A Review of Current Knowledge

ENDOCRINE DISRUPTERS in the Environment

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This review is one of a series of Reviews Of Current Knowledge (ROCKs) produced by FWR. They focus on topics related to water supply, wastewater disposal and water environments, which may be the subject of debate and inquiry. The objective of each review is to produce concise, independent scientific and technical information on the subject to facilitate a wider understanding of the issues involved and to promote informed opinion about them.

ENDOCRINE DISRUPTERS
in the Environment

Front cover image © Ivana Wilson

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Endocrine Disrupters[1] (EDCs) in the Environment

1 Introduction to the Third Edition

Following the First Edition of this ROCK (published in November 2000) the interest in, and research into, Endocrine Disrupting Chemicals (EDCs) - sometimes referred to as Endocrine Modulators (EMs) or Endocrine Active Chemicals (EACs) - had grown sufficiently to require a revised and updated Second Edition which was published in July 2002. However, research into, and general concern about, EDCs has continued apace and so the Foundation for Water Research considered that it would be useful to provide a further, third, update on the subject. In the first and second editions the use of the less tendentious term "Endocrine Modulators" was preferred; however, since the term Endocrine Disrupter (or Disruptor) has become the most widely used term it is now the one used in this Third Edition.

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. This arises partly because there are many factors which influence the effects of chemicals on biological systems, and partly because evolution has equipped living organisms with the ability to resist chemical attacks. A good example of this sort of evolution is the appearance of the superbug MRSA. MRSA is a strain of *Staphylococcus aureus* (MRSA is an acronym for Methicillin Resistant S. aureus) which has evolved a resistance to a wide range of antibiotics (Hunt et al., 1999; Kingman, 2001).

Since the Second Edition of this ROCK the Commission of the European Community has produced a series of strategy documents, the most recent being a ***Community Strategy for Endocrine Disrupters*** (EU, 2007). There is also a European Union website which gives details of research in the EU[2]**.** Extensive research into endocrine disrupters is being undertaken in many countries across the world. In the UK research has been commissioned by the Department for the Environment Food and Rural Affairs (Defra)[3], the Medical Research Council and the Environment Agency, and a joint research programme has been established with Japan[4]. In the USA the Environmental Protection Agency identified research

[1] In the USA the word is commonly spelled "disruptors", whereas in the UK the usual spelling is "disrupters".
[2] see http://ec.europa.eu/research/endocrine/index_en.html
[3] see Defra website at: http://collections.europarchive.org/tna/20080726154834/http://www.defra.gov.uk/environment/chemicals/hormone/index.htm
[4] see http://www.uk-j.org/text/uk-j.html

into EDCs as one of its top six research priorities. This interest has continued to grow rapidly and investigations and research have generated considerably more information on endocrine disrupters since the Second Edition was published. There has also been a growth in misinformation and alarmist reports on EDCs from pressure groups, in the popular press and on a number of websites. It is therefore important to have a source of balanced and objective information on this topic. However, a short summary report such as this cannot hope to do more than give a broad overview of this large, important, and growing area of concern and if the reader requires more information it can be found by following up the references and bibliography at the end of this ROCK.

2 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). Greenpeace began campaigning against persistent organic pollutants (POPs), which includes many EDCs, in the early 1990s.

The concerns over the presence of xenobiotics[5] in the environment extended to drinking water and in 1970 the WHO European Drinking-Water Standards (WHO, 1970) provided recommended limits for the first time on certain toxic chemical substances such as polycyclic aromatic hydrocarbons and pesticides.

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) although sales began to recover and then stabilise in the 2000s. The initial decline was partly due to the fact that, apart from the known toxicity of pesticides and other industrial organic chemicals, it was suspected that there were additional effects which might arise from long-term exposure to many xenobiotics. These possible effects included cancer, mutagenicity i.e. birth-defects (teratogenicity), reductions in fertility and effects on the functioning of organs of the body such as the liver, ovaries, testes, the brain etc. The situation has not been helped by exaggerated and lurid reports in the press; see, for example, the article by Butterworth (2009).

[5] 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.

These effects were generally shown by laboratory 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. One of the problems with tests on rats is that they are not human beings and the extrapolation from effects on rats to effects on people is unreliable (Dijkstra, 2011; vom Saal, 2005). There have been exceptions where human-based data have become available 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 TCDD[6], 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. This concern was a factor in the establishment of the Food Standards Agency in the UK in 2000.

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);
- A high incidence of fish exhibiting both male and female reproductive organs downstream of some sewage treatment works (Hotchkiss et al., 2008);
- 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.

In 2006 the EU introduced the Registration, Evaluation, Authorisation and restriction of Chemicals Regulations, known as REACH, (EC Regulation, 2006) which came into force on 1st June 2007. This regulation covers a wide range of chemicals and prohibits the use of certain classes of chemical unless their use has been authorised by the European Commission. Chemicals which require specific authorisation are defined as substances *"such as those having endocrine disrupting properties or those having persistent, bioaccumulative and toxic properties or very persistent and very bioaccumulative properties"* (Article 57(f), REACH Regulations).

[6] 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin, also known as dioxin.

3 What are Endocrine Disrupters?

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 blood stream and are carried to distant organs and tissues to modify their structure and function, for example by affecting growth, reproduction, metabolism[7] etc. A well-known example is the hormone adrenalin which is produced in people and animals under stress and which affects breathing, the heart-rate, muscular activity and carbohydrate metabolism. The primary oestrogen produced by the endocrine system in the human body is 17-beta-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 (or endocrine disrupting chemicals - EDCs), hormone mimics and by sensation-seekers as *gender benders*. Endocrine disrupters are not confined to the xenobiotics; many, if not the majority, occur naturally in the environment. Another class of EDC is synthetic hormones such as diethylstiboestrol (DES), which are deliberately designed to mimic hormones for some specific purpose such as contraception. DES was widely used to prevent miscarriage, as a post-coital contraceptive and as a growth hormone in cattle.

The Environment Agency (2000) has defined EDCs as:

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

The International Programme on Chemical Safety (IPCS), a cooperative venture between WHO, International Labour Organisation (ILO) and United Nations Environment Programme (UNEP), defines EDCs as:

[7] 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 such as amino acids which are required by the body for growth and maintenance.

> ***"Endocrine disrupters are exogenous[8] substances that alter function(s) of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub)populations."*** (Damstra et al., 2002).

Neither definition takes account of dose-size (usually measured as a quantity per unit body weight, e.g. mg of substance/kg of body weight), which is an important factor in assessing the effects of chemicals on living people, animals and plants.

Some of the alleged effects of endocrine disrupters include:

- decreasing thyroid function and increasing parathyroid hormone activity caused by ingesting fluoride (National Research Council, 2006);
- causing reproductive abnormalities (Guillette et al, 1994);
- causing decreased sperm counts in men (Carlsen et al, 1992; Sonnenschein, 1998);
- effects on the brain of developing foetuses (McCally, 1997);
- causing cancers;
- acting synergistically with other chemicals to cause, or intensify, the above effects.

Other factors of concern, and which apply to many other chemicals as well as EDCs, are environmental persistence and bioaccumulation (DETR, 1999).

4 Which chemicals are Endocrine Disrupters?

There is no comprehensive list of endocrine disrupters. A major problem in deciding whether a substance is an endocrine disrupters or not is the absence of internationally accepted tests for endocrine disrupters, and until such tests are developed the description of a substance as a suspected endocrine disrupter is generally hypothetical. As a consequence a significant part of the research effort is directed towards developing such tests. The OECD has established a *Task Force on Endocrine Disrupter Testing and Assessment* which reports regularly on tests and protocols. A key activity in this work was to develop new Test Guidelines to detect endocrine disrupters (OECD, 2011), and OECD Guidelines for the Testing of Chemicals were finally published in November 2010[9]**.** The EU has established a database of possible EDCs which can be found on the relevant website (EU, 2006).

[8] A substance not manufactured within the cells or organism it affects. Adrenaline, for example, is thus not exogenous.

[9] Up-to-date information can be found on the OECD Task Force website at http://www.oecd.org/department/0,3355,en_2649_34377_1_1_1_1_1,00.html

The Environmental Protection Agency (EPA) in the USA issued a list of chemicals to be screened for their potential as EDCs in April 2009 and a second list in November 2010 (EPA, 2010)[10].

A wide variety of different chemicals have been suggested as potential endocrine disrupters. These include the following groups of chemicals:

- **insecticides**:- aldrin; beta-HCB; carbaryl; chlordane; dimethoate; 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 heat-transfer fluids 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**:- BPA - this is a monomer used in the production of many plastics, some of which are used as canned food tin liners.[11]

- **phthalates** - phthalates are used as “plasticisers”, substances which make plastics more flexible. They are most commonly used to make PVC plastics flexible. PVC is used in a wide variety of products such as food-packaging (eg “cling-film”), toys, blood-bags, electrical cabling, footwear and so on.

[10] Details of the EPA program and its lists of chemicals and can be found on the website http://www.epa.gov/endo/

[11] A study for the UK Foods Standards Agency found that there is no risk from the bisphenol A used in tinned food can liners (Food Standards Agency, 2001). This is supported by many other sources, but remains controversial.

- **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 (Purdom et al., 1994; Williams, 2000).

- **pharmaceuticals and personal care products (PPCPs)**:- these are chemicals used to combat disease and health problems and as cosmetics. They are also used in agriculture to boost output from livestock. PPCPs have been found in water around the world. There is little evidence so far that they have a net adverse effect on human health.

- **perchlorates**:- perchlorates, which have been shown to have EDC characteristic, are both naturally occurring and synthetic. They have been found in water bodies, drinking water supplies and in powdered infant formula (Anon., 2011).

- **Phytoestrogens**:- these are naturally occurring substances found in plants and which are part of the normal diet. Phytoestrogens are found in broccoli, cauliflower, soybeans, carrots, oats, rice, onions, legumes, apples, potatoes, beer, and coffee (EXTOXNET , 1998)

Since the number of potential endocrine modulating substances is so large the EU's ***Community Strategy for Endocrine Disrupters*** lists 553 substances in its "Candidate List" of EDCs for further investigation. EDCs are included in the ***Framework Programme of the European Community for Research, Technological Development and Demonstration Activities 2007–2013*** (EU, 2007).

Not all endocrine disrupters, or suspect endocrine modulators, are xenobiotic (or synthetic). A large group of pesticides occurs naturally in plants, which have evolved defence mechanisms against attack by insects and moulds. Pyrethrins for example, 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.

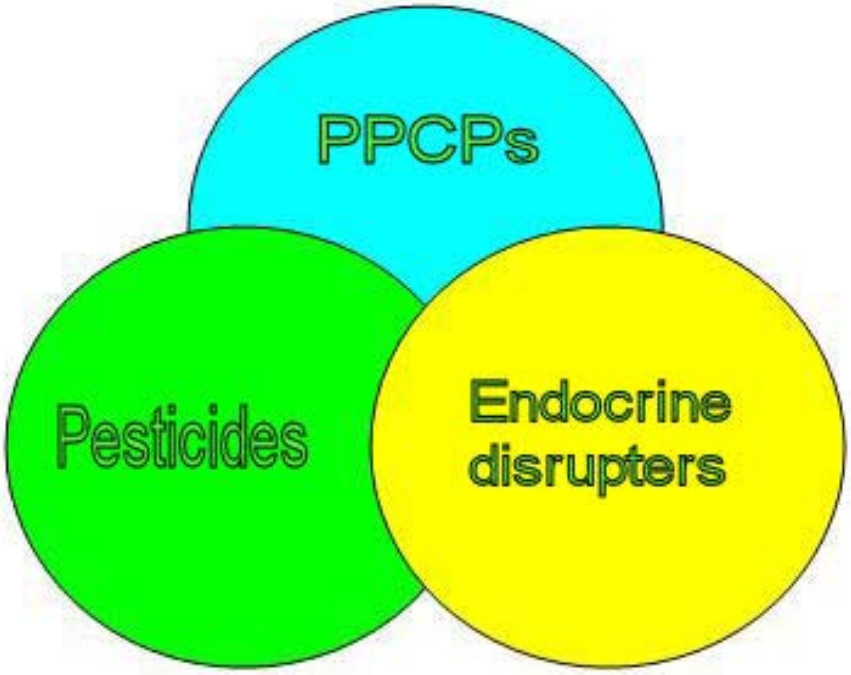

Fig. 1: Not all PPCPs and pesticides are EDCs. The diagram indicates the relationship between three groups of chemicals

Many fruits and vegetables contain substances which are, or are suspect, endocrine disrupters. The best known example is soya beans (Doerge et al., 2002) and soya products such as tofu, but a wide range of other fruits and vegetables in our diet contain EDCs and mankind has evolved to cope with them in the quantities found in a normal diet.

5 How serious is the risk from endocrine disrupters?

The two risks we are concerned with are the effects on wildlife and the environment in general, and the effects 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[12]. 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 ppm.

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 disrupter 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. Furthermore, it should not be forgotten that DDT has been instrumental in the battle against malaria and has saved - and still is saving - untold numbers of human lives.

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

[12] This process of concentration up a food chain is sometimes called bioaccumulation or biomagnification.

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

CHEMICALS	% CAUSING CANCER
chemicals tested on both rats and mice	59%
naturally occurring chemicals	57%
synthetic chemicals	60%
chemicals tested on both rats and/or mice	
chemicals in Carcinogenic Potency	52%
Database	52%
natural pesticides	61%
mould toxins	70%
chemicals in roasted coffee	49%
drugs	

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***".

The assessments of the limits to which human beings can be exposed for regulatory purposes generally assume a linear model, for example in setting drinking water standards. This assumes that the effect produced is directly proportional to the dosage. In simple terms, this assumes that 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 affects 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. This is sometimes also referred to as the No Observable Effect Level or NOEL[13]**.** The tolerable or acceptable daily intake - the TDI or ADI is estimated thus:

$$TDI = NOAEL / UF \qquad \text{or} \qquad TDI = LOAEL / UF$$

where UF is an uncertainty factor which typically varies between 10 and 1,000.

[13] NOEAL or NOEL. This is the highest level of concentration or quantity at which a chemical can be administered or ingested without any adverse effect being observed on, for example upon health, growth, development, reproductive capacity or lifetime.

The various uncertainties and their factors which are used in deriving the WHO drinking water standards 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

Thus the theoretical minimum is 1 (i.e. 1x1x1x1) and the maximum is 10,000 (i.e. 10x10x10x10).

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, 2010).

In order to estimate the potential risk of an endocrine disrupter 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 beta-oestradiol, a natural hormone produced in the human body. The relative potencies of selected endocrine disrupters is shown in Table 3 below (Gaido et al., 1997; ACSH 1999).

It has been pointed out, especially by activists concerned about environmental pollution and health risks arising from chemicals in general and EDCs in particular, that the adverse effects of chemicals may not become apparent for many years after they have been introduced and used. Examples used include cigarette smoking, thalidomide, DDT, dioxins, and so on. This concern led to the introduction of the Precautionary Principle which, in effect, said that no chemicals should be introduced into the environment until proved to be non-harmful. This is virtually impossible and could lead to the loss of potentially valuable benefits, so

the principle was modified by the Rio Declaration[14] which stated that a ***"lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation".***

However, public anxiety has been compounded by the so-called "low-dose hypothesis" which asserts that environmental exposure to EDCs is capable of causing effects in laboratory animals at "low doses" and that these effects have not been detected earlier because standard toxicology studies have been performed at high doses. This hypothesis has been exploited by well-meaning but ill-informed activists who have established pressure groups opposing the use of all chemicals which have been shown to have endocrine effects. However, if a chemical interacts with the endocrine system it does not necessarily follow that there will be adverse effect. With the right dose and timing of exposure, almost anything – including everyday food – can, and often does, elicit an endocrine system response (Dooley, 2010).

Table 3: Relative potencies of some oestrogenic endocrine disrupters compared with oestradiol. (Gaido, 1997; ACSH 1999)

Chemical	Oestrogenic potency ratio (potency of the chemical to that of oestradiol)
oestradiol (a naturally occurring hormone present in all normal human beings)	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 - five thousand times less potent than oestradiol.
bisphenol A (a monomer used to manufacture certain plastics, e.g. coatings for tins of food)	0.00007 - fifteen thousand times less potent than oestradiol.
beta-siterol (a natural plant chemical used as an anti-cholesterol agent)	0.0000045 - two hundred and twenty thousand times less potent than oestradiol.

[14] see http://www.pprinciple.net/PP%20Guidelines_english.pdf

Methoxychlor (a pesticide)	0.0000002 - five million times less potent than oestradiol.
DDT (a pesticide)	0.000000125 - eight million times less potent than oestradiol.
DDE (a breakdown product of the pesticide DDT)	0.000000042 - twenty four million times less potent than oestradiol.

However, comparisons as represented by Table 3 above, 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 and inter-species variations. For example, Ethynyl Estradiol, a synthetic hormone, has a reported potency ratio of anything from 1.2 (Voogt, 2003) to 11-27 (Thorpe et al., 2003).

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

There is unquestionably some risk to parts of the environment from endocrine disrupting substances. Examples include 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 (Mathiessen, 1998) subjected to the biocide tributyl tin which was used in anti-fouling paints on boats and ships until it was banned by the ***International Convention on the Control of Harmful Anti-fouling Systems on Ships***[15] (Environment Agency, 2011) and the feminisation of fish subjected to natural hormones in treated sewage discharges into rivers. Although some evidence continues to accumulate on adverse effects on the development of fish, especially from sewage discharges, the overall effects are not serious (EDMAR, 2002) and can be mitigated by more modern treatment processes (Koh et al., 2008). Nevertheless, much of the possible risk to the environment is unclear. The UK Environment Agency (2000) 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 disrupters, the risk of adverse

[15] The convention came into effect in September 2008.

effects is other than low. The work on the decline in male sperm concentration in adult males reported by Carlsen et al., (1992) and Sonnenschein (1998) has not been confirmed by subsequent studies (Lukachko, 1999; Jørgensen et al., 2001).

7 Do the risks from endocrine disrupters 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 disrupters there is considerable uncertainty on the extent of the potential risk to the environmental and human health. There is a large number of chemicals which are known to be, or are suspected of being, endocrine disrupters 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. Indeed, 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).

Therefore, when we consider the risks of individual endocrine disrupters 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; in 2008 there were between 200 million and 300 million cases, of which between 0.71 and 1 million die; every day over 2,000 children under the age of 5 die from malaria (WHO, 2009). 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. It has been estimated that the cost of malaria to sub-Saharan Africa is 1.3% of GDP with direct losses arising from the costs of medical support, lost labour and death of US$12 billion (WHO, 2009).

It is important that the risks from endocrine disrupters and other potentially harmful chemicals are put into a wider context. Table 4 below gives examples of risks taken by people in the normal course of their lives.

Table 4: Examples of risks involved in normal activities[16].

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

We do not yet have comparable data for the risks involved for human beings as a result of the effects of endocrine disrupters. However, we do know that the exposure levels of human beings to endocrine disrupters and suspected disrupters are very low compared to the levels of hormones in the body. Furthermore, with a few exceptions such as Ethynyl Estradiol (EE) which is used in contraceptive pills, the potency of the endocrine disrupters is very low in comparison to the body's natural hormones (see Table 3 above) 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 (1998). However, this work has been

[16] Data taken by the author from various sources including, *inter alia*, the Health & Safety Executive (HSE) and "Risk Assessment: A study group Report" from the Royal Society, 1983.

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). Nevertheless, there is still much uncertainty concerning the risks to human beings especially when assessing the potential effects on, for example, the developing foetus and young children. Despite this lack of data there has been an intensive campaign over many years against BPA (bisphenol-A), a chemical used in the manufacture of the plastics from which baby-bottles, refillable water-containers, CDs and the resins which line the inside of tin cans used for food and drinks are made.

Anti-chemical lobby groups frequently publish alarmist studies in which EDCs have been found in body tissue (e.g. blood or urine samples) whilst ignoring the fact that the concentrations are well below the NOEL. An example of this poor quality science can be found in the study by lobbying groups on the detection of BPA and phthalates in urine samples (Rudel et al., 2011) which was reported in popular journals. However, the levels found were 1,000 times below the precautionary American Federal Limits which are, in turn, considerably below the NOEL (ACSH, 2011a).

Professor Robert Brent[17] has written that "***The overwhelming scientific evidence points to the conclusion that at current exposure levels, BPA is not toxic***." (Brent, 2010), and the European Food Safety Authority (EFSA) issued a press release in September 2010 saying that the Tolerable Daily Intake for BPA of 0.05 mg/kg body weight does not need to be revised. A major study (Galloway et al., 2010) concluded that higher exposure to BPA may be associated with endocrine changes in men although another study (Mendiola, 2010) came to a similar cautious conclusion that exposure to low levels of BPA in fertile men may be associated with a modest reduction in free testosterone but effects "***are likely to be small and of uncertain clinical significance***".

Furthermore, it has been claimed that there is an even greater risk if pressure groups succeed in achieving a complete ban on the use of BPA. Entine (2011) has pointed out that

> ***"Among its myriad uses, [BPA] can be found in can liners that increase the shelf life of food and prevent botulism, which is a genuine health threat. There are no effective substitutes. Ban BPA, and people will die."***

[17] Distinguished professor of pediatrics, pathology and radiology at Jefferson Medical College, duPont Hospital for Children, Wilmington, Delaware.

8 What action is being taken over endocrine disrupters?

Notwithstanding the fact that there is very little positive evidence of risks arising in human beings from the use of BPA - as pointed out above - the Canadian government took the unjustifiable decision to ban its use in October 2010 (Canada Gazette, 2010). Generally, other governments and the EU are taking a more evidence-based approach to the matter and Canada remains alone in applying a complete ban on the use of BPA.

In 2002 the EU issued a framework directive authorising the use of a wide range of plastics and monomers (the chemicals from which plastics are made) for products intended to come into contact with foods which included BPA as an approved chemical (EU, 2002a). In 2010 both Denmark and France banned the use of BPA in the manufacture of infants' feeding bottles (Harrington, 2010) although a subsequent study by the European Food Standards Authority (EFSA) found that there is no evidence to justify banning the use of BPA in the manufacture of infants' feeding bottles (EFSA, 2010). Notwithstanding this opinion the EU, under pressure from Denmark, has introduced a Directive banning the use of BPA in the manufacture of infants' feeding bottles (EU, 2011). In April 2011 Denmark also formally requested the EU to ban the use of four of the eight phthalates used as plasticisers in the manufacture of plastics (ECHA[18], 2011) despite the lack of evidence of harm caused by phthalates in the small quantities in which they are used (ACSH, 2011b).

The risks from endocrine disrupters in the environment are still uncertain and as a consequence governments continue to maintain a "watching-brief" and to fund research into the topic and EDCs are being constantly investigated. This uncertainty, coupled with public concern and uninformed, alarming, media reports, makes EDCs currently one of the highest research priorities in the USA, Europe and Japan. The EPA's Science to Achieve Results (STAR) program on endocrine disrupters is described in its Star Report (EPA, 1998). 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) had a joint programme with the UNEP and the ILO on the "Global Assessment of the State-of-the-science of Endocrine Disrupters" which finished in 2002 (WHO, 2002).

[18] ECHA is the European Chemicals Agency Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland.

A major undertaking, called the Global Endocrine Disruptor Research Inventory (GEDRI) listing all international research into EDCs was started in 1996 by the US Environment Protection Agency. The undertaking was transferred to the European Joint Research Centre in Italy and by 2011 the total number of listed projects had risen to 778 (EPA, 2011).

The International Programme on Chemical Safety (IPCS) under the aegis of WHO undertook studies on EDCs (Damstra et al., 2002). WHO no longer considers EDCs to be a major public health hazard and does not now include them on its list of the 10 chemicals or groups of chemicals of major public health concern. This list consists of: Air pollution, Arsenic, Asbestos, Benzene, Cadmium, Dioxin and dioxin-like substances, Fluoride in excess, Lead, Mercury and highly hazardous pesticides (WHO, 2010).

The Commission of the European Union's Community Strategy for Endocrine Disrupters lists 553 substances in the EU "Candidate List" of EDCs, and includes EDCs in the Framework Programme of the European Community for Research, Technological Development and Demonstration Activities 2007–2013 (EU, 2007). As noted above, the EPA has produced two lists of chemicals to be investigated for endocrine disruption characteristics (EPA 2009, EPA 2010).

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 investigated the oestrogenic (or feminising) effects of chemicals in estuarine waters and was undertaken by the Centre for Environment, Fisheries and Aquaculture Science (CEFAS – see http:/www.cefas.defra.gov.uk). This research finished in 2001 and the Final Report (EDMAR, 2002) was issued in 2002 . The UK Water Industry also undertook some research through UKWIR[19] on the endocrine disrupting effects of sewage effluents, endocrine disrupters in sewage sludge and a study of treatment options with the potential costs for treating endocrine disrupting substances in wastewater (UKWIR, undated).

9 Conclusions

The Precautionary Principle agreed at the Rio Summit stated 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***".

[19] UK Water Industry Research. See http://www.ukwir.org/

Much of the evidence at present is that the environmental threats from the majority of endocrine disrupters 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 in certain circumstances of diethylstilboestrol (DES), EDCs pose a significant threat to human health. The use of DES in animal feed was banned in the USA in 1979 (Brower, 2001) and subsequently in 1988 in all food-producing animals in the EU (EU, 2002b). It should be noted, however, that DES is still used in treatment of certain conditions (Cox, 2008).

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 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."***

WHO does not list EDCs among the chemicals and groups of chemicals of major public concern. Nevertheless, the occurrence of observable changes in the reproductive physiology of certain aquatic species in some eco-systems supports the call for further research. Given the large numbers of chemicals that may have some endocrine properties, and the numerous endocrine functions in different animal species, and the variety of other potential hazards from chemicals, there is a need for continuing 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 (OECD, 2000); a key activity in this work is to develop new, and revise existing, Test Guidelines to detect endocrine disrupters. By 2006 50 test procedures had been published (OECD, 2006).

However, caution should be exercised in the direction of the research into EDCs. There is no firm evidence that bisphenol A is a hazard for human health, yet, as Professor Richard Sharpe of Edinburgh University has pointed out:

> "***Fundamental, repetitive work on bisphenol A has sucked in tens, probably hundreds, of millions of dollars from government bodies and industry which, at a time when research money is thin on the ground, looks increasingly like an investment with a nil return***." (Sharpe, 2010)

Information produced by a number of international programmes currently being undertaken on endocrine disrupters will become part of larger initiatives concerning the delivery of public information about the properties of chemicals. This includes initiatives such as The US Chemical Right-to-Know data collection exercise, and the CEFIC Confidence in Chemicals initiative (Stevenson, 2000). Negative reports in the press and elsewhere on EDCs should be read with caution since there are many pressure groups willing to misrepresent scientific findings and exploit scientific uncertainty.

Finally, it should be borne in mind that many plants contain naturally occurring EDCs. Mankind eats plants and plant products and in so doing consumes EDCs (e.g. in soya, carrots, broccoli, beer, oats etc.) and has been doing so for millennia without becoming extinct. Life has evolved to be able to deal with naturally occurring phytoestrogenic EDCs when consumed in moderation and the evidence so far is that most synthetic EDCs do not pose a significant risk either in the concentrations in which they are found in the environment nor when present in products such as plastic wrapping and containers, household goods, soaps and personal care products etc.

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Websites

Note: Web sites which have been superceded or closed down are usually archived on the Wayback Machine on site: http://www.archive.org/ Some closed websites can also be found cached by the Google search engine. In the UK digital government information from central government websites is regularly archived in The National Archives at http://www.nationalarchives.gov.uk/webarchive/. So, if you get an "unobtainable" message when trying to access a reference to a website, try one of the archive sites.

The Government's Chemicals Strategy: Sustainable production and use of chemicals - a strategic approach. Search for "endocrine disrupters" in the document.
http://archive.defra.gov.uk/environment/quality/chemicals/documents/chemicals-strategy0904.pdf

"Endocrine Disrupters: a Scientific Perspective."
http://www.acsh.org/publications/booklets/enddis.html

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC)
There are a series of useful reports on EDCs, eg report TR106 “Guidance on Identifying Endocrine Disrupting Effects.” Technical Report No. 106, June 2009.
see http://www.ecetoc.org/publications

The EPA website at http://www.epa.gov/endo

European Environment Agency website:
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