

**ENDOCRINE DISRUPTERS
in the Environment**

A Review of Current Knowledge

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Endocrine Disrupters in the Environment

A Review of Current Knowledge



Introduction to the Second Edition

Since the First Edition was published in November 2000 the interest in endocrine disrupters (or endocrine modulators as they are generally termed in this ROCK) has grown considerably. Although none of this has served to contradict the conclusions reached in the First Edition the Foundation for Water Research considered that it would be useful to provide information on new sources of information and developments since November 2000 in this fast changing area of interest.

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In the First Edition it was noted that, although there is undoubtedly some risk to some organisms, the risk to human beings is less clear. It was also noted that the Commission of the European Community and the EU Parliament were investigating the concerns over endocrine disrupters and that in the UK, some research was being sponsored by government departments and environmental regulators. This interest has continued to grow rapidly and investigations have generated more information on endocrine disrupters since the First Edition was published. However, a short summary report such as this cannot hope to give more than a broad overview and if more information is required this can be found by following up the references and bibliography at the end of this ROCK.

Background

During the 1960s and 70s public interest grew in the potential effects on wildlife and human beings of substances used by agriculture and industry which inevitably found their way into the environment (from soil and thence via rainwater run-off to streams, lakes and underground water and even to the air). A major factor in this interest was the publication in 1962 of Rachel Carson's book, *Silent Spring* (Graham, 1970). This interest was instrumental in the foundation of the pressure groups Friends of the Earth in the USA in 1969 and in the UK in 1970 (Barr, 1971), and Greenpeace in the mid-1970s.

These concerns over the presence of xenobiotics¹ in the environment also extended to drinking water and in 1970 the WHO European Drinking-Water Standards (WHO, 1970) for the first time provided recommended limits for certain toxic chemical substances, polycyclic aromatic hydrocarbons and pesticides.

¹ *Xenobiotics is a term used to cover all non-naturally occurring chemicals and which may have some biochemical function. In reality this applies to all synthetic chemicals.*

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Pesticide sales increased throughout the 1970s and 1980s, but by the early 1990s sales of pesticides in many European countries had started to decline (Edwards, 1994). This was partly due to the fact that apart from the known toxicity of pesticides and other industrial organic chemicals, there were possible additional effects, which were suspected to arise from long-term ingestion of many xenobiotics. These possible effects included cancer, mutagenicity (i.e. birth defects), reductions in fertility, effects on the functioning of organs of the body such as the liver, ovaries, testes, the brain etc.

These effects were generally shown by tests undertaken on animals, especially rats, and the possible effects on human beings were deduced from these animal experiments rather than from data on human beings. There have been exceptions where human-based data has arisen from tragic pollution incidents such as the Seveso disaster in Italy. [In July 1976 a rupture occurred on a chemical reactor in a plant near Seveso in Italy which resulted in a number of chlorinated compounds, including small quantities of the toxic dioxin TCDD², being discharged over the local countryside causing some animals to die and people to fall ill (Lees, 1996).] Occasional, but nonetheless tragic examples of this kind have alerted the public to the risks of polluting substances and consequential concern over the presence of chemicals in the environment and the quality of food and drinking water.

During the 1980s, scientists identified other changes in certain marine and freshwater organisms. These changes concerned the reproductive systems of aquatic species and included the following observations: -

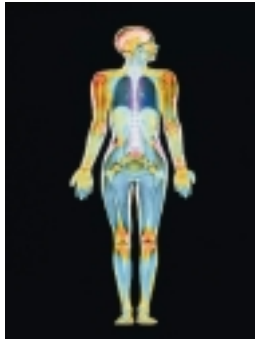
- The development of male characteristics in female dog whelks associated with contamination by the anti-fouling agent tributyl tin (TBT);

² 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin, also known as dioxin

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- A high incidence of fish exhibiting both male and female reproductive organs downstream of some sewage treatment works;
- A decline in the population of alligators in central Florida linked to low levels of certain hormones in male alligators.

These observations turned the spotlight on the so-called endocrine disrupting effects of chemicals in the environment.



What are Endocrine Disruptors?

The system in the body which produces hormones is called the endocrine system. Hormones are "chemical messengers" which are produced by glands in one part of the body, enter the circulation and are carried to distant organs and tissues to modify their structure and function, for example by affecting growth, reproduction, metabolism³ etc. A well-known example is the hormone adrenalin (also known as epinephrine) which is produced in people and animals under stress and which affects breathing, the heart rate, muscular activity and

³ *Metabolism is the process in which complex substances in the body—for example food—are broken down to provide energy, and synthesised to produce substances required by the body for growth and maintenance*

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carbohydrate metabolism. The primary oestrogen produced by the endocrine system in the human body is 17beta-oestradiol, which is used as the standard against which "oestrogen activity" of other substances is measured.

Examples of other hormones produced in the human body are testosterone, progesterone and insulin (which plays an important role in carbohydrate metabolism).

Many xenobiotics have been shown to be capable of mimicking or interfering with the reactions of hormones in animals and people. These compounds are variously referred to as "endocrine modulators", "endocrine disrupters"⁴, "hormone mimics" and by sensation seekers as "gender benders"! Because the mode of action is to mimic or interfere with the action of hormones the preferred term used in this report is "Endocrine Modulator". However endocrine modulators are not confined to the xenobiotics; many, if not the majority are naturally occurring in the environment. Another class of modulators are synthetic hormones such as diethylstilboestrol (DES), which are deliberately designed to mimic hormones. DES has been widely used to prevent miscarriage, as a post-coital contraceptive and as a growth hormone in cattle.

The Environment Agency (2000) has defined endocrine modulators as:-

Naturally occurring or synthetic substances that interfere with the functioning of endocrine systems resulting in unnatural responses.

This definition does not take account of dose-size, which is an important factor in assessing the effects of chemicals on living people, animals and plants.

⁴ *The word disrupter is sometimes spelled "disrupter" in European English and "disruptor" in American English. Database searches on the topic should take account of both spellings*

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Alleged effects of endocrine modulators include:-

- causing reproductive abnormalities (Guillette *et al*, 1994);
- causing decreased sperm counts in men (Carlsen *et al*, 1992; Sonnenschein and Soto, 1998);
- effects on the brain of developing foetuses (McCally, 1997);
- causing cancers;
- acting in addition with other chemicals to cause, or intensify, the above effects.

Other factors which are of concern, which apply to many other chemicals as well as endocrine modulators are environmental persistence, whether there is a tendency to bioaccumulate and toxicity.

Which chemicals are suspected Endocrine Modulators?

There is no comprehensive list of endocrine modulators. A major problem in deciding whether a substance is an endocrine modulator or not is the absence of internationally accepted tests for endocrine modulators, and until such tests are developed the description of a substance as a potential endocrine modulator is generally hypothetical. As a consequence a significant part of the research effort is directed towards developing such a test. The OECD has established a Task Force on Endocrine Disrupter Testing and Assessment; a key activity in this work is to develop new and revise existing Test Guidelines to detect endocrine modulators (OECD, 2000).

A wide variety of different chemicals have been suggested as potential endocrine modulators. These include the following compounds:-

- **insecticides**:- aldrin; beta-HCB; carbaryl; chlordane; dimethoate;

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dinitrophenol; fenitrothion; lindane; malathion; pentachlorophenol (also a fungicide and herbicide); pyrethrins.

- **herbicides**:- 2,4 D and 2,4,5, T (a 50:50 mixture of these was used as a defoliant by the USA in the Vietnam War under the name "Agent Orange"); atrazine; linuron; paraquat; simazine.
- **fungicides**:- benomyl; fenarimol; hexachlorobenzene; mercuric chloride; tributyltin; zineb.
- **dioxins**:- (There are 75 different types of dioxin, many of which are not significantly toxic.)
- **PCBs**:- Polychlorinated bi-phenyls; this is a family of more than 200 compounds used as a heat-transfer fluid in refrigerators and as a coolant in electrical equipment, for fire-retardant coatings, in newsprint inks and a number of other applications.
- **THMs**:- Trihalomethanes, which may be produced during the chlorination of drinking water when chlorine reacts with naturally occurring organic substances.
- **alkylphenol polyethoxylates**:- APEO—used in detergents.
- **bisphenol A**:- This is a monomer used in the production of many plastics, some of which are used as canned food tin liners⁵.
- **synthetic hormones**:- stilboestrol, contraceptive pills.
- **natural hormones**:- sewage contains human waste and therefore contains endocrine chemicals produced by the human body. Some work has suggested that the presence of hormones of human origin in treated sewage (especially from pregnant women) has caused the feminisation of fish in rivers into which treated sewage is discharged (Desbrow *et al*, 1998).

Since the list of potential endocrine modulating substances is so large the EU has established a list of 564 “candidate substances” for further investigation (EU,

⁵ *Recent work by the UK Food Standards Agency has reported that there is no risk from the bisphenol A used in canned food tin liners (Food Standards Agency, 2002)*

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2001). Not all endocrine modulators, or suspect endocrine modulators, are xenobiotic. For example a large group of pesticides are naturally produced in plants as defence mechanisms against attack by insects and moulds. Pyrethrins, which are listed by pressure groups as endocrine disrupters, are derived from plants. In fact Ames & Gold (2000) have estimated that 99.99% of all pesticides in the average diet are of natural origin - in other words only 0.01% are xenobiotic.

How serious is the risk from endocrine modulators?

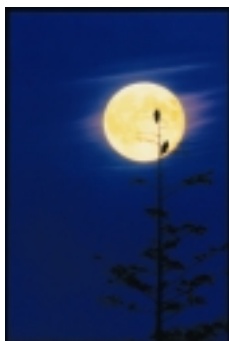
The two risks we are concerned with are the effects on wildlife and the environment in general, and on human beings.

Some chemicals can unquestionably have an effect on the endocrine systems of animals and human beings. Apart from those hormones which are manufactured by the body, some xenobiotics are designed specifically to function as hormones such as those used for contraceptive purposes. Chemicals that mimic or interfere with the functioning of hormones may also be toxic, or may have relatively low toxicity. For example, DDT, a highly effective insecticide which is no longer used in many developed countries and which was the main subject of the criticism in *Silent Spring* (Graham, 1970), is relatively non-toxic to man (Timbrell, 1995). However, although the toxicity of DDT is comparable to that of aspirin (Mellanby, 1969), it is a fat-soluble substance which can become concentrated as it passes up the food-chain. Timbrell (1995) quotes the example of a lake in California in which the plankton contained 4 ppm of DDT, the bass in the same area contained 138 ppm, and grebes feeding on them contained 1,500 ppm⁶.

⁶ *This process of concentration up a food chain is sometimes called bioaccumulation or biomagnification*

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Although DDT is relatively non-toxic to mammals (Tomalin, 1994) one of the side effects of the bioaccumulation of DDE (produced in the environment by the breakdown of DDT) in birds was the 10% thinning of egg-shells and a consequential increase in breakage (Lincer, 1975) which could have led to a decline in the affected species.



The fact that an endocrine modulator can have an effect on the endocrine system should not be taken as indicating that it is harmful. The physiological effect of any chemical depends on the quantity ingested or absorbed by the organism. Furthermore, the effect is also species-dependent. In the case of DDT it is highly toxic to insects whereas (as noted above) it is relatively non-toxic to human beings.

Some chemicals which are known or suspect endocrine modulators have been shown to be capable of causing problems in laboratory animals such as cancer, liver damage, infertility, growth abnormalities and sexual abnormalities.

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However, the fact that a chemical can have adverse effects in laboratory animals does not necessarily indicate an unacceptable risk for humans, although in most cases this is the only available data concerning hazard.

Ames and Gold (2000) point out that about 50% of chemicals, both naturally occurring in plants and animals, or synthetic, that have been tested in standard, high-dose animal cancer tests cause cancer in rodents, see Table 1 below.

Barlow *et al* (1992) comment that the human diet is known to contain many components which can be shown experimentally to be mutagens or carcinogens.

Table 1: Proportion of chemicals evaluated as carcinogens (Ames & Gold, 2000)

CHEMICALS	% CAUSING CANCER
chemicals tested on both rats and mice	
naturally occurring chemicals	57%
synthetic chemicals	60%
chemicals tested on both rats and/or mice	
chemicals in Carcinogenic Potency Database	52%
natural pesticides	52%
mould toxins	61%
chemicals in roasted coffee	70%
drugs	49%

Ames and Gold conclude that "*the very low levels of chemicals to which humans are exposed through water pollution or synthetic pesticide residues may pose no or minimal cancer risks*".

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The assessments of the limits to which human beings can be exposed for regulatory purposes, for example in setting drinking water standards, assume a linear model - that is to say that the effect produced is assumed to be directly proportional to the dosage. In simple terms, half the dosage will produce half the frequency of abnormalities or cancers.

Most kinds of toxic substance can be metabolised by the body, frequently with no undesirable side-effects, provided the dose does not exceed a certain value. Therefore in setting limits, it is assumed that there is a dosage level below which no observed adverse effects occurs - the NOAEL, measured in mg per kg bodyweight per day - or that there is a lowest-observed-adverse-effect-level, the LOAEL measured in mg/kg/day. The tolerable or acceptable daily intake - the TDI or ADI is estimated thus:

$$\text{TDI} = \text{NOAEL} / \text{UF} \quad \text{or} \quad \text{TDI} = \text{LOAEL} / \text{UF} \quad \text{where UF is an uncertainty factor which typically varies between 10 and 1,000.}$$

In the derivation of the WHO drinking water standards the various uncertainties and their factors are given in Table 2.

Table 2: Uncertainty factors used in setting WHO drinking water standards

SOURCE OF UNCERTAINTY	FACTOR
interspecies variation (animals to humans)	1 to 10
intraspecies variation (individual variations)	1 to 10
adequacy of studies or database	1 to 10
nature and severity of effect	1 to 10

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Thus the theoretical minimum uncertainty factor is 1 (i.e. $1 \times 1 \times 1$) and the maximum is 10,000 (i.e. $10 \times 10 \times 10 \times 10$).

In the case of substances such as food additives or pesticide and drug residues which may be ingested by other means (i.e. in food) a typical uncertainty factor is 100, although it may also be as high as 1000. Exposure in the industrial environment is regulated in the USA by the Threshold Limit Value (TLV) or Minimum Risk Levels (MRL), and in the UK by the Maximum Exposure Limit (MEL) which is usually based on an eight-hour working day (Timbrell, 1995). Minimum Risk Levels for a wide range of chemicals, together with associated uncertainty factors ranging from 3 to 1000, can be found on the website of the American Agency for Toxic Substances and Disease Registry (ATSDR, 2000).

In order to estimate the potential risk of an endocrine modulator to the endocrine system it is helpful to compare their hormonal potency against some common standard. As noted above, the primary oestrogen which is used as the standard against which the "oestrogen activity" of other substances is measured is 17 β -oestradiol, a natural hormone produced in the human body.

Table 3, adapted from Gaido *et al* (1997), compares the relative potencies of selected endocrine modulators.

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Table 3: Relative potencies of some oestrogenic endocrine modulators compared with oestradiol.

CHEMICAL	OESTROGENIC POTENCY RATIO (POTENCY OF THE CHEMICAL TO THAT OF OESTRADIOL)
oesdradiol	1
diethylstiboestrol (DES, a synthetic hormone)	0.64—slightly over half as active as oestradiol
Coumestrol (a phyto-oestrogen; an oestrogen-like chemical found in plants)	0.0129 77 times less active than oestradiol
p-nonylphenol (a chemical used in certain plastics)	0.0002 5,000 times less potent than oestradiol
bisphonel A (a monomer used to manufacture certain plastics, e.g. coatings for tins of food)	0.00007 15,000 times less potent than oestradiol
beta-siterol (a natural plant chemical used as an anti-cholesterol agent)	0.0000045 220,000 times less potent than oestradiol
Methoxychlor (a pesticide)	0.0000002 5 million times less potent than oestradiol
o.p'-DDT (a pesticide)	0.000000125 8 million times less potent than oestradiol
o.p'-DDE (a breakdown product of the pesticide DDT)	0.000000042 24 million times less potent than oestradiol

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However, comparisons as represented in Table 3 should be treated with caution because the effects in various living organisms will depend on factors such as the rate of uptake, the duration of exposure, the quantity of the chemical, whether the effects on the affected endocrine system are irreversible and the maturity of the affected organism.

So what are the risks to the environment and human beings?

There is unquestionably some risk to parts of the environment from endocrine modulating substances, for example the thinning of the eggs of some species of bird resulting in lower hatching success rates as a result of exposure to DDT and its by-product DDE; the masculinisation of whelks (Matthiessen and Gibbs, 1998) subjected to the biocide tributyl tin used in anti-fouling paints on boats—which will be banned world-wide by 2003, and the feminisation of fish subjected to natural hormones in treated sewage discharges into rivers. Nevertheless, much of the possible risk to the environment is unclear. The UK Environment Agency (2000) in its endocrine disrupting substances strategy has commented that

"much of the published data relate to laboratory conditions and do not necessarily reflect the responses which would occur in an animal in the environment".

The risk to human beings is even less clear. It appears from most of the published objective studies that little evidence has been found that, at the concentrations at which human beings are subjected to endocrine modulators, the risk of adverse effects is other than low. The work on the decline in male sperm concentration in adult males reported by Carlsen *et al* (1992) and

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Sonnenschein and Soto (1998) has not been confirmed by subsequent studies (Lukachko, 1999; Jørgenson *et al.*, 2001).

Do the risks from endocrine modulators justify strong action and expenditure?

Following the United Nations Conference in 1992 principle 15 of the Rio Declaration provided that:

In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. 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.

It is true to say that so far there is a lack of full scientific certainty. Unfortunately there is no such thing as "full scientific certainty". All scientific knowledge is based on probabilities rather than certainty, and at the present stage of knowledge on endocrine modulators there is considerable uncertainty on the extent of the potential environmental and human risk. There is a large number of chemicals which are known to be, or are suspected of being, endocrine modulators, but very few of these have been proven to pose a threat of **"serious or irreversible environmental damage"**. Even DDT, which was the primary target in Rachael Carson's book *"Silent Spring"*, did not cause irreversible damage, and the degree of the seriousness of the damage it caused is debatable. It can be argued that judicious use of DDT can be beneficial to mankind. It has been estimated that over a period of two decades the use of DDT has prevented 500 million deaths that would otherwise have been inevitable (National Academy of Sciences, 1970).

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Therefore, when we consider the risks of individual endocrine modulators we must also consider the benefits which arise from their use. Many of the proven or suspect chemicals are valuable, most notably the pesticides. We must not lose sight of the fact that a significant number of the population in the world suffer from serious diseases carried by insects and parasites which can be controlled by pesticides. The World Health Organisation reports that malaria is the second most serious tropical disease after tuberculosis; each year there are between 300 million and 500 million cases, of which between 1.7 and 2.3 million die; every day over 3,000 children under the age of 5 die from malaria (WHO, 1998). Many of these lives could be saved by the use of DDT and pyrethrum. Many of the affected countries are among the poorest who cannot readily afford more expensive means of combating the disease. WHO reports that, according to 1997 estimates, the costs to sub-Saharan African countries in medical support, lost labour and death exceed \$2 billion (WHO, 1998).

It is important that the risks from endocrine modulators and other potentially harmful chemicals are put into a wider context. Table 4 provides some examples.

Table 4: Examples of risks involved in normal activities.

ACTIVITY	RISK OF	CASES PER MILLION
travel 1000 miles by air	fatal accident	3
travel 1000 miles by car	fatal accident	20
travel 1000 miles by motorcycle	fatal accident	400
working 10 years in a factory	fatal accident	300
1 glass of wine a day for 10 years	cirrhosis	1,000
1 cigarette a day for 10 years	heart attack or lung cancer	2,500
living for 1 year at age 30	death from all causes	1,000
living for 1 year at age 55	death from all causes	10,000

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We do not yet have comparable data for the risks involved for human beings as a result of the effects of endocrine modulators. However, we do know that the exposure levels of human beings to endocrine modulators and suspected modulators are very low compared to the range of hormones in the body. Furthermore, the potency of most endocrine modulators identified is very low in comparison to the body's natural hormones (see Table 3) so that the potential for disrupting the body's hormones would appear to be low in adults at least. One effect which might appear to contradict this is the alleged reductions in sperm counts in adult males reported by Carlsen *et al* (1992) and Sonnenschein and Soto (1998). However, this work has been shown to be inconclusive (Ames & Gold, 2000; Lukachko, 1999) and remains a hypothesis. In fact, out of 22 studies undertaken between 1973 and 1996 only 9 found a decrease in sperm concentration, 5 found an increase and 9 found no change (Damstra *et al* 2002). However, there is much uncertainty concerning the risks to humans especially when assessing the potential effects on say the developing foetus and young children.



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What action is being taken over endocrine modulators?

The risks from endocrine modulators in the environment are still uncertain and this, coupled with public concern, makes it currently one of the highest research priorities in the USA (Kavlock *et al*, 1996; EPA, 1998a; Kavlock, 1999). The EPA's *Science to Achieve Results* (STAR) programme on endocrine modulators is described in its Star Report (EPA, 1998b). The Environment Agency in the UK is sponsoring additional research into aspects of the subject (Environment Agency, 2000). As a result of growing international interest a number of co-ordinating groups have been established. The OECD (Organisation for Economic Co-operation & Development) has a Task Force on Endocrine Disrupter Testing and Assessment, which covers work in the UK, Japan, the USA, Europe and Korea. The World Health Organisation (WHO) has a joint programme with the United Nations Environment Programme (UNEP) and the International Labour Organisation (ILO) on the "Global Assessment of the State-of-the-science of Endocrine Disrupters" (see www.who.int/pcs/). The German Environment Agency is developing an inventory of research outside the USA; the European Chemical Industry Council (CEFIC) is undertaking and sponsoring research. The European Union Joint Research Centre (JRC) in Italy is undertaking work and has a global inventory of ongoing research on endocrine disrupters (JRC, 1999) as part of the International Programme on Chemical Safety (see www.who.int/pcs/). The Commission of the European Union and the EU Parliament are investigating the matter and are developing long-, medium- and short-term actions. In December 1999 the Commission proposed a Community Strategy (EU, 1999) with a number of key requirements including:

- further research;
- international co-operation;

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- communication to the public;
- appropriate policy action;
- the establishment of a priority list of substances to be evaluated for their role in endocrine disruption.

A major European initiative is the COMPREHEND Partnership in which 13 research laboratories in 7 European countries are co-operating in a programme of research into the possible effects on fish of endocrine modulators in the aquatic environment. The UK input is co-ordinated through the Centre for Ecology and Hydrology⁷.

In addition to its international co-operation, the UK has a number of active programmes being undertaken nationally. These include the study on Endocrine Disrupters in the Marine Environment (EDMAR) which is investigating the oestrogenic (or feminising) effects of chemicals in estuarine waters which is being undertaken by the Centre for Environment, Fisheries and Aquaculture Science (CEFAS—see www.cefas.co.uk) on behalf of the European Joint Research Centre. The UK Water Industry is also undertaking some research through UKWIR on endocrine modulating effects of wastewater treatment effluents, endocrine disrupters in sewage sludge and: a study of treatment options and potential costs for treating endocrine disrupting substances in wastewater (see www.ukwir.org).

⁷ *The NERC Centre for Ecology and Hydrology (CEH) was established in April 2000 by combining into a single unit the four NERC centres; The Institute of Freshwater Ecology, The Institute of Hydrology, the Institute of Terrestrial Ecology and the Institute of Virology and Environmental Microbiology*

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Conclusions

The precautionary principle agreed at the Rio Summit says that "**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**". Much of the evidence at present is that the environmental threats from the majority of endocrine modulators are not serious or irreversible and that simple measures for reducing environmental impact may be achievable without sacrificing the benefits. Similarly there is no good evidence that, with the exception of diethylstilboestrol (DES), endocrine disrupters pose a threat to human health.

The *European Workshop on Endocrine Disrupters* (EU, 2001) concluded that the area of endocrine disrupters is one of concern, but that

“there are still problems (particularly for human health) in establishing causal links between exposure to suspected endocrine disrupters and any effects measured.”

The more recent and voluminous UNEP/ILO/WHO draft report on Global assessment of the state-of-the-science of endocrine disrupters (Damstra *et al*, 2002) came to a similar conclusion, namely that although the potential risks to human beings and wildlife have not been adequately addressed,

“there is weak evidence that human health has been adversely affected by exposure to endocrine-active chemicals”.

Nevertheless, the occurrence of observable changes in the reproductive physiology of certain aquatic species in some ecosystems supports the call for

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further research. Given the vast array of chemicals that may have some endocrine modulation properties, the numerous endocrine functions in different animal species, and the variety of other potential hazards from chemicals there is a need for concerted action on the development of test procedures to reveal all potentially harmful effects of chemicals. The OECD has established a Task Force on Endocrine Disrupter Testing and Assessment; a key activity in this work is to develop new, and revise existing, Test Guidelines to detect endocrine modulators (OECD, 2000).

Information produced by a number of international programmes currently being undertaken on endocrine modulators will become part of larger initiatives concerning the delivery of public information about the properties of chemicals, including initiatives such as The US Chemical right to know data collection exercise and the CEFIC Confidence in Chemicals initiative (Stevenson, 2000).

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