Endocrine Disruptor Elimination Campaign (EDEC)

Plan of Action

for the protection of the constitutional rights violated by our continuous and unavoidable exposure to harmful and persistent endocrine disrupting chemicals

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Definition of Endocrine Disruptors:
Chemicals (or mixtures) from outside the body that can interfere with the development or functioning of body systems in humans, wildlife, and especially their offspring, and may lead to irreversible adverse health effects.

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1. Executive summary

In the last century over 70'000 new manmade chemicals were synthesised and released into our environment without proper and adequate testing. Recent studies and laboratory experiments within the science of endocrine disruption have revealed the frightening extent of the impact that many of these chemicals have on our health and environment when they disrupt the delicate yet vital endocrine systems found in most vertebrate animals. Overwhelming and alarming evidence indicates that exposure to concentrations measured in parts per trillion (i.e. less than one drop in 25 olympic-size swimming pools) of these endocrine disrupting chemicals (EDCs) can lead to diseases. For example: cancer, immune system suppression, damages to the reproductive system, birth defects and abnormal expression of sexual characteristics. These findings have been verified and endorsed by scientists and endocrinologists across the globe, the most notable endorsements being the Wingspread Consensus Statement (Appendix G) and the Yokohama Consensus Statement (Appendix H).

Scientists now recognise that it is not possible to accurately determine the safe level of exposure to these chemicals. Unlike the traditional toxicological paradigm of monotonic dose-response curves, just a few EDC molecules can operate like terrorists and hijack the hormonal control of development and cause intense, life-long damage, undermining the immune system, eroding intelligence and/or diminishing reproductive capacity.

Most EDCs are also persistent organic pollutants (POPs) because they do not break down easily and tend to bio-accumulate in the environment. They can also be passed on in the womb and through breast milk. Analysis of polar bear fatty tissue indicates that POPs can be bio-magnified over 25 million times between the top & bottom of the food chain. The recent 184 page European Community (EU) report entitled: **"**Dioxins and other POPs in by-products, recyclates and wastes and their potential to enter the food chain – Stage II" [Authors: European POPs Expert Team, September 2002] clearly indicates that modern man can not avoid exposure to many of these chemicals.

These dangerous background levels of EDCs in our food chain are being linked to increased incidences of endocrine related diseases. Cancer, particularly those forms related to endocrine dysfunction, such as pancreatic, prostate, breast, ovarian and cervical cancer, has reached alarming levels. The latest statistics show that 49% of American males will contract cancer in their lifetimes. In England, testicular cancer has increased in incidence by 55% between 1979 and 1991.

At present in South Africa, large quantities of EDCs are being released into our atmosphere, soil and groundwater through the manufacture, use and waste disposal of EDC containing products. Of particular concern is the use of highly toxic endocrine disrupting chemicals in their direct form such as DDT and pentachlorophenyl (PCP). Both PCP and DDT are already banned in many countries. Another area of immediate concern is the informal policy of open-fire burning of combustible waste at municipal dumpsites, which creates and releases large volumes of dioxins into the atmosphere. According to the Chlorine Chemical Council, open fire burning of waste emits up to 10,000 times more pollutants than waste incineration within a modern municipal waste combustor.

The extent of EDC environmental contamination in South Africa is not well known. South Africa does not even have a dioxin testing facility. Extrapolating international data into the South African context, based on its current EDC use and waste disposal practices, would imply that it is impossible at present for any South African to prevent harmful exposure to these highly toxic chemicals.

As South Africans, we are blessed with a constitution that protects our human rights. It is clear that at least three of these rights are being violated as follows:

(i) The ubiquitous presence of these harmful and persistent EDCs in our environment directly violates the rights outlined in chapter 2, section 24 of the Constitution, namely that: **"Everyone has the right -**
   (a) to an environment that is not harmful to their health or well-being.
   (b) To have the environment protected, for the benefit of present and future generations, through reasonable legislative and other measures that prevent pollution and ecological degradation"

(ii) The fact that it is impossible to prevent harmful exposure to these manmade chemicals violates the rights outlined in chapter 2, section12 (2) of the Constitution, namely that **"everyone has the right to bodily and psychological integrity, which includes the right to security in and control over their body"**.

(iii) The fact that these unsafe and untested manmade chemicals have and are still being released into our environment without adequate testing constitutes what is now being acknowledged within the scientific community as the largest uncontrolled (albeit unintended) experiment in our history. Therefore the continued production and release of these persistent EDC chemicals can be seen to further violate the rights outlined in chapter 2, section 12 (2) of the constitution, namely that everyone has the right **"not be subjected to medical or scientific experiments without their informed consent"**. The ethics of spraying DDT in homes without informing the residents of the dangers, particularly to pregnant mothers, is highly questionable. (Before DDT can be used on laboratory rats at any South African university, no matter how small the amount, the experimenters have to convince an ethics committee. The residents of the Limpopo province and KwaZulu Natal are afforded no such protection.)

This document contains a summary of the known endocrine system disruptors and their proven effects in order to clearly show that our constitutional rights listed above have been and are continuously being violated by the release of these EDCs into our environment. The document also contains a plan of action to help Government with the development and implementation of a safe, practical and effective strategy that would eliminate EDC pollution. The plan contains a list of non-negotiable measures that should be implemented swiftly by Government should they wish to uphold their constitutional duty of protecting present and future citizens in the light of overwhelming recent scientific evidence documenting the dangers relating present practices of use and disposal of EDC containing products within South Africa. We believe that it is reasonable to expect that by the end of November 2004 the following non-negotiable measures should be in place, namely:

- The approval of an emergency budget, as recommended in section 15.1, in order to effectively initiate appropriate responses in the fight against EDCs.
- The banning of all EDCs in their direct form as outlined in section 15.2.
- The elimination of unsafe waste disposal practices as outlined in 15.3.
- The phased elimination of products linked to direct EDC contamination of our food-chain and body systems, as outlined in section 15.4.
- The establishment of an EDC-taskforce to assess South African EDC exposure levels, as outlined in 15.5.
- The adoption of the precautionary principle when evaluating the safety of new technologies, products and materials, as outlined in section 15.11.

Safe alternatives to nearly all EDC containing products do exist but they have not been adopted because of a lack of market awareness combined with the prohibitive manufacture start-up costs associated with new tooling and processes. There are, however, many positive economic benefits linked to the development and adoption of new safer technologies, some of these include:

- The creation of jobs in research and development that would place South Africa on the cutting edge of environmentally safe technologies.
- The creation of new jobs in the manufacturing sector required for the production of EDC-free products and materials.
- The reduction in foreign expenditure linked to the importation of toxic EDC containing chemicals and materials into the country.
- The creation of new jobs in the farming sectors to support the manufacture of EDC-free plant fibre based bio-plastic alternatives such as PLA.
- Exports of manufactured EDC-free products and materials to markets concerned with health and environment protection.
- Exports of agricultural products to markets concerned with food safety.
- Patent profits from EDC-free alternatives developed in South Africa.
- The cost savings on cost of health care relating to EDC diseases.
- Benefits related to an increase in society's average IQ as a result of not disrupting the cognitive development of children.

2. Understanding the endocrine system

Our endocrine system is a very delicate chemical messenger system which uses hormones released in minute quantities (parts per trillion) to control and regulate all the major functions and processes of the body including:

(i) Energy control

(ii) Reproduction

(iii) Immunity

(iv) Behaviour (e.g. fight or flight response)

(v) Growth and development

(vi) Basic cell division from the fertilised egg to the fully grown adult

(vii) Mental development in children

(viii) Sexual development, including sexual persuasion

(ix) Other possible and yet unknown functions (There are at least five hormones which we know nothing about. These mysterious hormones have aptly been named ghost hormones)

Hormones interact to maintain the above functions and help to regulate our responses to disease, our ability to reproduce and even influence our relationships and behaviour (such as mother-child bonding).

Hormones work by attaching to specific receptor sites found within our cells, stimulating the cell to perform specific tasks. The natural level of hormones are found in extremely low concentrations, sometimes even measured in parts per trillion (i.e. one part per trillion is equivalent to 1 drop in 25 olympic-size swimming pools), and are therefore difficult and expensive to measure. This is perhaps the reason why we know so little about the entire functioning of this delicate system. Our lack of understanding of the full workings of this delicate yet all important chemical messaging system is highlighted by the acknowledged presence of mysterious ghost hormones.

For more information on the endocrine system please refer to Appendix F

3. Mechanisms of endocrine disruption

Endocrine disrupting chemicals (EDCs) act on the endocrine system to disturb the homeostatic mechanisms of the body or to initiate processes at abnormal times in the life cycle. These chemicals can exert their effects through a number of different mechanisms:

(i) They may mimic the biological activity of a hormone by binding to a cellular receptor, leading to an unwarranted response by initiating the cell's normal response to the naturally occurring hormone at the wrong time or to an excessive extent (agonistic effect).

(ii) They may bind to the receptor but not activate it. Instead, the presence of the chemical on the receptor will prevent binding of the natural hormone (antagonistic effect).

(iii) They may bind to transport proteins in the blood, thus altering the amounts of natural hormones that are present in the circulation.

(iv) They may interfere with the metabolic processes in the body, affecting the synthesis or breakdown rates of the natural hormones.

It is interesting to note that the hormonal receptor sites are so promiscuous that they bind with these unknown manmade EDCs. Some scientists speculate that this may be a mechanism for nature to exercise some control over the population on the planet through the release of natural oestrogen-like compounds called phytoestrogens in the plants that we eat.

These phytoestrogens are found in low levels in certain plants such as wild carrot and pomegranate. Many of these plants have been used for centuries as a form of natural birth control. The main difference between these natural “plant estrogens” and the manmade endocrine disruptors is that natural compounds break down in the body within minutes or a few hours. By contrast, the manmade endocrine disruptors do not break down easily and they tend to accumulate in our body tissue, reaching very high concentrations over time… concentrations millions of times higher than plant-based phytoestrogens.

4. The largest uncontrolled experiment in history

One of the unintended consequences of the modern chemical revolution has been the worldwide dispersal of contaminants. In the last century man has synthesised over 70'000 new manmade chemicals, many of which (for example dioxins, furans and PCBs) interfere with the body's own hormones disrupting the delicate endocrine system in a variety of ways (refer to section 4).

These endocrine disrupting chemicals (EDCs) find their way into our bodies through a variety of pathways. They build up over time, often over years. No ecosystem has been left untouched. No human has been born since the middle of the 20th century without some exposure to these hormonally active synthetic compounds.

When a woman becomes pregnant, some fraction of her EDC contaminant burden is transferred to the foetus where theses endocrine terrorists then interfere with the hormonal signals directing development and thus disrupt foetal growth. Sometimes the effects are conspicuous and sometimes they are not.

Some EDCs alter sexual development. Some undermine intelligence and behaviour. Others make our bodies less resistant to disease. Sometimes the effects don't appear until the child reaches puberty or afterwards, even though the exposure took place in the womb.

EDC exposure poses the greatest hazard in the earliest phases of life because hormones orchestrate development and because foetal development is exquisitely sensitive to tiny variations in hormone signals. For a foetus to grow up according to its genetic blueprint, the right hormone message has to arrive at the right place in the right amount at the right time.

So it is clear that we are all unwillingly (and unwittingly) participating in this uncontrolled and unintended experiment from the moment of our conception. These toxic EDCs also accumulate in our bodies over our lifetime creating a long-term exposure unprecedented in our evolutionary experience. The fact that extremely low-level exposure to these chemicals has been positively linked* to endocrine disruption related diseases is a huge cause for concern. It is blatantly obvious that the only logical, safe and effective and solution to this problem of EDC exposure to current and future generations is to stop the manufacture, use and unsafe waste disposal of all EDC containing products.

* Nagel, SC, FS vom Saal, KA Thayer, MG Dhar, M Boechler and WV Welshons. 1997. "Relative binding affinity-serum modified access (RBA-SMA) assay predicts in vivo bioactivity of the xenoestrogens Bisphenol A and Octylphenol". Environmental Health Perspectives 105:70-76, see also US National Toxicology Program's Endocrine Disruptors Low-Dose Peer Review Report, October 2000, as well as vom Saal, F, BG Timms, MM Montano, P Palanza, KA Thayer, SC Nagel, MD Dhar, VK Ganjam, S Parmigiani and WV Welshons. 1997. "Prostate enlargement in mice due to fetal exposure to low doses of estradiol or diethylstilbestrol and opposite effects at high doses." Proceedings of the National Academy of Sciences USA 94:2056-61.

5. The endocrine disruptor chemical family

The common link between most EDC-containing chemicals and compounds is the presence of chlorine attached at some point to a carbon chain and their persistence in nature. Persistent organic pollutants (POPs) are so named because nature has no natural defence against them and they are not easily broken down into safer molecules. This means that the EDC toxins that we release into our environment now will still be present in the environment of future generations to come.

The most common of these 'hand-me-down' persistent endocrine disrupting toxins are:

(i) Dioxins, a family of 75 chemicals, 1000 times more toxic than arsenic and which includes the infamous 2,3,7,8 TCDD, the most toxic chemical on earth

(ii) Poly Chlorinated Phenyls (PCBs), a family of 209 chemicals

(iii) Furans, a family of 135 chemicals

(iv) Other organohalogen compounds such as some pesticides, fungicides, herbicides and insecticides.

(v) Additives used in plastic manufacture such as Bisphenol A in clear polycarbonate plastic and certain phthalates found in soft plastics.

(vi) Suspected additions to the POP EDC family include Poly Aromatic Hydrocarbons (PAHs) released from automobile exhausts and Trihalomethane (THM), a chemical released as a by-product of water chlorination found in tap water which is formed when the chlorine reacts with organic matter.

For the full list of all known EDCs and their proven effects on the endocrine system please refer to Appendix A.

6. Known effects of endocrine disruption on our bodies

Most endocrine disrupting chemicals are lipophilic and will accumulate in the body tissue of animals, particularly those at the top of the food chain. It is only in the last three decades that we are beginning to understand the full scope of the disaster that we have created. The nature and extent of the effects of exposure on humans has been difficult to establish. This is because information is limited concerning the disposition of these contaminants within humans, especially data on concentrations of contaminants in embryos. This is compounded by the lack of measurable endpoints (biologic markers of exposure and effect) and the lack of multi-generational exposure studies that simulate ambient concentrations.

One of the major factors restricting the release of adequate independent findings into the effects of EDCs on animals and humans has been the high cost relating to EDC testing and research. A single dioxin test, for example, can cost about US$1000. The conclusions of EDC related research are often damaging to the multinational petrochemical, agrichemical and pharmaceutical companies and conglomerates who profit from the sale of EDC containing products. It is usually these very companies who have traditionally funded ‘independent’ research, by means of financial contributions to academic institutions. It is therefore of no surprise that proper funding has not been forthcoming for necessary research into EDCs. Nevertheless, there has been plenty of progress in this field. The most comprehensive work documenting the effects EDCs can be found in the book ‘Our Stolen Future' (Colburn, Dumanoski, Meyers) which was compiled from a database of over 4,000 scientific publications. Over 100 scientists participated directly in the deliberations that produced a series of consensus statements about the nature of the problem. Many scientists reviewed their sections of the book word-by-word to ensure that their findings were not misrepresented.

Much of our knowledge about the effects of EDC exposure is based on laboratory experiments on animals as well as the observed effects of EDC exposure in wildlife populations. Results do vary between species and exposure, but, overall, four general principles apply, namely:

I. EDCs may have entirely different effects on the embryo, foetus, or peri-natal organism than on the adult.
II. The effects are most often manifested in the offspring, not in the exposed parent.
III. The timing of exposure in the developing organism is crucial in determining its character and future potential.
IV. Although critical exposure occurs during embryonic development, obvious manifestations may not occur until maturity.

As all vertebrates have the same basic endocrine system, it was no surprise to notice parallel effects of EDC exposure in humans. This was first confirmed when studies into the effects of human exposure to DES (diethylstilbestrol) matched the effects of similar in-utero DES exposure for laboratory rats. DES is a synthetic therapeutic agent (and an oestrogen-mimicking EDC) which was prescribed recklessly to expectant mothers in the late 1950s and early 1960s. The thalidomide tragedy in the early 1960s showed that placenta was not the impenetrable barrier it had been thought to be. DES was withdrawn from the market soon after that and the trans-generational effects of exposures to DES then became apparent. Daughters born to mothers who took DES suffered increased rates of vaginal clear cell adenocarcinoma cancer, various genital tract abnormalities, abnormal pregnancies, and some changes in immune responses. Both sons and daughters exposed in utero experience congenital anomalies of their reproductive system and reduced fertility.

Current research indicates that EDC exposure may result in the following diseases and abnormalities:

(i) Cancer, particularly those forms related to endocrine dysfunction, such as pancreatic, prostate, breast, ovarian and cervical cancer. The latest statistics show that one in two American males will contract cancer. In England, testicular cancer has increased in incidence by 55% between 1979 and 1991.

(ii) Immune system disruption, suppression and the reduction of T-helper cell count.

(iii) Birth defects and miscarriages

(iv) Abnormal physical sexual development, including feminisation of men and defeminisation of women

(v) Diabetes

(vi) Asthma

(vii) Potential corruption of gene code where dioxin enters a cell nucleus and bonds to the DNA by occupying the Aryl Hydrocarbon (AH) receptor

(viii) Suppression of adrenal glands (such as the thyroid gland which can lead to diseases such as breast cancer)

(ix) Sperm loss, low sperm count, including possible damage to sperm DNA

(x) Disruption of gene expression where genes are silenced or activated inappropriately by low level doses of certain EDCs

(xi) Female related diseases such as endometriosis, cervical dysplasia, early onset of annovulatory cycles, polycyctic ovaries, uterine fibroids, infertility due to luteal phase failure leading to early miscarriage, early onset of menstruation, irregular periods, premenopausal bone loss and osteoporosis.

(xii) Behavioural effects and learning disorders *

(xiii) Increases in allergies, skin problems, severe teenage acne and chloroacne.

(xiv) Other symptoms include chronic fatigue, memory loss and foggy thinking, lacking power of concentration, decreased libido, thyroid problems and a sluggish metabolism.

These symptoms only take into account exposure to one EDC. In reality, we are all exposed to a lethal cocktail made up of over 560 known EDCs. The synergistic effects this kind of this multiple EDC exposure is considered by experts to be far more damaging than single EDC exposure. These synergistic effects are not yet properly understood.

* *Studies show that high level of EDCs are passed on to the new-born child through mothers' milk. This is worrying because evidence shows that these chemicals can have a serious negative impact on the cognitive development of the child. See Appendix F for more details.*

7. Compromising our children

The ratio of chemicals to body weight often means they children receive much larger doses of EDCs than adults. The recent publication entitled "Compromising our children - chemical impacts on children's intelligence and behaviour", a WWF-UK Chemicals and Health Campaign Briefing June 2004, clearly highlights the concerns that many scientist in this field of EDC research are now beginning to express.

7.1. Foetal exposure

The most dangerous period of EDC exposure is in the womb. For a foetus to grow up according to its genetic blueprint, the right hormone message has to arrive at the right place in the right amount at the right time. EDCs crossing the placenta can seriously interfere with the hormonal signals directing development and thus disrupt foetal growth. Some of these chemicals alter sexual development. Some undermine intelligence and behaviour. Others make our bodies less resistant to disease. Sometimes effects (such as the unusual cancers related to DES exposure) don't appear until the child reaches puberty or afterwards, even though the exposure took place in the womb.

Scientists have shown that foetal exposure to existing environmental background levels of just one chemical, Bisphenol A, are enough to create such disruptions (Nagel, SC, FS vom Saal, KA Thayer, MG Dhar, M Boechler and WV Welshons. 1997).

7.2. Into the mouths of babes

Apart from exposure to EDCs in the womb, babies and young children are particularly at risk because they are exposed to a number of child-only sources of EDCs, namely:

- Breast-milk. Lipophilic EDCs are passed on to breastfeeding children. It is estimated that a mother's first breastfeeding child will receive over 30% of the mother's 'toxic payload'
- Polycarbonate baby bottles which have been shown to leach out hormone disrupting Bisphenol A (BPA).
- Soft plastic toys and teethers containing EDCs in the form of plastisers (phthalates) which leach out of the material.

The synergistic effects of a child's exposure to the over 500 known EDCs have yet to be explored but most experts believe that this is a huge cause for concern which could explain the increase in the number of incidences of diseases and disorders such as allergies, asthma, ADD and ADHD in children. Please refer to Appendix F for more details.

8. Common sources of endocrine disrupting compounds

Endocrine disruptors are found or released in the following products and processes:

(i) Plastics such as PVC and certain cling-wraps, polystyrene, including clear polystyrene release EDCs as follows:
  a. Dioxin emissions during the manufacture and moulding processes
  b. Dioxins and plasticisers (phthalates) leaching out of the plastic over time
  c. Dioxin emission and creations if the plastic is burnt

(ii) Clear rigid polycarbonate plastic leaches out the known hormone disruptor bisphenol A (BPA). Products containing BPA include adhesives, pipes, thermal fax paper, car dashboards and electronic goods, but its presence in the linings of food cans and in baby feeding bottles causes the greatest concern.

(iii) Synthetically produced pharmaceuticals that are intended to be highly hormonally active, e.g. the contraceptive pill, HRT and treatments for hormone-responsive cancers may also be detected in sewage effluent. Synthetic hormones and oestrogenic compounds are now also found in meat, much of which is hormone fed. Cattle are given bovine growth hormones or D.E.S. (diethol stilbestrol) to fatten them. Chickens are also fed hormones to promote growth.

(iv) Agro-chemicals: Highly poisonous pesticides such as DDT. EDCs also exist in other pesticides in use such as dieldrin, toxaphene, mirex, heptachlor and kepone as well as many other herbicides and fungicides.

(v) Wood preservatives such as Pentachlorophenol (PCP)

(vi) Some paints & inks

(vii) PVC-based insulation on electricity cable and other forms of heat-resistant plastic

(viii) Waste from pulp and paper mills

(ix) Waste from iron ore sintering plants

(x) Dioxin emissions from hospital incinerators, municipal incinerators, low temperature burning of plastic waste at dump sites, backyard rural and urban burning of waste

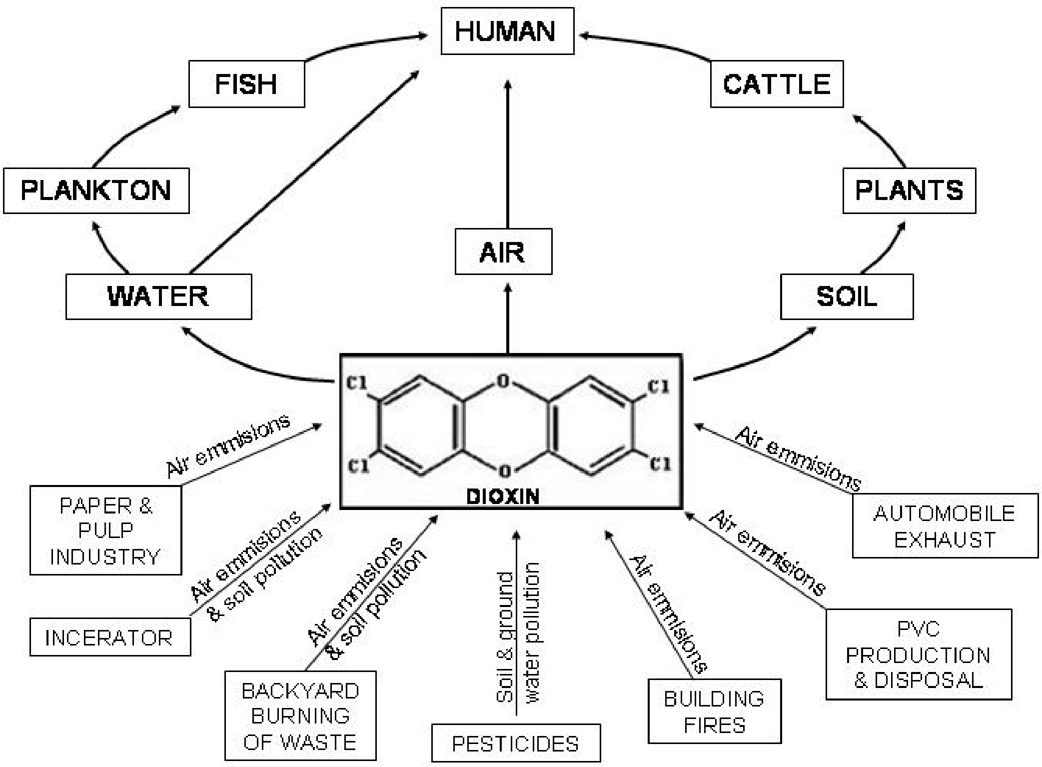
(xi) Generation of poly-aromatic hydrocarbons (PAHs) and other possible dioxins in petrol based car exhaust fumes

(xii) Polychlorinated biphenyls (PCBs) used in the manufacture of electronic devices.

(xiii) Fire-retardants such as polybrominated diethyl ethers (PBDEs), used in many household items such as bed mattresses, duvets, sofas, carpets, etc.

(xiv) Accidental chemical spills and fires, especially in plastic manufacturing plants and warehouses

(xv) There are still many chemicals that are yet to be tested. So far, scientists have identified at least 560 known EDCs, these are listed in Appendix A. Other chemicals under suspicion include trihalomethane (THM), a by-product of chlorinated water sterilisation that is formed when chlorine reacts with organic matter in the water.



ANTHROPOGENIC SOURCES OF DIOXINS

9. Common methods of endocrine disruptor environmental contamination

Toxic endocrine disruptors enter our environment in the following ways:

9.1. The use of highly toxic of endocrine disruptors in their pure form:

In many cases, endocrine disruptors are manufactured and sold in their pure or diluted form. For example the highly toxic dioxin Pentachloraphenyl (PCP) is manufactured and sold as a wood preservative under the brand name Timber-life. Another highly toxic dioxin DDT is being manufactured and sprayed into homes as part of the South African Government's anti-malaria campaign, even though safer and effective malaria control alternatives exist and have shown to have been effective in other countries. A study published in July 2001 by scientists from the US Centre for Disease Control and the National Institute of Environmental Health Sciences, clearly repudiates any notion that DDT is without human health risk (Both PCP and DDT are banned in the many countries).

9.2. As a by-product of manufacturing processes:

Dioxins are released during the manufacture and moulding of certain plastics such as PVC and polystyrene dioxins. In this context, polystyrene not only includes white styrofoam but also clear polystyrene and high impact polystyrene (HIP).

9.3. Leaching of EDCs out of certain plastics products during use:

Plastics are not as stable as we have been led to believe. Dangerous levels of EDCs in the form of dioxins and plasticisers such as DEHP leach out of products made out of PVC and polystyrene in the following applications:

(i) Beverage and food packaging, e.g. polystyrene foam cups, some soft plastic and clear polystyrene bottles, high impact polystyrene (HIP) packaging, polycarbonate bottles, as well as certain EDC containing cling wraps. Leaching is exaggerated when food (particularly oily or fatty food) is micro-waved in plastic containers.

(ii) Children's toys and baby teethers. As highlighted by the recent action in the 1990s when Mattel posted consumer warnings concerning the high levels of endocrine disruptors leaching out of old Barbie dolls. PVC-based baby teethers are now banned in certain European countries.

(iii) In the medical profession, where the use of PVC blood-bags, intravenous drips (including tubing) and high impact polystyrene (HIP) blister-type packaging are used, even though it is well documented that endocrine disrupting plasticisers and dioxins leach out of these materials.

9.4. The use of EDC containing chemicals in agriculture:

(i) Agro-chemical companies continue to supply farmers with toxic EDC-based chemicals in the form of pesticides, herbicides and fungicides, even though they are aware of the impact of these chemicals on our health and environment.

(ii) Farmers also use synthetic hormones such as bovine growth hormone and DES to accelerate animal growth and fatten the animals. These hormones also affect our endocrine system.

(iii) Raw or composted sewerage sludge, which usually contains high levels of EDCs, is sometimes used to fertilise fields.

The fact that these chemicals are added directly to our food is of particular cause for concern.

9.5. During waste disposal of products:

Dioxins and other endocrine disruptors found in products such as PVC are released after the product is disposed of in the following ways:

(i) Incineration: In theory, unless the incinerator operates at over 850.75 degrees Celsius, the dioxins contained in compounds such as PVC will not be broken down and will instead be freed from the compound and released into the atmosphere. However, even the latest, most advanced high temperature incinerators still release EDCs in the form of highly toxic fly ash (3-5% of weight of what enters the incinerator) this is because many dioxins are formed when the high temperature gases from the combustion process begin to cool.

(ii) Backyard burning: Homeowners and farmers who burn plastic and other waste containing dioxins are freeing the toxins from their host compound and releasing them into the atmosphere. In the USA, backyard burning accounts for over 50% of dioxin emission into the environment.

(iii) Burning of combustibles on dump sites: In South Africa, many municipal dumps have adopted the informal and extremely dangerous policy of burning all combustible waste in open fires in order to reduce the waste volumes on site. These methods are shown to produce over 10,000 times more EDC pollutants than high temperature burning in modern waste incinerators.

(iv) Landfills: Waste containing EDCs such as plasticisers and dioxins breaks down over time leaching a steady stream of toxic endocrine disruptors into the soil and groundwater.

9.6. Accidental release:

This includes accidental fires in plastic factories and warehouses, accidental spills from trucks and ships containing EDCs in liquid form. One of the most frightening examples of this was the accidental release of thousands of litres of the most toxic chemical in existence a dioxin called 2,3,7,8 TCDD at Seveso (Italy) in 1976. There have been other similar documented spills of 2,3,7,8 TCDD in the USA by its manufacturer Monsanto.

10. What are safe levels of EDC exposure?

Sheldon Krimsky's book, Hormonal Chaos, describes endocrine disruption as a paradigm shift in toxicology. At the core of this shift are scientific results demonstrating that endocrine disruption has impacts at contamination levels far beneath those of traditional concern to toxicologists. These levels are often so low that they are measured in parts per trillion.

Traditional toxicology as used by regulatory authorities is based on the assumption that dose-response curves were always monotonic: that is, higher doses have a greater effect than lower doses. The old paradigm focused on acute toxicity. How do high levels of contamination affect health? How do they cause cancer? How do they kill directly? How do they overcome the body's defences, like a massive invading army overwhelming the defenders simply by brute force and large numbers?

The new toxicological paradigm recognises that there are other ways in which contaminates like EDCs can work. Think of how terrorists overwhelm larger forces. Instead of using the brute force of large numbers, a small number of molecules can hijack the hormonal control of development and cause intense, life-long damage, undermining the immune system, eroding intelligence, and diminishing reproductive capacity.

This terrorist attack on foetal development works because some chemicals act as impostors, insinuating themselves in the body's natural hormone system that normally directs foetal development. These natural hormone signals work at very low concentrations. And the impostors do also, sometimes at levels tens of thousands of times lower than the brute force approach considered by traditional toxicology. For example, fluctuations by amounts as low as 30 parts per billion of oestrogenic chemicals during critical stages of foetal development have been shown to affect the process of cell division thereby disrupting the development of the foetus according to its genetic blue print.

Another important assumption of the old paradigm as used by regulatory authorities is that there is a threshold beneath which no effect occurs. Here, too, endocrine disrupting chemicals violate long-held, but not tested, assumptions. What we now realise is that there is no real safe EDC exposure level. Experts now acknowledge that “tolerance daily intake” (TDI) standards for dioxins, such as 0.006 pg TEQ1/kg body weight as set by the EPA in USA, are both meaningless and deceiving. The simple truth is that even one endocrine disrupting molecule can act as a silent terrorist, with the potential to enter a cell and disrupt natural cellular functioning, even on a genetic level, in ways that result in diseases such as cancer.

One of the biggest concerns is that our bodies do not have any natural defences against these endocrine disrupting terrorists.

11. Natural phytoestrogens vs. synthetic manmade EDCs

Many plants produce oestrogen-like substances called phytoestrogens. These “plant oestrogens” can interfere with the interactions between mammalian oestrogens and their oestrogen receptors. Phytoestrogens are widespread in our diets and when eaten in large volumes they can cause serious problems. In fact they have been used as anti-fertility agents by many cultures for a long time. Normal diets usually, however don't create risks because our gut chemistry quickly flushes them through and because there are special proteins in our blood that are effective at ensuring that many (but not all) of these natural compounds don't reach the foetus at levels sufficient to have an effect.

The main differences between natural plant phytoestrogens and the manmade endocrine disruptors is that:

(i) Manmade endocrine disruptors also interfere with hormones other than oestrogen.

(ii) The body is quite capable of avoiding the impact of many (but not all) phytoestrogens because we have evolved defences to cope with them.

(iii) Natural plant oestrogens break down within in our bodies within a few minutes to a few hours, whereas manmade EDCs break down over many years.

(iv) Manmade EDCs are not flushed through our bodies. Chemical accumulation in the fat tissue and breast milk can reach very high concentrations over time, concentrations millions of times higher or more than plant oestrogens.

12. EDC effects on other natural systems

EDCs are very small molecules that do not breakdown easily. They are able to travel thousands of kilometres in the atmosphere as well as in the body tissue of migrating animals. Billions of litres of highly toxic chemicals like DDT and 2,3,7,8 TCDD have already been released into the environment and many wildlife populations are already affected by these compounds. Extremely high concentrations of EDCs have been found in the tissue cells of animals on the top of the food-chain such as dolphins, seals, polar bears and seabirds. In fact, our oceans are now being referred to as 'seas of oestrogen'. Male fish have been found with eggs formed in their testes. Other impacts include thyroid dysfunction in birds and fish; decreased fertility in birds, fish, shellfish, and mammals; decreased hatching success in birds, fish, and turtles; gross birth deformities in birds, fish, and turtles; metabolic abnormalities in birds, fish, and mammals; behavioural abnormalities in birds; demasculinisation and feminisation of male fish, birds, and mammals; defeminisation and masculinisation of female fish and birds; and compromised immune systems in birds and mammals.

There are other impacts that EDCs have on our bodies and our environment apart from endocrine system disruption, such as the disruption of gene expression, with genes being silenced or activated inappropriately. Research is revealing that a surprisingly large number of contaminants are capable of interfering with gene expression at very low levels of exposure, and that the genes (and gene families) vulnerable to disruption are tied to a wide array of diseases and to very basic developmental processes. A high priority should be placed on identifying environmental agents that can disrupt gene expression and to begin implementing public health standards that reduce exposures.

Natural chemical signals are important at all levels of life - within cells, among cells, between organs, even between organisms, including from one species to another. Any of these chemical signals, in principle, is vulnerable to disruption. Scientists, for example, have just begun to look at the chemical signals that mediate communication between symbiotic organisms, such as nitrogen-fixing bacteria and the roots of the plants, in which they live. They are examining how synthetic chemicals might interfere with these signals. Disrupting these 'signals of life' could have important ecosystem impacts.

13. Safe alternatives

Safe alternatives to nearly all EDC-containing products do exist. These include:

13.1 Medical consumables: At present there is a choice of three tested and approved commercially available EDC-free alternative to the existing PVC blood bags, intravenous drip bags and tubing.

13.2 PVC: EDC-free alternatives exist to in almost all applications including electrical conduit insulation.

13.3 Agrichemicals: EDC-free synthesised and natural (plant based) pesticides and as well as organic farming practices such as companion planting techniques.

13.4 Bio-plastics, a new generation of EDC-free materials made from plant matter (not fossil fuels). These are commercially available as: Polylactic acid (PLA), Earthshell, Eastar-Bio and Ecoflex, all of which are fully biodegradable and even compostable.

13.5 Cellulose-based alternatives to polystyrene fast food packaging as used by the Wimpy fast-food chain.

13.6 Malaria control: Alternatives to DDT have been documented as safe and effective and have been used in Africa and Asia. The following is a list of safe alternatives that could be evaluated for use in the South African context:

(i) Human-safe coconut-incubated bacterial toxin from *Bacillus thuringiensis israelensis* (*Bti*) can be sprayed into breeding sites as a highly specific agent against mosquito larvae. Tests demonstrate that Bti kills nearly all the mosquito larvae in a typical pond, halting breeding for up to 45 days. The CSIR should investigate the cheap propagation of this alternative.

(ii) Pyrethroids such as deltamethrin and lambdacyhalothrin are effective at far lower doses than DDT (c.25 mg/m^2 compared with 2 gm/m^2). Any synthetic pyrethoids will, however, need to be evaluated as potential EDCs.

(iii) Impregnated bed nets containing natural or synthetic EDC-free insecticide.

(iv) Solar-powered high frequency electronic mosquito repellents.

(v) Topical application of oils and herbal extracts like coconut oil, cymbopogan, lantana, geranium and neem oil.

(vi) Other complementary measures include the use of bed nets and house screens, planting lemon trees, fumigating homes by burning eucalyptus branches and leaves, paving irrigation channels, stocking breeding sites with larvivorous fish, screening water storage tanks and eliminating waste water.

The reason why many of these safe EDC-free alternatives have not been adopted is mostly due to a lack of market (consumer) awareness combined with the prohibitive manufacture start-up costs associated with new tooling and processes. There are, however, many positive economic benefits linked to the development and adoption of new safer technologies, some of these include:

- The creation of jobs in research and development that would place South Africa on the cutting edge of environmentally safe technologies.
- The creation of new jobs in the manufacturing sector required for the production of EDC-safe products and materials.
- The reduction in foreign expenditure linked to the importation of toxic EDC-containing chemicals and materials into the country.
- The creation of new jobs in the farming sectors to support the manufacture of EDC-free plant fibre-based bio-plastic alternatives such as PLA.
- Exports of manufactured EDC-free products and materials to markets concerned with health and environment protection.
- Exports of agricultural products to markets concerned with food safety.
- Patent profits from EDC-free alternatives developed in South Africa.
- The cost-savings on cost of health care relating to EDC diseases.
- Benefits related to an increase in society's average IQ as a result of not disrupting cognitive development in children.

14. Defending our constitutional rights

The ultimate purpose of this document is to defend the Constitutional rights that we (the EDEC) feel have been violated with regard to the past and present production and release of EDCs into our environment. These rights are namely:

I. The right to a safe environment that is not harmful to our health or well-being.
II. The right to have the environment protected, for the benefit of present and future generations, through reasonable legislative and other measures that prevent pollution and ecological degradation.
III. The right to bodily and psychological integrity, which includes the right to security in and control over our bodies.
IV. The right not to be subjected to medical or scientific experiments without our informed consent.

The overwhelming and alarming evidence pertaining to manmade endocrine disruptors and their effect on the environment and the human body has been documented in the book 'Our Stolen Future' (Colburn, Dumanoski, Meyers) which was compiled from a database of over 4,000 scientific publications. This leaves no doubt that we ***no longer have a safe environment***. In addition to this evidence there have been three separate consensus statements compiled by scientists and experts (see appendices G, H & J), as well as reports presented by governments and organisations such as the WWF and the WHO, the USA's EPA and FDA, and the in particular the EU who have published two comprehensive reports on how EDCs enter the food chain.

The lack of legislation or concern by government ***to have the environment protected*** against contamination by persistent endocrine disrupting pollutants ***for the benefit of present and future generations*** is indicated by its recent policy of spraying DDT to prevent malaria as well as the fact that South Africa has no dioxin testing facilities.

The persistent nature of these EDCs accumulating in our food chain and the fact that no one can escape exposure to these endocrine disrupting terrorists means that ***we no longer have control over our own bodies***.

The fact that over 70'000 manmade chemicals were released into our environment without adequate testing. The fact that many of these persistent and unsafe manmade chemicals continue to be released into our environment amounts to us being unwilling and ***unconsensual participants*** in what is now commonly regarded by the scientific community as ***the largest uncontrolled and unintended experiment*** in the history of our planet. We feel that it is also unethical to perpetuate the experiment without adequately informing the public of the associated dangers EDC exposure.

15. The plan of action

Government must take the following steps to ensure that the constitutional rights mentioned in section 14 of this document are upheld:

15.1. The approval of the emergency funding required in order to begin the necessary processes of EDC research and screening, education and awareness, and waste management and reduction as outlined in this plan of action. It is recommended that this amount be at least R350 million, which is equivalent to USA's EPA 2004 budget of US$50 million for EDC, pesticide and toxin research & screening alone. A comprehensive annual EDC expenditure amount should also be determined for inclusion into the Government's budgets for 2005 and beyond.

15.2. The immediate banning and safe disposal of products containing highly toxic EDCs in their pure form such as PCP (Pentachlorophenyl). DDT, however, should only be phased out once EDC-free alternatives such as those outlined in section 13.6 can be safely and effectively implemented. Government must prioritise this strategy of DDT replacement by providing adequate research funding. People exposed to DDT must be adequately informed of its dangers, especially pregnant women. Prescriptive use of DDT versus the right to an informed choice should also be investigated.

15.3. The immediate establishment of a safe and effective waste-stream for the disposal of products containing EDCs, including:

(i) The elimination of the informal policy of burning waste at landfill sites in open fires in order to reduce volumes

(ii) The establishment of legislation outlawing the burning of plastic.

(iii) The introduction of a plastic and EDC waste collection service to rural communities and farmers to prevent backyard burning.

(iv) The evaluation of all forms of waste incineration to ensure zero emissions of EDCs from these facilities. This includes the immediate termination of the incineration of medical and other waste at less than 851 degrees Celsius.

(v) The establishment of safe procedures to safely dispose of highly toxic EDCs such as 2,3,7,8 TCDD and PCBs, trace historic waste disposal sites and test soil and groundwater.

(vi) The implementation of a nationwide EDC education campaign in schools and the media in order to educate the public on the dangers of backyard burning of plastic waste and other waste containing EDCs.

15.4 The phased elimination over a period of six months of the sale and use of the following EDC-containing products and compounds:

(i) Agro-chemicals in the form of pesticides, herbicides, fungicides, fertilisers and growth hormones. The agro-chemical companies should also bear part of the cost of the safe disposal of existing EDC-containing products in their warehouses, in shops and in the farming community. The government should provide assistance to farmers making the transition from EDC chemicals to the safer alternatives, namely by:

a. Providing mechanisms for the safe disposal of old stocks of these chemicals, including EDC-containing tick dip in farmers dipping tanks
b. Providing financial assistance to farmers with dipping tanks to convert over to the new dipping tanks
c. Supporting the transition to safe farming practices like organic farming and permaculture.

[Many multinational agro-chemical companies have been making profits out of these unsafe products with full knowledge of their effects even though safer alternatives exist. These unscrupulous companies should in theory bear the cost to farmers of the changeover to safer EDC-free alternatives.]

(ii) Products that leach EDCs directly into the food chain, e.g. polystyrene cups and food containers, certain makes of cling film, certain plastic containers for food storage, certain baby bottles and teats.

(iii) Medical products containing EDCs such as PVC blood-bags, intra-venous drips and tubing, high impact polystyrene (HIP) blister-type packaging, etc. (Safer non-leaching alternatives to PVC and HIP products do exist and are commercially available).

(iv) Children's toys and baby teethers that leach out plasticisers, dioxins and other EDCs.

15.5. The establishment of an EDC taskforce comprising of local and international experts whose objective would be to assess the extent of EDC contamination within South Africa. The taskforce should aim to produce a comprehensive ‘first assessment report’ within six months. To be effective, this workgroup will require adequate funding which would be similar to what the EU paid for their reports on Dioxins and other POPs in by-products, recyclates and wastes and their potential to enter the food chain.

15.6. The phased elimination over five years of all other EDC-containing products and pollution with the following conditions:

(i) Effect immediate mandatory labelling of EDC content (such as phthalates and Bishphenol A) on all products.
(ii) Implement and enforce legislation that would require manufacturers and downstream users to report the release of suspected endocrine disrupting substances into air, water and land, and also the amounts released from the works in products.
(iii) Implement and enforce legislation requiring stricter fire prevention methods in areas of bulk plastic storage in plastic factories and warehouses.

(iv) Implement and enforce legislation requiring stricter spill prevention and safer clean-up and disposal methods to deal with EDC-containing liquids and dissolvable solids.

(v) After two years all companies still selling products containing EDCs must take financial responsibility and legal accountability for the collection and safe elimination or recycling of the EDC portion of their products.

(vi) Exemptions from this five year phased elimination should only be given to products used in applications critical to the safety of human life and where no other safe non-EDC containing alternatives exist. These exemptions should be granted by a panel of judges and reviewed every two years.

(vii) Companies selling these exempted products will still have to take responsibility for the safe disposal or recycling of the EDC portion of the product waste. These companies must also allocate half of the profits made from the sale of these products (or alternatively five percent of the retail price, whichever is the greater) into research into alternative and safer technology.

15.7. The immediate establishment of a screening and testing centre in South Africa to monitor levels of EDCs such as dioxins, PCBs, furans and other known endocrine disruptors in our food chain and environment. This should include the monitoring of contamination levels of soil and ground water near present and past waste disposal sites (South Africa has no dioxin testing facilities at present).

15.8. The immediate establishment of a Endocrine Disruption Research Centre with the aim of identifying all products containing endocrine disruptors and their effects, including suspected EDCs such as poly-aromatic hydrocarbons (PAHs), nonylphenol and trihalomethanes. This centre should also research the other impacts that these EDCs may have on our bodies such as the disruption of gene expression, with genes being silenced or activated inappropriately. There should be a significant commitment of government spending to resolve scientific questions and determine which of these potential risks are real and which ones are not. Industry should be encouraged to support research on these issues, but the funds should be placed in a trust fund overseen by a governing body including appropriate representation of all major stakeholders to insulate researchers from the pressures of special interests.

15.9. The establishment of a research centre in order to identify safe alternatives to products containing endocrine disruptors.

15.10. The reduction of global emissions of endocrine disruptors, leading by example by following this plan of action as well as exerting international pressure through its presence on forums such as CODESA, the UN and the Commonwealth.

15.11. The immediate establishment an effective regulatory body to adequately test the release of any new manmade products manufactured or sold in South Africa. This body should implement the precautionary principle. Current regulatory practices give chemical manufacturers the benefit of the doubt. At present, substances can be removed from the market only if their health impacts can be demonstrated with scientific certainty. This burden of proof needs to be shifted. If plausible doubt can be justified about the safety of chemical compounds, their use should be allowed only if the manufacturer can prove that they represent no inappropriate threat to human or ecosystem health.

15.13 We recommend that government sets targets for organic agriculture similar to those in the EU, e.g. 15% of all farms should be fully organic within ten years. This should be backed up with firm financial commitment from government.

EDEC calls for swift response from Government in the fight against EDCs and expects that within three months, by 30 November 2004, regulations will be in place to achieve steps 15.1, 15.2, 15.3, 15.4, 15.5 and 15.11.

APPENDIX A

List of known endocrine disrupting chemical pollutants and their proven effects on the endocrine system

Persistent organohalogens

Compound(s)	Hormone system affected	Mechanism if known	References
Benzenehexachloride (BHC)	Thyroid		Akhtar *et al*. 1996
1,2-dibromoethane	Reproductive		Brittebo *et al*. 1987
Chloroform	Reproductive		Brittebo *et al*. 1987
Dioxins and furans (in order of antiestrogenic potency : 2,3,7,8-tetrachlorodibenzo-p-dioxin > 2,3,7,8-tetrachlorodibenzofuran > 2,3,4,7,8-pentachlorodibenzo-furan > 1,2,3,7,9-pentachlorodibenzofuran > 1,3,6,8-tetrachlo-rodibenzofuran)	Estrogen	work as anti-estrogen through binding with Ah receptor, which then inhibits estrogen receptor binding to estrogen response elements, thereby inhibiting estrogen action	Krishnan and Safe 1993 Klinge *et al*. 1999
Octachlorostyrene	Thyroid		Sandan *et al*. 2000
PBBs	Estrogen/ Thyroid		Bahn *et al*. 1980 Henderson *et al*. 1995
PCBs (in order of antiestrogenic potency: 3,3' - pentachlorobiphenyl > 3,3,4,4,5,5'-hexachlorobiphenyl 3,3',4,4-tetrachlorobiphenyl > 2,3,3',4,4',5'-hexa, 2,3,3',4,4'- and 2,3,4,4',5-pentachlorobiphenyl > Aroclors 1221, 1232. 1248, 1254, and 1260 were inactive as antiestrogens at the highest concentrations used in this study (10-6 Ni)	Estrogen/androgen/Thyroid Adverse outcomes in reproductive systems.	Inhibits estrogen binding to the receptor; works as anti-estrogen. anti-androgenic via Ah receptor interaction	Korach *et al*. 1988 Zoeller *et al*. 2000 Grey *et al*. 1999
PCB, hydroxylated	Thyroid	Binds to thyroid hormone binding protein, but not to the thyroid hormone receptor.	Cheek *et al*. 1999
PBDEs	Thyroid	Interfere with thyroxine (T4) binding with transthryetin	Ilonka *et al*. 2000
Pentachlorophenol	Thyroid	Reduces thyroid hormone possibly through a direct effect on the thyroid gland.	Bear *et al*. 1999 Gerhard *et al*. 1999

Food Antioxidant

Compound	Hormone system affected	Mechanism	References
Butylated hydroxyanisole (BHA)	Estrogen	Inhibits binding to the estrogen receptor.	Jobling *et al.* 1995

Pesticides

Compound	Hormone system affected	Mechanism	References
Acetochlor	Thyroid (decrease of thyroid hormone levels, increase in TSH)		Hurley *et al.* 1998
Alachlor	Thyroid (decrease of thyroid hormone levels, increase in TSH)		Wilson *et al.* 1996
Aldrin	Estrogen	Binds to estrogen receptors; competes with estradiol.	Jorgenson 2001
Allethrin, d-trans	Estrogen		Go *et al.* 1999
Amitrol	Thyroid	Thyroid peroxidase inhibitors; inhibits thyroid hormone synthesis.	Hurley *et al.* 1998
Atrazine	Neuroendocrine-pituitary (depression of LH surge), testosterone metabolism.	Inhibits ligand binding to androgen and estrogen receptors.	Danzo 1997
Carbaryl	Estrogen and progesterone		Klotz *et al.* 1997
Chlofentezine	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al.* 1998
Chlordane	Testosterone and progesterone		Willingham *et al.* 2000
Cypermethrin	Disruption of reproductive function		Moore and Waring 2001
DDT	Estrogen	DDT and related compounds act in a number of ways to disrupt endocrine function by binding with the estrogen receptor, including estrogen mimicry and antagonism, altering the pattern of synthesis or metabolism of hormones, and (4) modifying hormone receptor levels	Soto *et al.* 1994 Lascombe *et al.* 2000 Kupfer *et al.* 1980 Rajapakse *et al.* 2001

DDT Metabolite, p,p'-DDE	Androgen	Inhibits androgen binding to the androgen receptor, androgen-induced transcriptional activity, and androgen action in developing, adolescent and adult male rats.	Kelce 1995
Dicofol (Kelthane)	Estrogen		Vinggaard *et al*. 1999
Dieldrin	Estrogen	Binds to estrogen receptor; competes with estradiol.	Arnold *et al*. 1997 Soto *et al*. 1994 Jorgenson 2001
Endosulfan	Estrogen		Soto *et al*. 1994 Soto *et al*. 1995
Ethylene thiourea	Thyroid	Thyroid peroxidase inhibitor.	Hurley *et al*. 1998
Fenarimol	Estrogen	Estrogen receptor agonist.	Vinggaard *et al*. 1999
Fenbuconazole	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Fenitrothion	Antiandrogen	Competitive androgen receptor antagonist.	Tamura *et al*. 2001
Fenvalerate	Estrogen		Go *et al*. 1999
Fipronil	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Heptachlor	Thyroid		Akhtar *et al*. 1996 Reuber 1987
Heptachlor-epoxide	Thyroid/Reproductive	Metabolite of heptachlor	Reuber 1987
Iprodione	Inhibition of testosterone synthesis		Benhamed 1996
Karate	Thyroid	A decrease of thyroid hormone in serum; direct effect on the thyroid gland?	Akhtar *et al*. 1996
Kepone (Chlordecone)	Estrogen	Displays androgen and estrogen receptor-binding affinities.	Waller *et al*. 1996 Soto *et al*. 1994 McLachlan(ed)
Ketoconazole	Effects on reproductive systems		Marty *et al*. 1999 Marty *et al*. 2001

Lindane (Hexachlorocyclohexane)	Estrogen/Androgen	Inhibits ligand binding to androgen and estrogen receptors.	Danzo 1997
Linuron	Androgen	Androgen receptor antagonist.	Waller *et al*. 1996 Lambright *et al*. 2000 Grey *et al*. 1999
Malathion	Thyroid	Significant decrease of thyroid hormone in serum, with perhaps a direct effect on the thyroid gland.	Akhtar *et al*. 1996
Mancozeb	Thyroid	Thyroid peroxidase inhibitors.	Hurley *et al*. 1998
Maneb	Thyroid	The metabolite ethylenthiourea inhibits thyroid hormone synthesis.	Toppari *et al*. 1995
Methomyl	Thyroid		Porter *et al*. 1993 Klotz *et al*. 1997
Methoxychlor	Estrogen	Through mechanisms other than receptor antagonism. Precise mechanism still unclear.	Pickford and Morris 1999
Metribuzin	Thyroid		Porter *et al*. 1993
Mirex	Antiandrogenic activity; inhibits production of LH. Potentially thyroid.		Chen *et al*. 1986 Chernoff *et al*. 1976
Nitrofen	Thyroid	Structural similarities to the thyroid hormones; nitrofen or its metabolite may have thyroid hormone activities.	Stevens and Summer 1991
Nonachlor, trans-	Estrogen	Estrogen receptor agonist?	Willingham *et al*. 2000
Oxychlordane	Reproductive		Guillette *et al*. 1999
Pendimethalin	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Pentachloronitrobenzene	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Permethrin	Estrogenic		Go et al. 1999
Procymidone	Androgen	Androgen receptor antagonist.	Ostby *et al*. 1999 Grey *et al*. 1999

Prodiamine	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Pyrimethanil	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Sumithrin	Androgen		Go *et al*. 1999
Tarstar	Thyroid	A decrease of thyroid hormone in serum; direct effect on the thyroid gland?	Akhtar *et al*. 1996
Thiazopyr	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Thiram	Neuroendocrine-pituitary (depression of LH surge), thyroid (decrease of T4, increase of TSH)		Stoker *et al*. 1993
Toxaphene	Estrogen/ Thyroid		Soto *et al*. 1994
Triadimefon	Estrogen	Estrogen receptor agonist.	Vinggaard *et al*. 1999
Triadimenol	Estrogen	Estrogen receptor agonist	Vinggaard *et al*. 1999
Tributyltin	Reproductive		Horiguchi *et al*. 2000
Trifluralin	Reproductive/ Metabolic		Rawlings *et al*. 1998
Vinclozolin	Androgen	Anti-androgenic. (Competes with androgens for the androgen receptor (AR), inhibits AR-DNA binding, and alters androgen-dependent gene expression.)	Soto *et al*. 1994 Soto *et al*. 1995 Kelce *et al*. 1994 Grey *et al*. 1999
Zineb	Thyroid	The metabolite ethylenthiourea inhibits thyroid hormone synthesis.	Toppari *et al*. 1995
Ziram	Thyroid	Inhibits the iodide peroxidase. Structural similarities between ziram and thiram; ziram can be metabolized to thiram in the environment.	Marinovich *et al*. 1997

Phthalate

Compound	Hormones affected	Mechanism	References
Butyl benzyl phthalate (BBP)	Estrogen	Inhibits binding to the estrogen receptor	Jobling *et al.* 1995
Di-n-butyl phthalate (DBP)	Estrogen Androgen	Inhibits binding to the estrogen receptor. anti-androgenic	Jobling *et al.* 1995 Harris *et al.* 1997 Grey *et al.* 1999
Di-ethylhexyl phthalate (DEHP)	Estrogen Androgen	Inhibits binding to the estrogen receptor. anti-androgenic	Jobling *et al.* 1995 Harris *et al.* 1997 Moore *et al.* 2001 Grey *et al.* 1999
Diethyl Phthalate (DEP)	Estrogen		Harris *et al.* 1997

Metals

Compound	Hormones affected	Mechanism	References
Arsenic	Glucocorticoid	Selective inhibition of DNA transcription normally stimulated by the glucocorticoid-GR complex.	Kaltreider *et al.* 2001
Cadmium	Estrogenic	Activates estrogen receptor through an interaction with the hormone-binding domain of the receptor.	Stoica *et al.* 2000 Johnson *et al.* 2003
Lead	Reproductive		Telisman *et al.* 2000 Hanas *et al.* 1999
Mercury	Reproductive/ Thyroid		Facemire *et al.* 1995

Other Compounds

Compound	Hormones affected	Mechanism	References
Benzophenone	Estrogen	Binds weakly to estrogen receptors, roles of its metabolite remain to be clarified.	Schlumpf *et al.* 2001
Bisphenol A	Estrogen	Estrogenic; binds to estrogen receptor	Fisher *et al.* 1999 Anderson *et al.* 1999 Rajapakse *et al.* 2001
Bisphenol F	Estrogen	Estrogenic; binds to estrogen receptor	Perez *et al.* 1998
Benzo(a)pyrene	Androgen	anti-androgenic	Thomas 1990
Carbendazim	Reproductive		Gray *et al.* 1990
Ethane Dimethane Sulphonate	Reproductive		Gray *et al.* 1999
Perfluorooctane sulfonate (PFOS)	Thyroid, reproductive	suppression of T3,T4; mechanism unknown	3M data
Nonylphenol, octylphenol	Estrogen	Estrogen receptor agonists; reduces estradiol binding to the estrogen receptor.	Soto *et al.* 1991 Soto *et al.* 1995 Danzo 1997 Lascombe *et al.* 2000 Rajapakse *et al.* 2001
Resorcinol	Thyroid		Lindsay *et al.* 1989
Styrene dimers and trimers	Estrogen	Estrogen receptor agonists	Ohyama *et al.* 2001

APPENDIX B
New sources of exposure to endocrine disruption

As scientific research on endocrine disruption has advanced, the scope of the research has broadened significantly. The list of hormonally active compounds is longer than anyone had previously imagined in the early days of the research. Not only are more compounds involved, but also more hormone systems are now known to be vulnerable. And within each hormonal system, new mechanisms of interaction between compounds and receptor systems are being explored to understand how a compound exerts its effects. Research on leguminaceous plants and their symbiotic rhizobial bacteria show that chemical communication between organisms is also vulnerable to disruption by contaminants.

New compounds: Accidental discoveries and systematic testing have revealed a broader array of modern use compounds capable of interfering with the sex steroids hormones. New results come in regularly, identifying yet another hormonally active compound.

Most notably, because of their ubiquity, certain compounds in plastics began to attract attention, especially nonylphenol and bisphenol-A (Our Stolen Future, Chapter 8). Nonylphenol is used widely as a surfactant (for example, in pesticides and detergents) and as an additive to certain plastics. Bisphenol-A, the basic building block of polycarbonate plastic, not only enters our lives in every object made from polycarbonate, for example clear plastic baby bottles, it also enters children's mouths when their teeth are coated with polycarbonate to prevent cavities. And, like nonylphenol, bisphenol-A is used as a surfactant in pesticides. The ubiquity of exposure is breathtaking.

Concern began to turn to phthalates in the late 1990s after studies showed their potency as a reproductive toxicant during crucial windows of development. The first issues raised were about their use as additives to PVC plastics that make them flexible, and thus useful in children's toys and medical devices, among many uses. But then in mid-2000, the CDC opened a dramatic new chapter in the phthalate story with convincing demonstration of the ubiquity of phthalate contamination, and a particularly troubling revelation for women of childbearing age.

Even bakelite (also known as bisphenol-F), the first of the modern plastics, has been found to be estrogenic. This pushes widespread exposure to synthetic oestrogen back to the first decade of the 20th century.

More hormone systems: The initial concern in endocrine disruption had focused on contaminants capable of interfering with the sex steroid hormones, especially oestrogen. Research in the past emphasised the classic oestrogen mimics and antagonists--DES, certain PCBs, DDT, etc.

But hormone disruption is neither limited to oestrogen compounds nor the oestrogen receptor. To begin with, scientists have learned that there is more than one oestrogen receptor. Furthermore, the mechanisms of disruption are diverse and complex; a compound may be an agonist (mimicking the actions of a hormone) or antagonist (interfering or blocking actions of a hormone); it may alter the transport of a hormone; or it may bind to more than one hormone receptor. Research on the sex steroids has been broadened to include anti-estrogenic and anti-androgenic activities.

And, because every hormone system is potentially vulnerable to disruption or alteration, the list of hormone systems investigated has broadened beyond the sex steroids. Scientists have begun to look at other hormone signalling systems... thyroid, progesterone, retinoids, glucocorticoids, etc. Compounds capable of interfering with each of these systems have now been reported. And even though hormone disruptors have not yet been identified for every hormone system, the lack of data is most safely attributed to the diversity and sheer number of compounds yet untested.

Perhaps the most troubling aspect of many of these discoveries was their accidental nature. Acknowledging this and also the strong likelihood that many compounds might possess disruptive capabilities, the US Congress in the United States unanimously passed the Food Quality Protection Act in 1996. FQPA established a new committee, the Endocrine Disruption Screening and Testing Advisory Committee (EDSTAC), to advise EPA on the development of a screening program that would systematically survey a variety (i.e, 15,000) of modern day use compounds whose effects on the endocrine system were virtually unknown.

Recent discoveries:

(i) EDCs disrupt the symbiosis between legumes and rhizobium, undermining nitrogen fixation, a process essential for life on earth.
(ii) Phthalate contamination is widespread in the American public.
(iii) Polybrominated diethyl ethers (PBDEs) are steroid and thyroid disruptors. They are used as flame retardant in many modern consumer products. They are more persistent than PCBs and have become ubiquitous contaminants throughout the world, including remote ocean life.
(iv) Soccer shirts manufactured by a large consumer product firm contain tributyltin, an endocrine-disrupting compound known to have dramatic impacts on marine life.
(v) Methoprene (a common active ingredient in insecticides) and the breakdown products of methoprene interfere with retinoid signalling.
(vi) Synthetic pyrethroids, widely used to combat ticks, mosquitoes and even head lice, are powerful endocrine disruptors.

APPENDIX C
A brief history of PCBs

In 1929 Scientists add chlorine to two joined hexagonal benzene rings known as biphenyls, creating a family of 209 chemicals collectively known as PCBs or poly-chlorinated biphenyls. PCB application was widespread because they are non-flammable & extremely stable. They were used for:

- coolant for transformers inside buildings,
- lubricants,
- hydraulic fluids,
- cutting oils,
- liquid seals,
- wood and plastic non-flammable products,
- preserved and protected rubber,
- weatherproof stucco
- ingredients in paints and inks,
- pesticides,
- carbonless copy paper

1964 PCB danger first recognised

1976 The world (excluding the USSR) produced 3.4 billion tons of PCBs.

1990s PCB levels in seals are 384 million times the concentration found in the water they swim in.

1990's PCB levels in polar bears' fatty tissue found to be 3 billion times the concentration levels in arctic seawater.

1990's Breast-fed babies in Europe and America on average contain five times the allowable daily level of PCBs for a 150 pound adult, as set by the FDA, EPA and the WHO.

APPENDIX D
Dioxin facts

1. Some dioxins are 1000 times more deadly than Arsenic.
2. Dioxins are the most potent carcinogens ever tested.
3. In 1997, the International Agency for Research on Cancer concluded that there was sufficient evidence from human studies to classify dioxins as a "known human carcinogen" the "highest" level of certainty.
4. Of the 75 known dioxins, 2,3,7,8 TCDD is the most lethal and is also the most toxic chemical on earth.
5. Guinea pigs die after swallowing just 1 millionth of a gram of 2,3,7,8 TCDD per kilogram of body mass.
6. Nature has no natural defence mechanisms to break down dioxins into safer molecules, so these lipophilic molecules bio-accumulate up the food chain.
7. Dioxins are hormonally active synthetic chemicals that can damage the reproductive system, alter the nervous system and brain, and impair the immune system. Studies show that exposure to hormonally active chemicals in the womb or in adulthood increases vulnerability to hormone-responsive cancers, such as malignancies in the breast, prostate, ovary and uterus.
8. Animals contaminated by these chemicals show various behavioural effects, including abherrent mating behaviour and increased neglect of offspring.
9. Dioxins can derail the normal expression of sexual characteristics of animals, in some cases masculinising females and feminising males. Laboratory experiments link dioxins with a variety of male & female reproductive problems that appear to be on the rise on the general human population - problems ranging from testicular cancer to endometriosis.
10. Dioxins are found in the company of furans, a family of 135 chemicals with a similar structure and toxicity to dioxins.
11. One litre of milk can deliver as much dioxins as a human would get from air in eight months. In one day a grazing cow can put as much dioxin into its body, (from dioxin which has deposited on the grass), as a human being would get from air over fourteen years.
12. The most dramatic and troubling sign that hormone disruptors such as dioxins may already have taken a major toll comes from reports that human male sperm counts have plummeted over the past half-century [approx. 50%].
13. In June of 1998, the World Health Organisation acknowledged that dioxin exposure is linked to severe health effects and lowered its recommended "tolerance daily intake" (TDI) by more than half to 1-4 pg TEQ1/kg body weight (including dioxin-like PCBs). In the USA the EPA has set the safe TDI levels to 0.006 picograms per kg of body mass for its citizens.
14. Many scientists now argue that there is no safe level of dioxin exposure. This is because dioxins (like other EDCs) appear to act in the same manner as terrorists in that a small number of molecules are able to hijack the hormonal control of development and cause intense, life-long damage, undermining the immune system, eroding intelligence and diminishing reproductive capacity.

APPENDIX E
The Impacts of endocrine disruptors
on intelligence and behaviour.

During the nine months between conception and birth, the foetal brain is transformed from instructions in genes to a complex, highly differentiated mass of organised cells capable of interacting with the outside world and prepared for learning.

Those first nine months lay the groundwork for all of what happens later in life. Get it wrong, and the consequences can diminish a person's capacity to participate in society and compete throughout life.

Like virtually all development, the transformation is guided by natural chemical signals instructing cells to differentiate, form brain structures, forge links of immense complexity, and even to die (in a process that is thought to carefully prune unnecessary connections). Normal brain development is heavily influenced by a host of hormonal signalling systems. Thyroid hormones play a major role. The sex steroids (testosterone, oestrogen, etc.) contribute to, among other things, sexual differentiation of brain centres, and thereby, to the development of sexual identity and sexual behaviours.

Dependent upon natural hormone signals, brain development is therefore vulnerable to endocrine disruption. A rapidly increasing body of scientific research is revealing mechanisms of action, demonstrating impacts of disrupted development, and exploring links between intelligence, behaviour and contamination experienced in the womb. What is emerging from this research is that brain and behaviour are likely to be the most sensitive endpoints vulnerable to endocrine disruption. Many synthesised compounds in commercial use today, moreover, can derail neurological development.

An important aspect of this research is the realisation, discussed in the book, Our Stolen Future (Chapter 13), that small losses in intelligence might have large consequences for a society if they are experienced in a broad swath of the population.

In September 2002. Dutch scientists reported that boys exposed pre-nattily to higher levels of PCBs and dioxins are more likely to show demasculinised play behaviours. Girls and boys exposed to modestly elevated dioxin levels demonstrate more feminised play behaviours. The scientists suggest that that these alterations in play result from endocrine disruption of the development of sex-specific behaviours.

APPENDIX F
More about the Endocrine System

The endocrine system is a complex network of glands, hormones and receptors. It provides the key communication and control link between the nervous system and bodily functions such as reproduction, immunity, metabolism and behaviour.

In nearly all complex multi-cellular animals, there are two main systems controlling and co-ordinating the processes within the body:

- The nervous system, which exerts rapid point-to-point control by means of electrical signals passing down the nerves to particular organs or tissues.

- The endocrine system, which is a slower system, based on chemical messengers, the hormones, which are secreted into the blood (or other extra-cellular fluids) and can reach all parts of the body.

The nervous system works in tandem with the endocrine system to control all bodily functions and processes.

The endocrine system has three main components:

(i) ***Endocrine glands***, situated at various sites around the body, and in specialised areas of the brain. The cells in these glands secrete specific chemicals called hormones.

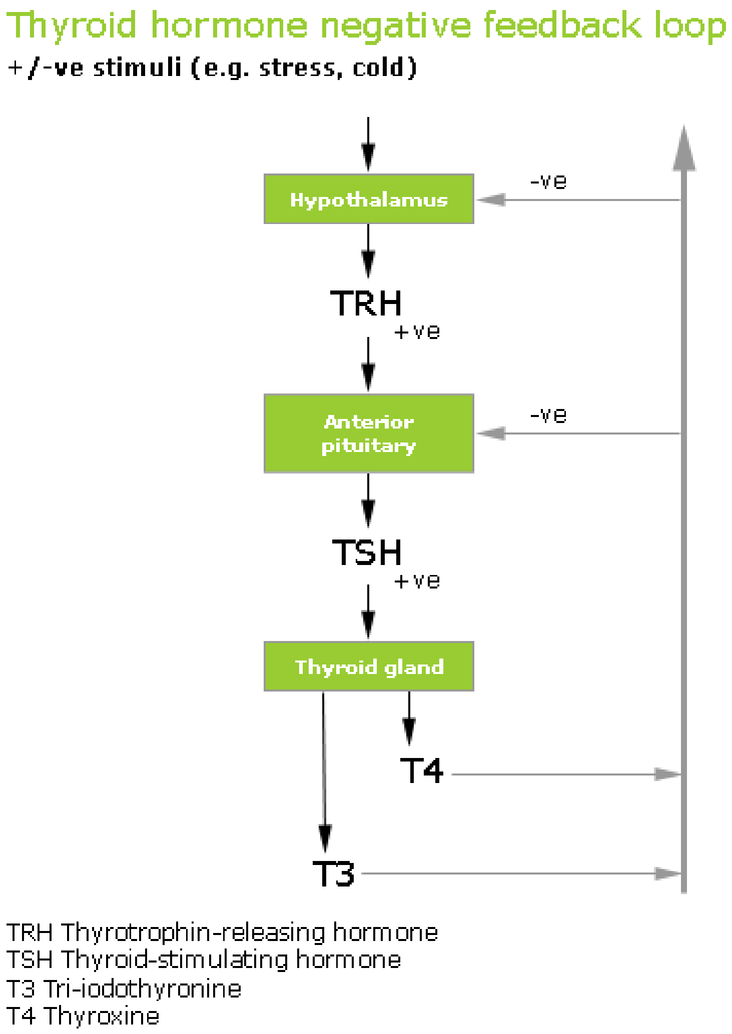
(ii) ***Hormones*** circulate around the body via the blood stream and modulate cellular or organ functions by binding with receptors in the target cells. Hormones that stimulate and control the activity of other endocrine glands are called trophic hormones.

(iii) ***Receptors*** in the target cells, once activated by binding of the hormone, regulate the functions and processes in the tissue through interactions with the cell's DNA or other complex intracellular signalling processes.

The main human hormones and their functions are shown below :

Gland	Hormones	Functions
Hypothalamus	Releasing hormones	Stimulate pituitary activity
Pituitary	Trophic (stimulating) hormones	Stimulate thyroid, adrenal, gonadal and pancreatic activity
Thyroid	Thyroid hormones	Regulate metabolism, growth and development, behaviour and puberty
Adrenal	Corticosteroid hormones Catecholamines	Regulate metabolism Regulate behaviour
Pancreas	Insulin and glucagon	Regulate blood sugar levels
Gonads	Sex steroid hormones (androgens and oestrogens)	Regulate development & growth, reproduction, immunity, onset of puberty and behaviour

The production and circulating levels of hormones are controlled by means of negative feedback processes. For example, synthesis of thyroid hormone is stimulated by thyroid stimulating hormone (TSH) produced by the pituitary gland. If blood levels of thyroid hormone fall, a part of the brain, the hypothalamus, responds to the change and releases thyroid hormone releasing hormone (TRH), which stimulates a particular cell type in the pituitary to increase TSH synthesis. As thyroid hormone levels in blood again rise in response to TSH, TRH production is reduced and, in turn, TSH secretion is suppressed. Such feedback systems maintain the balance of various body systems (operating in a fashion analogous to the system that controls a domestic central heating system) - a process known as **homeostasis**.



Why is the endocrine system important for life?

The endocrine system controls growth and development during childhood, regulation of bodily functions in adulthood, and the reproductive process.

The endocrine system is important for the control and regulation of all the major functions and processes of the body:

- Energy control
- Reproduction
- Immunity
- Behaviour (e.g. fight or flight response)
- Growth and development

Hormones interact to maintain the above functions and help to regulate our responses to disease, our ability to reproduce and even influence our relationships and behaviour (such as mother-child bonding).

As can be seen, many of the hormones act on tissues and organs at several sites throughout the body. The target cells in these tissues or organs contain specialised structures (**receptors**) to which only a specific hormone can bind. The response that occurs in the cell will depend on the receptor and cell type, and the effects of other hormones to which that cell may also be exposed. Also, a hormone that stimulates the activity of one cell type may suppress that of a different cell type.

A similar, but not identical, endocrine system to that of humans is found in nearly all vertebrates including other mammals, fish, amphibians, reptiles and birds. Although the precise structures and roles of the various organs and hormones differ between different groups, particularly in relation to the different life cycle and development stages in different species. Invertebrates such as molluscs, crustacean and insects also have endocrine systems that control a similar range of body functions although these have evolved along markedly different lines to those of vertebrates.

The hormones are released in extremely low concentrations, sometimes even measured in parts per trillion (i.e. one part per trillion is equivalent to 1 drop in 25 olympic-size swimming pools), and are therefore difficult and expensive to measure. This is perhaps the reason why we know so little about the entire functioning of this delicate system. The number of mysterious ‘ghost’ hormones whose functions are yet to be discovered clearly indicates our lack of understanding of this complex and delicate system and gives fuel to arguments for the adoption of the precautionary principles with respect to the release of potentially dangerous manmade chemicals into our environment.

APPENDIX G
THE WINGSPREAD CONSENSUS STATEMENT

NOTE: In July, 1991, a group of scientists including developmental biologists, endocrinologists, wildlife biologists, conservation biologists, fisheries biologists, reproductive toxicologists, marine biologists, immunologists, and pharmacologists, convened at the Wingspread Conference Center in Racine, Wisconsin. At the end of this session, the scientists issued a written warning, the Wingspread Consensus Statement. This document declared the consensus that humans are being exposed to chemicals that have significantly altered embryonic development in wildlife and in laboratory animals. Morever, it warned that human embryonic development, intellectual development, and immune capacities are being compromised by these chemicals. The names of the signataries has been left off since permission was not asked of each of them. Their names can be found in the book, Our Stolen Future (by T. Colborn, D. Dumanoski, and J. P. Myers. Duttun, NY, 1996). If what they warn is valid, then questions concerning Developmental Biology will shortly be at the forefront of environmental and conservation concerns. Most Developmental Biologists have been poorly trained to deal with environmental issues, and we should become educated as soon as possible.

Statement from the Work Session on Chemically-induced Alterations in the Developing Immune System: The Wildlife/Human Connection.

Racine, Wisconsin, February 1995, published in EHP Supplements, August 1996.

<u>The Problem:</u> Many compounds introduced into the environment by human activity are capable of disrupting the endocrine system of animals, including fish, wildlife, and humans. The consequences of such disruption can be profound because of the crucial role hormones play in controlling development. Because of the increasing and pervasive contamination of the environment by compounds capable of such activity, a multidisciplinary group of experts gathered in retreat at Wingspread, Racine, Wisconsin, 26–28 July 1991 to assess what is known about the issue. Participants included experts in the fields of anthropology, ecology, comparative endocrinology, histopathology, immunology, mammalogy, medicine, law, psychiatry, psychoneuroendocrinology, reproductive physiology, toxicology, wildlife management, tumor biology, and zoology.

The purposes of the meeting were:

- To integrate and evaluate findings from the diverse research disciplines concerning the magnitude of the problem of endocrine disruptors in the environment;
- to identify the conclusions that can be drawn with confidence from existing data; and

- to establish a research agenda that would clarify uncertainties remaining in the field.

<u>Consensus Statement:</u> The following consensus was reached by participants at the workshop

1. We are certain of the following:

- A large number of manmade chemicals that have been released into the environment, as well as a few natural ones, have the potential to disrupt the endocrine system of animals, including humans. Among these are the persistent, bioaccumulative, organohalogen compounds that include some pesticides (fungicides, herbicides, and insecticides) and industrial chemicals, other synthetic products, and some metals.*
- Many wildlife populations are already affected by these compounds. The impacts include thyroid dysfunction in birds and fish; decreased fertility in birds, fish, shellfish, and mammals; decreased hatching success in birds, fish, and turtles; gross birth deformities in birds, fish, and turtles; metabolic abnormalities in birds, fish, and mammals; behavioural abnormalities in birds; demasculinization and feminisation of male fish, birds, and mammals; defeminization and masculinization of female fish and birds; and compromised immune systems in birds and mammals.
- The patterns of effects vary among species and among compounds. Four general points can nonetheless be made: (1) The chemicals of concern may have entirely different effects on the embryo, foetus, or perinatal organism than on the adult; (2) the effects are most often manifested in offspring, not in the exposed parent; (3) the timing of exposure in the developing organism is crucial in determining its character and future potential; and (4) although critical exposure occurs during embryonic development, obvious manifestations may not occur until maturity.
- Laboratory studies corroborate the abnormal sexual development observed in the field and provide biological mechanisms to explain the observations in wildlife. Humans have been affected by compounds of this nature, too. The effects of DES (diethylstilbestrol), a synthetic therapeutic agent, like many of the compounds mentioned above, are estrogenic. Daughters born to mothers who took DES now suffer increased rates of vaginal clear cell adenocarcinoma, various genital tract abnormalities, abnormal pregnancies, and some changes in immune responses. Both sons and daughters exposed in utero experience congenital anomalies of their reproductive system and reduced fertility. The effects seen in in utero DES-exposed humans parallel those found in contaminated wildlife and laboratory animals, suggesting that humans may be at risk to the same environmental hazards as wildlife.

2. We estimate with confidence that:

- Some of the developmental impairments reported in humans today are seen in adult offspring of parents exposed to synthetic hormone disruptors (agonists and antagonists) released in the environment. The concentrations of a number of synthetic sex hormone agonists and antagonists measured in the U.S. human population today are well within the range and dosages at which effects are seen in wildlife populations. In fact, experimental results are being seen at the low end of current environmental concentrations.
- Unless the environmental load of synthetic hormone disruptors is abated and controlled, large scale dysfunction at the population level is possible. The scope and potential hazards to wildlife and humans are great because of the probability of repeated and/or constant exposure to numerous synthetic chemicals that are known to be endocrine disruptors. As attention is focused on this problem, more parallels in wildlife, laboratory, and human research will be revealed.

3. Current models predict that:

- The mechanisms by which these compounds have their impact vary, but they share the general properties of (1) mimicking the effects of natural hormones by recognizing their binding sites; (2) antagonizing the effect of these hormones by blocking their interaction with their physiological binding sites; (3) reacting directly and indirectly with the hormone in question; (4) by altering the natural pattern of synthesis of hormones; or (5) altering hormone receptor levels.
- Both exogenous (external source) and endogenous (internal source) androgens (male hormones) and estrogens (female hormones) can alter the development of brain function.
- Any perturbation of the endocrine system of a developing organism may alter the development of that organism: typically these effects are irreversible. For example, many sex-related characteristics are determined hormonally during a window of time in the early stages of development and can be influenced by small changes in hormone balance. Evidence suggests that sex-related characteristics, once imprinted, may be irreversible.
- Reproductive effects reported in wildlife should be of concern to humans dependent upon the same resources, e.g., contaminated fish. Food fish is a major pathway of exposure for birds. The avian (bird) model for organochlorine endocrine disruption is the best described to date. It also provides support for the wildlife/human connection because of similarities in the development of the avian and mammalian endocrine systems.

4. There are many uncertainties in our predictions because:

- The nature and extent of the effects of exposure on humans are not well established. Information is limited concerning the disposition of these contaminants within humans, especially data on concentrations of contaminants in embryos. This is compounded by the lack of measurable endpoints (biologic markers of exposure and effect) and the lack of multi-generational exposure studies that simulate ambient concentrations.
- While there are adequate quantitative data concerning reduction in reproductive success in wildlife, data are less robust concerning changes in behaviour. The evidence, however, is sufficient to call for immediate efforts to fill these knowledge gaps.
- The potencies of many synthetic estrogenic compounds relative to natural estrogens have not been established. This is important because contemporary blood concentrations of some of the compounds of concern exceed those of internally produced estrogens.

5. Our judgment is that:

- Testing of products for regulatory purposes should be broadened to include hormonal activity in vivo. There is no substitute for animal studies for this aspect of testing.
- Screening assays for androgenicity and estrogenicity are available for those compounds that have direct hormonal effects. Regulations should require screening all new products and by-products for hormonal activity. If the material tests positive, further testing for functional teratogenicity (loss of function rather than obvious gross birth defects) using multigenerational studies should be required. This should apply to all persistent, bioaccumulative products released in the past as well.
- It is urgent to move reproductive effects and functional teratogenicity to the forefront when evaluating health risks. The cancer paradigm is insufficient because chemicals can cause severe health effects other than cancer.
- A more comprehensive inventory of these compounds is needed as they move through commerce and are eventually released to the environment. This information must be made more accessible. Information such as this affords the opportunity to reduce exposure through containment and manipulation of food chains. Rather than separately regulating contaminants in water, air, and land, regulatory agencies should focus on the ecosystem as a whole.
- Banning the production and use of persistent chemicals has not solved the exposure problem. New approaches are needed to reduce exposure to synthetic chemicals already in the environment and prevent the release of new products with similar characteristics.

- Impacts on wildlife and laboratory animals as a result of exposure to these contaminants are of such a profound and insidious nature that a major research initiative on humans must be undertaken. The scientific and public health communities' general lack of awareness concerning the presence of hormonally active environmental chemicals, functional teratogenicity, and the concept of transgenerational exposure must be addressed. Because functional deficits are not visible at birth and may not be fully manifested until adulthood, they are often missed by physicians, parents, and the regulatory community, and the causal agent is never identified.

6. To improve our predictive capability:

- More basic research in the field of developmental biology of hormonally responsive organs is needed. For example, the amount of specific endogenous hormones required to evoke a normal response must be established. Specific biologic markers of normal development per species, organ, and stage of development are needed. With this information, levels that elicit pathological changes can be established.
- Integrated cooperative research is needed to develop both wildlife and laboratory models for extrapolating risks to humans.
- The selection of a sentinel species at each trophic level in an ecosystem is needed for observing functional deficits, while at the same time describing the dynamics of a compound moving through the system.
- Measurable endpoints (biologic markers) as a result of exposure to exogenous endocrine disruptors are needed that include a range of effects at the molecular, cellular, organismal, and population levels. Molecular and cellular markers are important for the early monitoring of dysfunction. Normal levels and patterns of isoenzymes and hormones should be established.
- In mammals, exposure assessments are needed based on body burdens of a chemical that describe the concentration of a chemical in an egg (ovum) which can be extrapolated to a dose of the chemical to the embryo, fetus, newborn, and adult. Hazard evaluations are needed that repeat in the laboratory what is being seen in the field. Subsequently, a gradient of doses for particular responses must be determined in the laboratory and then compared with exposure levels in wildlife populations.
- More descriptive field research is needed to explain the annual influx to areas of known pollution of migratory species that appear to maintain stable populations in spite of the relative vulnerability of their offspring.
- A reevaluation of the in utero DES-exposed population is required for a number of reasons. First, because the unregulated, large-volume releases of synthetic chemicals coincide with the use of DES, the results of the original DES studies may have been confounded by widespread exposure to other synthetic endocrine disruptors. Second, exposure to a hormone during fetal life may elevate responsiveness to the hormone during later

life. As a result, the first wave of individuals exposed to DES in utero is just reaching the age where various cancers (vaginal, endometrial, breast, and prostatic) may start appearing if the individuals are at a greater risk because of perinatal exposure to estrogen-like compounds. A threshold for DES adverse effects is needed. Even the lowest recorded dose has given rise to vaginal adenocarcinoma. DES exposure of fetal humans may provide the most severe-effect model in the investigation of the less potent effects from environmental estrogens. Thus, the biological endpoints determined in in utero DES-exposed offspring will lead the investigation in humans following possible ambient exposures.

- The effects of endocrine disruptors on longer-lived humans may not be as easily discerned as in shorter-lived laboratory or wildlife species. Therefore, early detection methods are needed to determine if human reproductive capability is declining. This is important from an individual level, as well as at the population level, because infertility is a subject of great concern and has psychological and economic impacts. Methods are now available to determine fertility rates in humans. New methods should involve more use of liver-enzyme-system activity screening, sperm counts, analyses of developmental abnormalities, and examination of histopathological lesions. These should be accompanied by more and better biomarkers of social and behavioral development, the use of multigenerational histories of individuals and their progeny, and congener-specific chemical analyses of reproductive tissues and products, including breast milk.

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APPENDIX H
The Yokohama Consensus Statement

International Workshop on the Effects of Endocrine Disruptors in Living Things

Yokohama City University
13 December 1999

The Yokohama International Workshop on the effects of Endocrine Disruptors in Living Things was held with particular focus on effects on human beings, following the 2nd International Symposium on Environmental Endocrine Disruptors '99, hosted in Kobe on December 9 to 11, 1999 by Japan's Environment Agency.

Responding to reproductive abnormalities reported worldwide in wildlife due to exposure to manmade chemicals, the Wingspread Statement was adopted at the July 1991 meeting in Wingspread, Wisconsin, USA. This statement identified the need to initiate investigations into human health hazards caused by endocrine disruptors.

Since the 1991 Wingspread Conference, there have been several significant advances in our scientific understanding of endocrine disruption.

It is now clear that exposure is ubiquitous. All humans have been exposed, to varying amounts.

Laboratory experiments show that exposures have impacts at levels far lower than had been considered possible in traditional toxicology.
Many more hormone systems, perhaps all chemically-mediated message systems, are now known to be vulnerable to endocrine disruptors.
Many more compounds are now known to be powerful endocrine disruptors.
Human health effects of concern now include adult impacts of foetal exposure.

In Japan, concerned ministries and research institutes have also been conducting similar investigations since 1997. At the Yokohama Workshop held on December 13-14, 1999, twenty-five scientists from Japan, North America and Europe agreed on the urgency of investigations and actions as follows:

Residual organochlorine chemicals working as endocrine disruptors have already accumulated in the body and effected the health of some wildlife species. Appropriate technologies must be developed to reduce organochlorine residues in the environment and consequently there effects on wildlife.

Basic research is needed to identify the relationships between endocrine disruptors and their effects on developmental mechanisms. The most vulnerable period is in the developmental stage. Effective dose level and metabolic factors can conceivably vary according to animal species. Also, studies must be conducted into the species specificity of their effects.

Further investigations should be carried out to clarify the effects of low doses of endocrine disruptors in organisms. In addition, it is desirable to conduct wildlife investigations not only at the individual level but also at the population and community level.

Epidemiological research must be continued to elucidate under what circumstances endocrine disruptors pose a threat to human health as well as to the intellectual development and mental health of children. Investigations must examine the compounded effects of endocrine disruptors, as exposure occurs to mixtures of substances rather than to single contaminants.

Because human beings are biological in nature, with varying genetic predispositions, and live in groups of individuals under diverse environmental factors including residence, occupation, lifestyle, etc., research must investigate individual variation in susceptibility to effects of endocrine disruptors. For example, study into the effects of phytoestrogens would be one such theme because Japanese ingest large amounts of phytoestrogens.

We need to determine an effective dose level and evaluate risks of endocrine disruptors by studying the relationship between concentration in the environment and intake. Also, study of methodologies for risk assessment should be promoted.

Until scientific conclusions are obtained, the "precautionary principle" should be applied to reduce the release of endocrine disruptors into the environment and the intake thereof.

The problem of endocrine disruptors should be addressed in all aspects of society. Information disclosure and the creation of educational curriculums on environmental problems are very critical social countermeasures.

The problem of endocrine disruption is a global issue. Solutions will therefore, of necessity, require international collaboration. Also, joint multidisciplinary research and conferences on the international level should be continued in order to promote research and countermeasures.

Yokohama City and Yokohama City University will promote both research and international conferences on endocrine disruptors. Yokohoma City University will also open its endocrine disruptor research facilities to researchers both inside and outside of the country in order to full utilize the benefits.

We, the participants in the Yokohama Workshop, hereby agree to this Yokohama Consensus Statement. December 13, 1999

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APPENDIX I

Joint statement – by the WWF and other concerned organisations

The following joint statement, which was signed by the WWF and a coalition of organisations and pressure groups, is being used to lobby for change inside the UK and the EU:

'People and wildlife across the globe, even the unborn, are contaminated with a cocktail of manmade chemicals which build up in the body and/or persist in the environment. This is unacceptable. Such chemicals must be phased out - whether or not they are currently known to be toxic. EU legislation currently being drafted presents an unprecedented opportunity for European Governments to protect us and our children from further contamination. This opportunity must not be wasted.

We urge the UK Government and MEPs, with other EU Member States, to put in place without delay new European legislation that eliminates the production, use and marketing of chemicals that build up in the body and/or persist in the environment.'

Baby Milk Action
www.babymilkaction.org

BEUC, the European Consumers' Organisation
www.beuc.org

European Public Health Alliance (EPHA)
www.epha.org/r/30

Friends of the Earth
www.foe.co.uk/campaigns/safer_chemicals

Greenpeace
www.greenpeace.org.uk/toxics

Women's Environmental Network
www.wen.org.uk

International Society of Doctors for the Environment
www.isde.org

London Hazards Centre
www.lhc.org.uk

National Childbirth Trust
www.nctpregnancyandbabycare.com

The National Federation of Women's Institutes
www.nfwi.org.uk

UNICEF UK Baby Friendly Initiative
www.babyfriendly.org.uk

APPENDIX J

European Scientists' declaration on chemicals, health and environmental protection

Over sixty top independent scientists from across Europe, working in the field of hazardous manmade chemicals, have signed the following WWF initiated declaration:

"Being aware of the problems that have become evident, over time, from the use of chemicals that persist and bioaccumulate in humans and wildlife, we consider that chemicals with these properties are undesirable.

For endocrine disrupting chemicals (EDCs), where there is good evidence that they can cause changes to the normal physiology of organisms, we suggest that it would be prudent to try to eliminate, or at least minimise, exposure. Recognising the uncertainty regarding the extent of the adverse effects of endocrine disrupting chemicals, and the fact that some of these chemicals can act in an additive manner, we suggest that exposure reduction is warranted. This exposure reduction should proceed even when there is a lack of evidence that predicted or actual exposure levels of the individual EDC causes population level effects in wildlife species, or harm to human health.

Therefore, we support a presumption against the use of very persistent and very bioaccumulative chemicals (vPvBs). We also support the move towards a reduction in the use of such EDCs. Therefore, for both vPvBs and EDCs, where safer alternatives are judged to be available, there should be a requirement to use such alternatives."

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APPENDIX K
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Our Stolen Future (Colburn, Dumanoski, Meyers)

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Schettler, T, J Stein, F Reich, and M Valenti. 2000. In Harms Way: Toxic threats to child development. A report by Greater Boston Physicians for Social Responsibility.

Laessig, SA, MM McCarthy and EK Silbergeld. 1999. Neurotoxic effects of endocrine disruptors. Current Opinion in Neurology 12:745-751.

Dioxins and other POPs in by-products, recyclates and wastes and their potential to enter the food chain – Stage II [EU Reports, Authors : European POPs Expert Team, September 2002] (See also stage I report)

US National Toxicology Program's Endocrine Disruptors Low-Dose Peer Review Report, October 2000

World Wildlife Foundation (WWF) toxic chemical websites and reports

Compromising our children - chemical impacts on children’s intelligence and behaviour. A WWF-UK Chemicals and Health Campaign Briefing June 2004

APPENDIX L
World Wide Web links

EU pages on Dioxins including the report on the evaluation of the occurrence of dioxins and POPs in wastes and their potential to enter the food chain
http://europa.eu.int/comm/environment/dioxin/

Green Peace POP report
http://www.greenpeace.org/~toxics/reports/tipoficeberg.pdf

Our Stolen Future
http://www.ourstolenfuture.org

Incineration
http://www.downtozero.ie/tour.htm

Endocrine Disruptors Research Initiative
www.epa.gov/scipoly/oscpendo

EPA's Endocrine Disruptor Screening and Testing Advisory Committee
www.epa.gov/oscpmont/oscpendo/history

Intergovernmental Forum on Chemical Safety
www.who.int/ifcs/ifcsinfo

International Agency for Research on Cancer
www.iarc.fr

International Organization Programme for the Sound Management of Chemicals (IOMC)
www.who.int/iomc

International Programme on Chemical Safety
www.who.int/pcs

OECD Environmental Health and Safety
www.oecd.org/ehs

TOXNET
www.toxnet.nlm.nih.gov

US NIEHS National Toxicology Programme
www.ntp-server.niehs.nih.gov

WWF International
www.panda.org/toxics