than by exposure to EDCs. However, there have been no direct studies that address whether or not human exposure to EDCs, in particular those used for growth promotion in livestock [Ref 18], might have contributed in some measure to growth changes in children, so it is not possible to completely exclude such a possibility.

2. Effects of EDCs released into the environment

2.1 Imposex in molluscs induced by tributyl tin (TBT)

Imposex, a type of inter-sexuality (in which females develop male sexual organs), in molluscs is the only well-documented

example to date of an identified EDC causing abundant, undisputed, and world-wide population-level effects in wildlife. Marine anti-fouling paints (designed to prevent growth of crustaceans such as barnacles) containing various organotin compounds were first introduced in the mid-1960s, and rapidly became very widely used on marine boats of all sizes because of their effectiveness. Quite soon thereafter, in 1970, the presence of a sexual abnormality in a mollusc, in this case dog whelks in Plymouth Sound, was first reported. This was quickly followed by reports of similar penis-bearing female snails along the Connecticut (USA) coast. Subsequent research has shown that an irreversible condition, usually called imposex, can occur in many species of molluscs exposed to TBT (tributyl tin), although its severity is species specific. In some species this disrupts the still present female reproductive system, preventing egg laying; hence, such females are effectively sterilised.

Imposex in molluscs was first linked to pollution in 1981, when it was shown that the incidence of the condition was highest close to marinas. At the same time, laboratory experiments confirmed that exposure to TBT led to the imposex condition. It is now known that the problems associated with TBT occur world-wide; problems have been reported in the UK, New Zealand, Japan, and Alaska.

Effects have not been limited only to small areas around harbours and marinas, but have, for example, also been documented offshore in the middle of the North Sea in the shipping lanes. Over 100 species of molluscs are known to have been adversely affected by TBT, and in at least some cases it has been shown that imposex has led to population declines and sometimes total disappearance of species due to its adverse effect on ability to reproduce.

Although the precise details of exactly how TBT causes imposex are not entirely clear, the mechanism undoubtedly involves endocrine disruption. It is established that TBT causes imposex in molluscs by interfering with the biosynthesis of sex steroid hormones, rather than by mimicking the action of androgens (such as testosterone) at the androgen receptor. Two hypotheses have been proposed to account for the action of TBT on steroid biosynthesis. One proposes that TBT inhibits aromatase (the enzyme that converts androgens to oestrogens), and the other that TBT inhibits the excretion of androgens by blocking their conjugation (a process that precedes their excretion). Considerably more evidence supports the former hypothesis than the latter, although both would lead to elevated androgen concentrations, and hence to masculinization of the females.

The example of the "TBT story" shows that the effects of TBT were completely unexpected and unpredicted, despite legislation governing new chemicals; nobody foresaw that TBT would cause endocrine disruption in molluscs. Based on what is known presently of the chemical structure of TBT its affect on sex steroid biosynthesis is not a result of its mimicking of the natural sex steroids and therefore it could not be predicted from chemical structure data alone that it would be an EDC. Instead, the effects were first discovered by accident by field biologists. This suggests that, until our understanding of how, and what, chemicals cause endocrine disruption improves very considerably, it is likely that other unexpected cases of endocrine disruption in wildlife will become apparent. This example also highlights the difficulty of predicting what effects a chemical will have in the wider environment where it may mix with other chemicals, get degraded, or come into contact with a variety of species of animals and plants.

2.2 Endocrine disruption in British fish

One of the most thoroughly studied, but still not completely understood, examples of endocrine disruption in wildlife concerns that of fish in British rivers. The story began nearly 20 years ago, with the chance discovery of a small proportion (5%) of grossly intersex (part male, part female) roach living in the settlement lagoons of two sewage treatment works (STWs) in the UK. An explanation put forward at the time was that powerful synthetic oestrogens, entering the STWs in the waste water from a local pharmaceutical company, were "feminising" some of the male fish. After a research programme dispelled most concerns about the possibility that such powerful oestrogens could be present at significant concentrations in potable (drinkable) water originating from the river receiving effluent from these two STWs, a research programme on the possible implications for fisheries of the presence of oestrogens in effluents was initiated.

Using fish held in cages, it was soon shown that the effluents of these two STWs did indeed simulate oestrogenic effects in male fish. A nation-wide survey followed, which showed that essentially all STW effluents were oestrogenic to fish and, therefore, whatever chemical, or mixture of chemicals, was causing the effects, it was ubiquitous. This discovery changed the thinking about the causative agent(s), and the focus shifted to widely-used, man-made chemicals. One possibility was nonylphenol, a chemical originating from the breakdown of a group of surfactants (these are the active constituents of detergents), which was known to be very widely present in the aquatic environment, and known to be a weak oestrogen mimic.

Some oestrogenic effluents were analysed to identify the causative agent(s). This showed that most of the oestrogenic activity in STW effluents did not come from man-made 'false' oestrogens, such as nonylphenol, but instead was contributed by natural oestrogens, such as oestradiol, and the synthetic oestrogen ethinyl oestradiol, which is the main active ingredient of the contraceptive pill. These oestrogens were all present at extremely low concentrations (parts per trillion), but subsequent laboratory tests in which fish were exposed to such low concentrations showed that they did cause oestrogenic effects. Thus, it appears that natural and synthetic oestrogens excreted by people are primarily responsible for the oestrogenic effects observed in fish.

Studies on wild populations of freshwater fish have shown that intersex fish are present in most rivers. In some of the poorer quality rivers, which receive large inputs of effluent from STWs, all of the male fish were intersex to varying degrees. Interestingly, the rivers containing the most severely affected fish also received significant inputs of industrial effluent, and hence it has not been possible to completely exclude a contribution from industrial chemicals in at least some cases of intersexualtiy in fish. This possibility is supported by the results of very recent research on a marine flatfish, the flounder. Flounders caught from estuaries around the UK often show some signs of exposure to oestrogenic chemicals, but the most pronounced effects, which included intersexuality in males, were found in flounders caught in estuaries such as the Mersey which receive

large amounts of industrial (as well as domestic) effluent.

The consequences of intersexuality in fish are unknown. Intuition would suggest that it would adversely affect the ability to reproduce, as it does with molluscs. However, these possible consequences of intersexuality induced by exposure to oestrogenic chemicals have yet to be demonstrated.

This example illustrates that even when a clear effect is demonstrated it is not necessarily easy to identify a single cause. It is likely that many chemicals in the environment, possibly interacting with one another, cause this condition in fish. It also highlights problems that may occur when there is a preconceived 'cause'; without thorough and meticulous testing it would have been easy to assume that the cause of the symptoms was primarily industrial chemical pollutants rather than oestrogens excreted by humans.

3. Risk assessment of EDCs

In order to develop policy and legislation to protect humans and the environment from EDCs it is first necessary to determine the risk of harm to human health and the environment. Assessment of the risk to man from EDCs is based on studies in experimental animals coupled with measurement of the hormonal potency of the chemicals of concern (hazard assessment) and, in limited cases, knowledge of the level of exposure of humans to the chemical in question. Risk assessment is particularly important for chemicals with unknown effects in those exposed, particularly if they may take a long time to occur (such as cancer, which can take 20 years or more after exposure to occur).

It is preferable to establish the likely effects of EDCs on organisms in the environment in order to prevent damage, rather than to wait until the damage has occurred and then try to establish the cause. Where such evaluation has been carried out, the results are generally reassuring for the limited numbers of endocrine disrupting chemicals that have been studied. Most identified environmental endocrine disrupters have relatively weak hormonal activity which means that human exposure would need to occur at high levels for any individual chemical to cause disruption of the endogenous androgen:oestrogen balance in the body. In most instances human exposure to such levels would be unlikely, based on present understanding. However, this presupposes that the EDCs can be considered just from the perspective of their estimated hormonal activity as measured in the laboratory. Other potentially important properties of individual EDCs need to be considered, such as their ability to accumulate in the body or to alter the production or metabolism of endogenous sex steroids (which have far greater potency). In this regard, the lesson learnt from tributyltin should not be forgotten.

In reality, humans are exposed not to a single endocrine disrupter but to a 'cocktail' of such chemicals, and the possibility that such chemicals have additive or reinforcing effects (e.g. combination of an oestrogenic with an anti-androgenic compound) has to be considered seriously. Using standard animal tests (acute toxicity tests) to evaluate these effects would be an extremely complex task with many potential problems. Alternative, indirect, approaches based on epidemiological studies of predicted effects in humans, or in wildlife, may therefore have to be developed.

Many other important factors must be taken into account when assessing the risk to humans from EDCs. Chemicals with oestrogenic activity are produced naturally by many plants (phytoestrogens) and fungi (mycoestrogens), and these can form important components of the diet. Soya and flax are the richest sources of phytoestrogens but many other plants (e.g. beans, hops, lupins) contain lower levels of similar compounds. In some species of animals (e.g. sheep), ingestion of phytoestrogens can cause serious reproductive or other disorders [Ref 14; Ref 20], though other (mainly indirect and inconclusive) evidence for humans suggests that such exposures may be beneficial in protecting against breast and prostate cancer and against heart disease.

Endogenous oestrogens also play an important positive role in humans, in maintaining bone strength, and bowel, cardiovascular and cognitive function, although such effects are poorly understood at present. Viewed in this context, it could be argued that some exposure to environmental, man-made chemicals with oestrogenic activity could be potentially beneficial rather than potentially harmful. Whether exposure to an environmental oestrogen exerts a beneficial or an adverse effect, or is without any effect, will depend on the level of exposure, the timing of exposure (fetal/infant life versus adulthood) and on the duration of exposure. Until further information is available, it is premature to make recommendations as to what is, and what is not, an acceptable level of exposure to an EDC or a phytoestrogen or what is a safe/beneficial or harmful level of these compounds in food or cosmetics.

4. Are EDCs regulated?

Although the issue of EDCs is confused by a lack of concrete data and many gaps in our knowledge, it is still necessary to develop policies to deal with the current concerns. Regulations cannot wait until all the data are available. Development of policies and regulations must go hand in hand with ongoing research and any legislation must be adaptable to rapid advances in scientific knowledge. At present there are a multitude of regulations covering the use, manufacture and disposal of all chemicals, but there is no legislation specific for EDCs. There is no regulatory definition of an EDC and no definitive list of all EDCs.

The use of chemicals and their release into the environment is controlled in the EC by a complex set of regulations. These originate as Directives agreed by Member States that are translated into National Law for the purposes of regulation. A large number of directives control the use and disposal of chemicals . In every case, new chemicals have to be tested before they are placed on the market. The types of test are specified and they have to be carried out according to Good Laboratory Practice regulations, which ensure that they are conducted as planned and reported fully. Once the required tests have been completed, the manufacturer has to notify the Government in the country in which the chemical is to be used. The purpose of the notification is to identify the hazards and ensure that they are clearly recorded on the label, thereby giving the user the information necessary for the safe use of the chemical. Also, the environmental hazard is identified and the distribution of the chemical after use is assessed.

Specific regulations are in place for chemicals with particular uses (e.g. pesticides, food additives, veterinary medicines and others - see Appendix 3). In these cases, the use is well defined and exposure can be predicted with a certain degree of accuracy. As a result, it is easier to define a level of exposure that will not cause undue risk. The use of pesticides is specified with precision, to protect the farm operators using the plant protection products and the consumer exposed to residues in the produce.

The discharge of chemicals into the environment from manufacturing facilities is also controlled by EC Directives which specify the approach to prevention and control of pollution. These regulations are also based on risk assessment, relying on both experimental data and estimates of exposure. Any data from observations or measurement of concentrations in the environment are used in preference to predictions. The level of discharge at which there will be no effect on the environment is then established and the regulations ensure that these standards are met.

Based on the reports of adverse effects of TBT on many mollusc populations, the use of organotin anti-fouling paints has been restricted. Legislation was first introduced in 1982 in France, banning the use of these paints on boats less than 25m in length. Similar legislation followed throughout Europe, North America, Australia, and Japan from 1987 onwards. However, use of organotin - containing antifoulants is still permitted on larger vessels (these are primarily naval and commercial), and hence contamination will still be occurring in ports where these large ships dock or are maintained, and in the shipping lanes. Pressure to ban completely organotin-based anti-fouling paints has, however, remained, and it seems likely that a world-wide ban on all uses of such paints will be agreed in the near future. The limited restrictions presently in place do appear to have led to the partial recovery of some populations of affected molluscs, but in other areas (of high boating activity), mollusc populations have continued to decline or even become extinct.

The EC Directives, implemented through National legislation, are designed to be flexible so that any toxic hazard (for example the potential to induce cancer, reproductive effects or toxic effects on the skin or the eye) can be dealt with. Once the hazard has been characterised and estimates or measurements of the likely environmental concentrations or human exposure have been carried out, the standard methods of chemical risk assessment are capable of providing assurance that the use and disposal of chemicals can be carried out safely. The chemical and biological issues surrounding EDCs are in general similar to those of other environmental chemicals and there is no obvious reason to treat them differently for regulatory purposes.

At the moment, the toxicological testing methods used for human health hazard characterisation are considered to require little modification in order to identify endocrine toxicity. An important exception is the detection of EDC-induced abnormalities of sexual differentiation/reproductive development where cause and consequence may be separated by a considerable period of time; such effects may not be detected reliably by currently used toxicity tests and modifications to the tests to remedy this deficiency have been broadly agreed to be necessary. However, if the current Directives controlling the use and disposal of chemicals had been working well, alarm over the potential adverse effects of EDCs might not have been raised. The current Directives failed to identify TBT as an EDC, and failed to identify several other chemicals of concern (e.g. the main metabolites of the fungicide Vinclozolin are anti-androgenic; the main degradation product of the insecticide DDT, namely p'-DDE, is anti-androgenic). Further, there are presently no guidelines on testing pharmaceuticals for environmental impact, despite the fact that these chemicals are designed to be extremely potent and to degrade slowly (and will therefore inevitably end up in the environment).

It seems that new tests which will detect the endocrine-disrupting activities of chemicals are necessary. Some additional screening methods are in the process of being evaluated by the Organisation for Economic Co-operation and Development (OECD) for their ability to identify EDCs whilst minimising the use of experimental animals. International co-operation through the Chemicals Division of the OECD has the advantage that results are acceptable to all OECD countries for the purposes of risk assessment.

Although most attention has been paid to synthetic chemicals in considering the potential impact on the environment and human health, natural chemicals are also significant sources of EDCs. Whilst environmental exposure may not be possible to control, it may be necessary to consider future legislation for specific aspects such as levels in food.

5. What further research is needed?

To date, essentially all research on EDCs has been driven by effects (or purported effects) many of which have caused public concern and made sensationalist stories in the media. Thus, for example, the possible decrease in sperm counts was very influential in highlighting the human issues, while intersex fish helped to highlight the wildlife aspects of the EDC issue. This is an extremely slow (and costly) way of going about things; when an effect is observed, research is then carried out to determine the cause. Because our understanding of the environment is very incomplete, there will always be a role for approaching many issues in this way. However, it would be more logical to start with a chemical, and make an assessment of what effects, if any, it will induce. This is the aim of toxicity testing. Sometimes the tests do not tell us what we would like to know and require further development.

The problem with starting with the chemical is that there are over 80,000 man-made (let alone natural) chemicals in everyday use. In turn, these will degrade in the environment to even more chemicals. Our knowledge of degradation processes (in the environment, but also within humans and wildlife) is often very poor, and hence it is inevitable that, once in a while, a chemical, or its degradation products, will be associated with some adverse effects or other in one, or more, organisms.

The USA is to screen a very large number of chemicals (probably 15,000!) through a tier of assays for ED activity. This program, termed the Endocrine Disrupter Screening programme (EDSP), has recently begun and will generate an immense amount of data. The Environmental Protection Agency (EPA) has been focusing on the development, standardisation and validation of screens and tests. The core elements of the tiered approach

include initial sorting, priority setting, tier One Screening, and tier two testing. Tier two testing is expected to follow tier one testing in 2004. The programme will undoubtedly detect endocrine activity, of various sorts, in many chemicals. The difficulty will be in interpreting these data, relating results to the development of policies for future research on EDCs, and subsequently developing legislation to protect human health and the environment.

EDCs have the potential to impede progress towards sustainable development by their effects, for example, on water supply and biodiversity. The report of the UK Round Table on Sustainable Development (April 2000) noted that other European countries have gone further in introducing economic instruments for sustainable development than the UK. A standing advisory body is needed to develop such instruments for sustainable development, taking into account the possible effects of endocrine disrupters released into the environment.

Future research on EDCs needs to address the following key issues:

- Identification of chemicals that have endocrine disrupting properties.
- Examination of interaction between chemicals that do not have endocrine disruptive effects individually, but might in combination.
- Examination of the length of time for which these chemicals persist in the environment.
- Analysis of the breakdown products of the chemicals.
- Determination of the levels of exposure of humans and wildlife to these chemicals and the levels at which they are likely to cause adverse effects.
- Standardisation of methods and recruitment of study groups in sperm count studies, allowing for known differences such as ethnic group, socio-economic group, abstinence, or year of birth.

These are the key questions and must be addressed before complex, internationally harmonised regulation can be attempted, otherwise the legislation will be unable to adapt to rapid increases in knowledge.

References

1. National Research Council. *Hormonally Active Agents in the Environment.* Washington DC: National Academy Press. July 1999.

2. IUPAC. Natural and Anthropogenic Environmental Oestrogens – the scientific basis for risk assessment. *Pure and Applied Chemistry* 1998;**70(9):**1617–1865.

3. POST. Hormone mimicking chemicals. *POST Technical Report* 1998;**108**.

4. Irvine DS. Declining sperm quality: a review of facts and hypotheses. *Bailliere's Clin Obstet Gynaecol* 1997;**11**:655–671.

5. Swan SH, Elkin EP, Fenster L. Have sperm densities declined? A re-analysis of global trend data. *Environ Health Perspect* 1997;**105**:1228–1232.

6. Swerdlow AJ. Epidemiology of testicular cancer. In: *Principles and Practice of Genitourinary Oncology*. Ed: Raghavan D *et al.* Philadelphia: Lippincott-Raven. 1997.

7. Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 1993;**341**:1392–1395.

8. Ursin G, Bernstein L, Pike MC. Breast cancer. In: *Trends in Cancer Incidence and Mortality.* Ed: Doll R *et al*. Cold Spring Harbor Laboratory Press. 1994.

9. Key TJ, Verkasalo PK. Endogenous hormones and the aetiology of breast cancer. *Breast Cancer Research* 1999, Vol 1, No. 1. 18-21.

10. Ingram D, Sanders K, Kloybab M, Lopez D. Case-control study of phyto-oestrogens and breast cancer. *Lancet* 1997;**350**:990–992.

11. Tanner JM. *Growth at Adolescence*. 2nd ed. Oxford: Blackwell Scientific. 1962.

12. Mascie-Taylor CGN. Biosocial influences on stature. *Journal of Biosocial Science* 1991;**23**:113–28.

13. Bateson P, Martin P. *Design for life*. London: CAPE. 1999.

14. Adams NR. Clover phyto-oestrogens in sheep in Western Australia. *Pure and Appl Chem* 1998;**70(9):**1855–1862.

15. Toppari J, Larsen JC, Christiansen P, *et al.* Male reproductive health and environmental xenoestrogens. *Environmental Health Perspectives* 1996;**104 (S4)**:741–803.

16. World Health Organisation. WHO laboratory manual for the examination of human semen and cervical mucus interaction. 4th ed. Cambridge: Cambridge University Press. 1999.

17. Miller WR, Sharpe RM. Review: Environmental oestrogens and human reproductive cancers. *Endocrine Related Cancer* 1998;**5**:69–96.

18. Andersson AM, Skakkebaek NE. Exposure to exogenous estrogens in food: possible impact on human development and health. *European Journal of Endocrinology* 1999;**140**:477–485.

19. Sharpe RM. Environmental oestrogens and male fertility. *Pure and Appl Chem* 1998; **70**:1685–170.

20. Kaldas RS, Hughes CJJr. Reproductive and general metabolic effects of phytoestrogens in mammals. *Reproductive Toxicology* 1989;**3**:81–89.

21. Johnson M and Everitt B. Essential Reproduction, 4th ed. Oxford: Blackwell. 1996.

22. Levi F, Lucchine F, La Vecchia C, Negri E. Trends in mortality from cancer in the European Union, 1955–94. *Lancet* 1999;**354**:742–744.

23. IEH. *Assessment on Environmental Oestrogens: Consequences for Human Health and Wildlife*. (Assessment 1). Leicester: Institute for Environment and Health. 1995.

24. DETR Government Interdepartmental group on Endocrine Disrupters –Report on activities between November 1995 and May 1999. London: DETR. 1999.

Appendix 1

List of Recent Government Research Related to Endocrine Disrupters

It should be emphasised that the following list is not intended to be complete, it presents some of the many recent research activities on endocrine disrupters. A more complete list of government research related to endocrine disrupters can be found in the DETR report Government Interdepartmental Group on Endocrine Disrupters- Report of activities between November 1995 and May 1999.

Table 1: Environmental Exposure

Title of project	Funding Body	Start/end date	Contractors
Priority Chemicals/ Exposure	DETR	Jun 1997 -	Institute for Environment and Health
Impact of oestrogenic substances on natural fish populations, including salmonids.	NERC	Oct 1995 - Mar 2000	IFE
Environmental fate and persistence of oestrogenic chemicals.	NERC	Apr 1995 - Mar 2000	IH
Community Programme of Research on Environmental Hormones and Endocrine Disrupters (COMPREHEND)	NERC, EC	Jan 1999 - Dec 2001	IFE Windermere

Table 2: Exposure From Diet

Title of project	Funding Body	Start/end date	Contractors
The National Surveillance Scheme (NSS) for residues of veterinary medicines in meat.	MAFF-VMD: Industry cost	Rolling programme	Various contractors
Chemical contaminants in human milk: A pilot study towards establishing an archive of samples from the UK	MAFF/ DH/ DETR/ HSE	Late 1999 for 18 months	University of Leeds
Survey of chemical migration from can coatings into food and beverages	MAFF	Feb 1998 - Jan 2000	Pira International
Measuring the Bioavailability of Human Dietary Intake of Dioxin-Like Compounds	MAFF	Oct 1998 – Sep 2000	Birmingham University
Study of the effects of dioxins and PCBs in river sediment, deposited on pasture by flooding, on concentrations in cows' milk	MAFF	Aug 1998 – Mar 2000	Central Science Laboratory

Table 3: Methods and Analytical Methodology

Title of project	Funding Body	Start/end date	Contractors
Synthesis of labelled and unlabelled isoflavonoid phytoestrogen standards.	MAFF	May 1996 – Apr 2000	St Andrews University
Development and application of screening assays for the beneficial/adverse effects of phytoestrogens in food.	MAFF	Apr 1997 – Mar	Veterinary Laboratories Agency, Weybridge
Identification and quantification of dietary lignans by liquid chromatography and mass spectrometry	MAFF	Apr 1999 - Mar 2001	Veterinary Laboratories Agency, Weybridge

Table 4: Ecotoxicology

Title of project	Funding Body	Start/end date	Contractors
Review of endocrine disrupting effects in invertebrates. Phase 2.	EA + others	start 1998/99	To be appointed
The oestrogenic potencies of combinations of environmental chemicals.	BBSRC	Oct 1996 – Oct 1999	Royal Free Hospital School of Medicine

Table 5: Aquatic - Marine

Title of project	Funding Body	Start/end date	Contractors
Endocrine Disruption in the Marine Environment (EDMAR).	DETR, EA, MAFF, SNIFFER, CEFIC/ EMSG	Jun 1998 – Mar 2001	CEFAS, PERC Plymouth University, CMCS Liverpool University, Zeneca, SEPA/FRS Aberdeen
Altered sex ratios in plaice in Scottish coastal waters.	SEPA	–	–
Metabolism of marine biotoxins by fish cells and whole animals and evaluation of the toxicity of their metabolites-2.	BBSRC	Apr 1998 - Apr 2001	Dept of Biological Sciences, University of Dundee.
Survey of imposex in the North Sea	DETR	Aug 1998 – Jul 1999	FRS Marine Laboratory, Aberdeen
Early life stage exposure to environmental oestrogens in relation to reproductive and developmental ecology of models and commercially important species	NERC	Oct 1998 - Sep 2001	Marine Biological Association
Metabolism of marine biotoxins by fish cells and whole animals and evaluation of the toxicity of their metabolites -2.	BBSRC	Apr 1998 – Apr 2001	Dept of Biological Sciences, University of Dundee.
Testing leach rates of booster biocides	HSE	–	–
The fate of TBT in spoil and feasibility of remediation to eliminate environmental impact.	MAFF	1999	CEFAS, Burnham; Environment Agency

Table 6: Aquatic - Freshwater

Title of project	Funding Body	Start/end date	Contractors
Identification of oestrogenic effects in wild fish- phase 2:Causes and consequences of intersex and other oestrogenic effects.	EA, NERC, DETR	1996/1997 - 1999/2000	Brunel University, EA Fisheries Laboratory Brampton
Fate and behaviour of oestrogenic steroids in UK rivers - phase 1.	EA, NERC	1997 – 1999	Institute of Hydrology
Reproductive capabilities of wild intersex fish	NERC, EA, DETR	Aug 1998 – Aug 2001	Brunel University, EA National Fish Farm Calverton UK
Assessment of the physiological impact of endocrine disrupters on salmonid fish from sites in Scotland and Northern Ireland.	SNIFFER, EA, IFE, NERC	Sep 1998 – Mar 2000	IFE Windermere Laboratory, Queens University Belfast

Table 7: Human Health - Metabolism

Title of project	Funding Body	Start/end date	Contractors
Male reproductive health: Historically perspective cohort study on Scottish Male Reproductive Health.	DETR, DoH, HSE, CEFIC/ EMSG	Apr 1998 – Apr 2001	MRC Reproductive Biology Unit, Edinburgh
Male reproductive health: Environmental risk factors for hypospadias - a population based control study in 3 health regions.	DETR, DoH, HSE, CEFIC/ EMSG	Apr 1998 – Apr 2001	Imperial College, London
Male reproductive health: An assessment and analysis of existing surveillance data on hypospadias in UK and Europe.	DETR, DoH, HSE, CEFIC/ EMSG	Apr 98 – Oct 1999	London School of Hygiene and Tropical Medicine
Effects of oestrogens on development of the testis and fertility.	MRC	Sep 93- 2000	MRC Reproductive Biology Unit, Edinburgh
Identification of the mechanisms by which environmental oestrogens and ICI 182780 cause rapid vasodilation.	BBSRC	Jan 1998 - Sep 2001	King's College London
Occupational hazards to male reproductive capacity	HSE	Jun 1995 - Nov 1999	Imperial School of Medicine
The geographical epidemiology of testicular cancer, prostate cancer and cryptorchidism.	DETR, DH, HSE, SO, WO	Mar 1998 - Sep 1999	SAHSU

Table 8: Human Health - Phytoestrogen Studies

Title of project	Funding Body	Start/end date	Contractors
Effects of phytoestrogens on hormonal status of women.	MRC	Apr 95-Mar 2000	Dunn Human Nutrition Unit
Possible effects of dietary phytoestrogens on prostate cancer and 5-alpha reductase activity.	MAFF	Jun 1998 – May 2001	Department of Public Health Sciences, University of Edinburgh
Absorption and metabolism of dietary phytoestrogens in humans - effect of age, gender, food matrix and chemical composition.	MAFF	Jul 1998 - Mar 2000	School of Biological Sciences, University of Surrey, Guildford
Influence of human gut microflora on dietary soya isoflavone phytoestrogen availability in adults and children.	MAFF	Oct 1998 – Sep 2001	Department of Nutrition, King's College London
Effects of phytoestrogens and related dietary components on bone metabolism.	MAFF	Feb 1997- Jan 2000	Rowett Research Institute, Aberdeen
Possible beneficial and adverse effects of dietary phytoestrogens in men.	MAFF	Feb 1997- Jan 2000	Rowett Research Institute, Aberdeen
Examination of the impact of phytoestrogens on oestradiol receptors and disease	MRC	Apr 2000- Mar 2005	Dunn Human Nutrition Unit
Health implications of phytochemicals in human diet	BBSRC	Apr 1998 – Mar 2001	Institute of Food Research, Norwich

Appendix 2

Routes Of Human Exposure To Oestrogens That Have Changed in the Past Half-Century

Source of oestrogens	Factors that may have altered exposure	Comments
Endogenous	Changes in diet DETR	Low-fibre diet may increase "recycling" of excreted oestrogens in women. Sugar-rich diet may alter levels of bioavailable oestrogen.
	Increase in body fat	Body fat can convert certain other steroids to oestrogens; obesity can increase bioavailable oestrogen.
Synthetic (eg, DES, hexestrol, ethinyl oestradiol)	Oral contraceptive use Hormone replacement therapy (HRT)	During water recycling, synthetic oestrogens that are excreted find their way into river water and very low levels may occur in some drinking water.
	Use of orally active anabolic oestrogens in livestock	Potentially important route of exposure in 1950s-1970s via residues in meat; banned in Europe in 1981 but still in use in USA
Plant	Changes in diet Increasing use of soy protein in processed foods	Many food plants contain weak oestrogens; soya is one of the richest sources. Paradoxically plant oestrogens may reduce exposure to endogenous oestrogens and therefore be beneficial.
Other dietary sources	Increased consumption of dairy produce	Dairy practices have changed this century, such that pregnant cows (which produce high levels of oestrogens) continue to be milked. Significant levels of conjugated (inactive) oestrogens are therefore present in cows' milk. The extent to which these conjugated oestrogens are activated in the human gut and how much oestrogen the consumer would then be exposed to is largely unknown.
Environmental "oestrogenic" chemicals	Production started in 1930s/1950s	Includes organochlorine compounds, such as DDT, PCBs, alklylphenolic,bisphenolic and many other phenolicindustrial chemicals. Usage of these chemicals is widespread, and they can be detected in many foods, rainwater and breastmilk.

Appendix 3

Directives and other regulations controlling chemicals.

Type of substance regulated	Directive
Dangerous substances	Council Directive of 27 June 1967 on the approximation of the laws of the member states relating to classification, packaging and labelling of dangerous substances (Directive 67/548/EEC)
Dangerous preparations	Council Directive of 26 June 1978 on the approximation of the laws of the member states relating to classification, packaging and labelling of dangerous preparations (Directive 78/631/EEC)
Animal nutrition products	Council Directive of 18 April 1983 on the fixing of guidelines for the assessment of certain products used in animal nutrition (Directive 83/228/EEC) Council Directive of 16 February 1987 on the fixing of guidelines for the assessment of additives in animal nutrition (Directive 87/153/EEC)
Veterinary medicinal products	Council Directive of 28 September 1981 on the approximation of the laws of the member states relating to veterinary medicinal products (81/851/EEC) Council Directive of 28 September 1981 on the approximation of the laws of the member states relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products (Directive 81/852/EEC)
Food additives	Council Recommendation of 11 November 1980 on the approximation of the laws of the member states concerning tests relating to the safety evaluation of food additives (Recommendation 80/1089/EEC)
Pesticides	EC Directive 91/414 evaluation and authorisation of plant protection products
Biocides	EC Directive 98/8 concerning the placing of biocidal products on the market [Member States must implement by May 2000]

A selection of reports and statements (most recent first)

***** The full text, or summary, of these reports can be found on the Royal Society's web page **www.royalsoc.ac.uk**

Endocrine Disrupting Chemicals (document 06/00, June 2000)

Towards sustainable consumption *A European perspective* (May 2000; £19.95; ISBN 0 85403 5370)

Towards a European research area (document 03/00, May 2000)*

Scientists and the media (document 01/00, March 2000; ISBN 0 85403 5354)*

Therapeutic cloning: A submission to the Chief Medical Officer's Expert Group (document 02/00, February 2000; ISBN 0 85403 5346)*

Complementary and alternative medicine (Response to the House of Lords inquiry into complementary and alternative medicine, statement 18/99, December 1999; ISBN O 85403 5311)*

Academic pay and conditions (Response to the *Independent Review of Higher Education Pay and Conditions*, statement 17/99, November 1999; ISBN 0 85403 529 X)*

National Curriculum Orders for Science (Response to the statutory technical consultation on the National Curriculum review, statement 16/99, October 1999)

Royal Society Links with Japan, (statement 15/99, October 1999)

Royal Society Links with Russia, (statement 14/99, August 1999)

The science National Curriculum (Royal Society response to the consultation on proposals for a revised National Curriculum for 2000, statement 13/99, July 1999)*

Science and Society (Royal Society response to the inquiry by the House of Lords Science and Technology Select Committee, statement 12/99, June 1999)*

Nuclear Energy - The Future Climate - Summary (8 pages 11/99, June 1999)*

Nuclear Energy - The Future Climate (joint report by the Royal Academy of Engineering and the Royal Society, statement 10/99, June 1999; £20; ISBN 0 85403 526 5)

Review of data on possible toxicity of GM potatoes (Royal Society statement 9/99, June 1999)*

GMOs and the environment (Royal Society response to the inquiry by the House of Commons Environmental Audit Committee, statement 8/99, April 1999)*

Scientific advice on GM foods (Royal Society response to the inquiry by the House of Commons Science and Technology Committee, statement 7/99, April 1999)*

Non-food crops (Royal Society response to the House of Lords Select Committee Inquiry on non-food crops, statement 6/99, April 1999)*

Devolution and science (14 page report by a Joint Working Group of the Royal Society of London and the Royal Society of Edinburgh, statement 5/99, April 1999)*

The teaching profession (6 page statement 4/99, April 1999)*

Regulation of biotechnology in the UK (Royal Society response to the Government's consultation exercise, 4 page statement 3/99, February 1999)*

Science and the revision of the National Curriculum (3 page statement 1/99, January 1999)*

Current issues in the scientific, technical and medical information system (report of a workshop held on 21 September 1998 and sponsored by the Association of Learned and Professional Society Publishers, the British Library, Blackwell Science Ltd and the Royal Society, 3 page report, December 1998)*

Use of a policy factor in research funding (response to HEFCE consultation document, 2 page statement 5/98, December 1998)*

Innovating for the future: Investing in R&D (response to the Department of Trade and Industry and the Treasury joint consultation paper, November 1998)*

Foresight (Royal Society response to the Office of Science and Technology Foresight consultation document, 4 page statement 4/98, October 1998)*

Technical and research support in the modern laboratory (Royal Society report, September 1998; £12.50; ISBN 0 85403 5206)

Technical and research support in the modern laboratory (3 page summary 3/98, September 1998)*

Genetically modified plants for food use (16-page statement 2/98, September 1998)*
Genetically modified plants for food use (2-page summary 1/98, September 1998)*

The Role of Academies in Advising National Governments (10 page statement; September 1998)

The Scientific Advisory System (submission to the House of Commons Science and Technology Committee, June 1998)*

UK Higher Education: Quality Assurance and Standards - a response to the Quality Assurance Agency consultation (June 1998)*

The Use of Cannabis and its Derivatives for Medical and Recreational Purposes (submission to the House of Lords Science and Technology Select Committee, June 1998)*

Policy on holding international meetings in the UK (June 1998)*

Cloning Issues in Reproduction, Science and Medicine (response to the HGAC/HFEA consultation document, May 1998)

Additional information

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