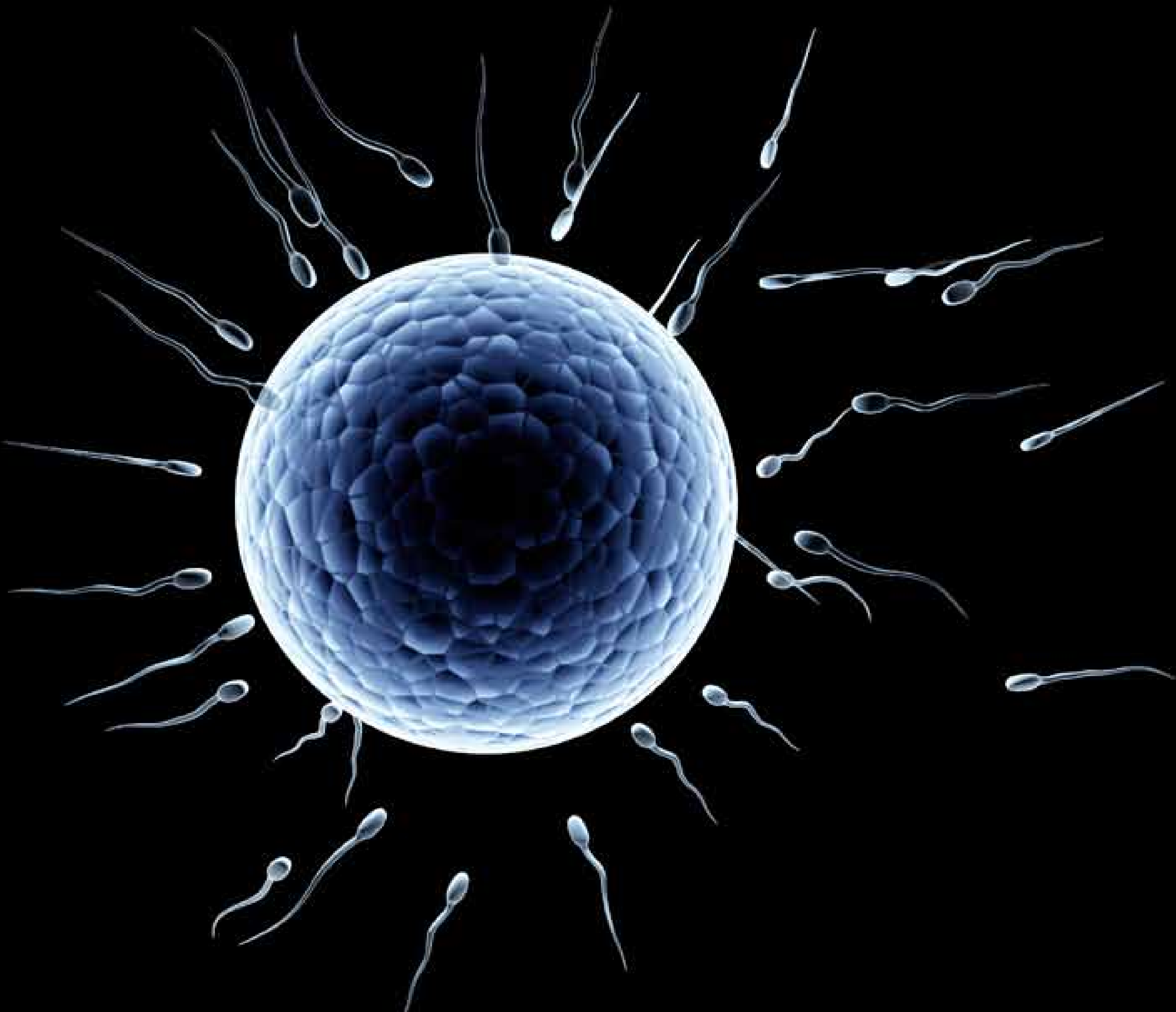

Swedish Society for Nature Conservation

Report

# Save the Men

- Environmental toxicants affect fertility and development

# Contents



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# Foreword

Hormones regulate everything from mood to gender. They are crucial to metabolism, the nervous system and reproduction. Although the detailed significance of hormones is not fully understood, research shows that there are fine balances between different substances so that a body's function will be triggered or suppressed. This vitally important chemistry is now threatened by chemicals.

Chemicals that disrupt hormones, known as endocrine disruptors, can strengthen, weaken or short-circuit the signals of the body's own substances. We have known for some time that individual substances – including DDT, PCBs, DEHP and tributyltin – can affect hormones leading to severe effects, but the properties of most substances are unknown. Studies show that environmental toxicants are spread for example from foods, clothes, toys, cosmetics, hygiene products and electronics, as well as from factory emissions. No one knows how the resultant cocktail of thousands of substances we live in affects us. Many substances have been found to be or suspected to be endocrine disruptors, but there is great uncertainty over long-term effects and possible combination effects.

Despite the gaps in our knowledge, the warnings issued by researchers have become shriller. In recent years, science has identified links between endocrine disruptors and obesity, diabetes and ADHD. There is particularly strong support for the notion that endocrine disruptors may harm the ability to reproduce. Shifts in development of puberty, deterioration in sperm production and deformities of genital organs are some of the effects – and unfortunately they are becoming more common.

The ability of humans to reproduce is seriously threatened. The fertility of men in particular is in danger. After working for decades on campaigns to save the peregrine falcon, white-tailed eagle and other species from environmental pollutants, the Swedish Society for Nature Conservation is therefore launching a new campaign – Save the Men!

Obviously not all chemicals are dangerous, but even substances that are merely suspected of being endocrine disruptors must be eliminated. It is better not to give the benefit of the doubt to chemicals that may harm human reproduction. This necessitates a new policy on¬ chemicals. To save male fertility, it is primarily necessary to protect foetuses, infants and children. This obvious also requires women to be protected.

The policy must be based on protecting foetuses and children, as they are most exposed and sensitive. Risk assessments must be made from a children's perspective. Substances that are found or suspected to be endocrine disruptors should, on principle, be banned or replaced in accordance with the precautionary principle. The asymmetry that prevails today – the fact that chemicals may be introduced without adequate risk assessment, but that a tough and costly risk assessment is required to regulate the same chemical – should be reversed. Experience of regulations shows that the chemical industry copes with such innovative challenges. Great progress is possible.

We consider that, on this basis, Sweden must pursue an ambitious policy in the EU and internationally. An important way of doing so is to set a precedent nationally. That would increase the pressure on other countries and bring about swifter protection in Sweden. Endocrine disruptors in notorious groups of chemicals such as brominated flame retardants, phthalates and organofluorine chemicals need to be regulated quickly.

It is difficult to imagine anything worse for humanity in the longer term than for these fertility problems to continue to worsen. If men are not saved, nothing else will matter in the long run. This must not happen – and it need not happen.

Mikael Karlsson
President of the Swedish Society for Nature Conservation

# 1. Humanity in a chemical cocktail

Many substances occur naturally in the environment, but in the past hundred years the manufacturing of synthetically produced chemicals has increased many times over. One million tonnes of chemicals were manufactured throughout the world in 1930. The European Commission reported in 2001 that the volume had risen to 400 million tonnes.[1] The number of chemicals in the world has also risen, partly because they can be customised with ever greater precision to meet ever more purposes. Many people's image of a chemical is a liquid in a test tube, an image that perhaps stems from chemistry lessons at school. In society there are chemicals in the form of fuels (such as petrol), various household products (such as dishwater detergents, laundry detergents or lighter fluids), cosmetics, medicines, pesticides or food additives. These are products that most people can picture being manufactured in chemical factories. On the other hand, it is less clear that the vast majority of the things we surround ourselves with have also been manufactured using various chemicals. An average of around three kilograms of chemicals is required, for example, to manufacture a one kilogram T-shirt.[2] Spinning oils, bleaches and dyes are just some of the chemicals needed to give a T-shirt its appearance. A computer contains large quantities of various materials that may have been treated with flame retardants, and the properties of various chemical compounds are utilised in the electronic components. Building materials are another example of articles that often contain various chemicals aimed at endowing them with desirable characteristics. Building materials have a long life, and it is therefore important not to use chemicals that may cause problems in the future, as the environmental toxicants PCBs have done in buildings.

Chemical emissions to the environment occur in the extraction of minerals, careless handling of chemicals in the manufacturing of products, use of the product, waste management or the use of pesticides. The effects may be acute, such as poisoning, or long-term, such as emissions of persistent and bioaccumulative environmental toxicants. Some groups that have been highlighted are brominated flame retardants, phthalates, antibacterial agents, medicines and perfluorinated substances. Several of the flame retardants in current use have a chemical structure similar to that of the classic environmental toxicants PCBs and DDT; several have proved to be persistent and bioaccumulative, and they often produce adverse effects in living organisms.[3]

Because of the large number of sources, there is a mixture of chemicals in the environment with an unknown composition. As the number of chemicals used is very large, the number in the environment is also very high. More than 145,000 different substances are registered in Europe alone. There is therefore an almost infinite number of conceivable mixtures, and we are consequently living in a cocktail of different chemicals. The impact of substances on health and the environment is at best studied for the individual substance, but very rarely for mixtures. A mixture is almost always more harmful than the concentration of the most harmful individual substance in the mixture. This is not currently included in the assessments made of the hazardousness of chemicals. We are consequently all guinea-pigs in a huge, uncontrolled chemical experiment. With this in mind, is it not particularly surprising that the Swedish Parliament's environmental quality objective of A Non-Toxic Environment is deemed by the authorities to be impossible to achieve by 2020.

### Chemical problems in the South too

Chemical problems today are global and on the increase. The manufacturing of articles has in many cases moved from countries in the North, such as Sweden, to developing countries in the South where manufacturing costs are lower. A classic example is textile production, which has been transferred from Sweden to Eastern and Southern Europe, and is now principally located in Asia. As a result of the transfer, the legislation of other countries is applicable to production. Many countries in the South have low requirements for health and the environment. Although this is only the reason for transferring production in exceptional cases, the consequence may be that the environmental effects increase and are made invisible to consumers in the North. In recent decades a large proportion of chemical production has also been transferred from OECD countries to non-OECD countries[4]. This has led to the consumption of chemicals having also increased in many countries in the South, and it quite often turns out that a particular product may have worse contents from the point of view of health and the environment in the South than in the North, despite being marketed under the same product name.

Well-known environmental toxicants that are often categorised as CMR (carcinogenic, mutagenic and/or toxic to reproduction) and PBT (persistent, bioaccumulative and/or toxic) are still used in many countries in the South. This means that, among other things, they may be difficult to break down and are stored in tissues, and they may disrupt development and reproduction in humans and animals and cause cancer. The consequence of this may be that people are harmed or die after being exposed through careless handling of chemicals.

Certain medicines, for example, have proved very harmful to nature, and the problems are exacerbated when manufacturing is transferred to countries with low environmental requirements. In Pakistan, for example, the Bengal vulture was almost completely wiped out (95% of the population disappeared) after cattle had been fed the painkiller diclofenac, which is sold in Sweden under the name Voltaren. When the cattle died, the vultures ate their carcasses, and were severely harmed as their kidneys could not handle the drug residues[5]. It has also been found that pharmaceutical factories can release huge quantities of active substances directly into the environment. When the antibiotic ciprofloxacin is manufactured in India, the concentration in the effluent around the factory has proved to be higher than the level in the blood of people who take the medicine[6]. Use of drugs also leads to emissions with, in some cases, unknown effects in the environment in which they are used.

In the South, more than a fifth of all work-related deaths and injuries are directly caused by incorrect handling of chemicals at work. As many as 439,000 deaths and 35 million injuries are caused by chemicals every year[7]. Inadequate working conditions lead to direct exposure of humans to chemicals, and careless management of chemicals leads to emissions of chemicals that are dispersed in the environment. In the manufacturing of textiles, toys, electronics, leather, detergents and cleaning products, plastic and petroleum products and other everyday products – which are often sent to consumers in the North – people are often exposed to harmful quantities of chemicals at their workplace. There are rarely directions on how the chemicals should be handled, and when there are they are often difficult to understand, particularly if many people are illiterate. In addition, protective equipment that may be too expensive and difficult to use in a hot climate is often required.

In broad terms, politicians, authorities, industry and the general public in poor countries find it difficult to check the use of chemicals, and other social problems are often prioritised ahead of issues related to chemicals. Chemicals legislation, or application of it and compliance with it, is often weak. Poor people are often badly affected by environmental toxicants, particularly if their state of health is already weakened due to malnutrition or diseases such as malaria and HIV/AIDS, which increase susceptibility to chemicals.

Poor people additionally live in areas where environmentally hazardous industrial activity, incinerators or landfill sites are located. At the same time, they are particularly dependent on local ecosystem services for their livelihood, which are adversely affected by pollutants. Polluted effluents from factories result in water that people use every day also becoming toxic and unusable, while fish and other animals in the water are harmed by the chemicals. The poorest people, who often grow their own food, or catch fish in nearby rivers, may consequently suffer.

Children are particularly prone to chemical exposure. Examples of sources of exposure are umbilical blood, breast milk and other food, contaminated air, toys and clothes. The estimated 250 million children (aged between 5 and 14) in the South who work may also be exposed to chemicals in their working environment[8]. Many children living in poor countries are malnourished, are in poor general condition and are therefore particularly sensitive to environmental toxicants.

**A closer look: DDT is still in use against malaria**
DDT continues to be used to control malaria in many poor countries, mainly because of its low cost in use[9]. Around 270 million people are infected with malaria annually, and around 2 million die from this disease. African countries south of the Sahara are worst affected, with 90% of all malaria cases[10]. The reason why DDT continues to be used to control malaria is that other methods of control, such as impregnated nets and biological control, are still very expensive or require greater knowledge. Several environmental toxicants spread over long distances, as has been seen for example in South Africa, Uganda and Kenya, where high levels of DDT have been found in breast milk, including in areas where DDT is not used for malaria control[11,12].

## Chemicals are spread globally

No one knows what quantities of chemicals are released around the world, but measurements show that they can be carried with water and wind across national boundaries. An enormous number of tonnes of chemicals that can disrupt development and reproduction or cause severe illnesses in humans are involved. Toxic substances that are persistent and are released tens of thousands of kilometres away in the South evaporate in the hot climate. They are then carried by winds until they condense in cold conditions and fall to the ground before possibly evaporating again and moving further across the globe. This phenomenon is known as the grasshopper effect, and the movements in the atmosphere can take place in both long and short hops, and take differing lengths of time for different substances, depending on their inherent properties. Volatile substances evaporate more readily than less volatile substances.

High levels of PCBs have been found in polar bears on Svalbard. PCBs affect the levels of the male sex hormone testosterone in the male polar bears, which can seriously impair their ability to reproduce[13] and even lead to hermaphroditic males. In recent years newer groups of chemicals such as perfluorinated substances and brominated flame retardants have also been found in polar bears[14]. The endocrine systems of polar bears do not differ greatly from those of humans, and many of the chemicals transported around the world end up in countries around the poles, such as Sweden.

Mercury is another example of a hazardous chemical transported over long distances. One of the largest sources today is coal-fired power stations, and a significant proportion of the mercury released in the South is transported through the air to countries in the North. In oxygen-poor aquatic environments mercury is converted to methylmercury, which is readily taken up by fish. Much of the mercury in fish thus originates far from the place where the fish has been caught. In Sweden, for example, women who are expecting babies are recommended only to eat certain types of fish a maximum of two to three times a year, because of the high levels of mercury they contain[15]. Substances such as DDT, PCBs and the pesticide hexachlorocyclohexane, sold under the name Lindane, are demonstrably transported from the South to the North as they are still used in other countries, even though they are banned in Sweden[16].

# 2 Assessments of the properties of chemicals

In order to estimate various properties and effects of chemicals, they are tested in many ways. It is assumed for many properties that the effect is proportional to the concentration or dose to which the test organism is exposed. This means that substances are regarded as safe at low concentrations. It is important to emphasise that this correlation does not apply to all properties and that it is unclear when it does and does not apply. In the case of endocrine disruptors, stronger effects can arise at low concentrations than at high ones, and for some carcinogenic substances it is not possible to state any safe level. Another example is asbestos, where exposure even to individual fibres can be dangerous.

Studies done on large groups of people who have been affected by a disease or other effect are known as epidemiological. These studies search for the explanation for what affects humans, for example exposure to various chemicals. An example of an epidemiological study is looking at how workers who have been affected by cancer have been exposed to a particular substance and comparing this with a control group that has not been exposed to the same substance. It is very difficult to show clear causal relationships in epidemiological studies as concentrations in the environment are often low and many factors are generally involved. On the other hand, it is possible to find factors that co-vary with the studied effect.

Tests on animals are often performed instead of epidemiological studies in order to induce effects rapidly. The concentrations in these tests are often far higher than those that normally occur in the environment. The difficulty then lies in drawing conclusions from animal studies where various chemicals have been tested for a short time and at a high concentration, with regard to effects to humans, who are exposed to substances at a low concentration over a long period, and often to many substances simultaneously.

It has been common for a long time to study how one substance at a time affects different organisms. This has also led to data of that type forming the basis for legislation and risk assessments of different chemicals. Various limit values for chemicals that occur for example in the working environment, as additives in foods or phthalates in toys are often set on the basis of a concentration having been identified at which harm has occurred and then adding a safety factor, for example 100, which is assumed to be sufficient to protect humans. Risk assessments then take this assumed safe level as a basis and compare it with the exposure from various sources of the substance in question, without looking at how it possibly interacts with other substances.

Knowledge of how chemicals affect the environment is generally even more inadequate than with regard to health effects. This is due to environmental effects being noted at a later time than effects on health. The data that exists often applies to the acute toxicity of individual substances, that is to say how high a level is needed to quickly kill or seriously harm a species. In reality the equivalent may be a large discharge of a toxic chemical that kills fish more or less immediately, but the common situation is that many chemicals occur at relatively lower levels. If individual chemicals have been inadequately studied, this applies to an even greater degree to how chemicals in a mixture affect the environment.

A closer look: Different measures of acute toxicity

A common toxicity test that has been used for a very long time is toxicity to rats (i.e. establishment of the dose that is lethal to 50% of the test animals).. The measure of this is known as LD50. LD stands for lethal dose, and 50 means 50%. Other types of toxicity tests are also used, for example chronic toxicity and damage to genetic material and reproduction are studied. Environmental effects may be measured on fish, crustaceans or algae. These species are studied to see what effect chemicals have in the aquatic environment. It is then tested at what concentration in the water half the population (LC50) die, for example, or fewer, for example LC10, where 10% of the population die. In the case of crustaceans what is known as effect concentration is looked at instead. EC50 is the concentration at which, for example, 50% of the population no longer move. In the case of algae the way in which algal growth is inhibited is looked at instead. This is known as immobilisation, and the effect is termed IC (inhibitory concentration). In some tests the highest level that does not cause any harm or measurable effect is also determined (No Observed Adverse Effect Level, NOAEL) or No Observed Effect Concentration, NOEC). However, these tests do not show endocrine disruptor effects, which often occur at even lower concentrations than NOEC.

## Different ways of estimating effects of mixtures

Cocktail effect or combination effect means that all the substances in a mixture contribute to the properties of the mixture, such as its toxicity. This may be obvious, but despite it only the toxicity of the individual substances contained in the mixture is generally assessed, not the aggregate effect. Using present-day methodology it is completely impossible to carry this out for all conceivable mixtures as animal tests take a long time. The reason why so few tests have been done is that it is difficult to know how different substances interact, and with regard to substances in the environment it is also difficult to establish all the different substances that are present. It is also more difficult to find correlations between different effects and levels in the environment if many different parameters, such as the concentrations of different substances, have to be studied.

There are several ways of estimating the toxicity of mixtures. The two most common are the concentration addition method and a concept based on independent action. These are purely theoretical methods based on knowing the properties of the individual substances contained in the mixture and calculating an expected aggregate effect. In the concentration addition method, the toxicity of the substances contained is added together in proportion to their concentration in the mixture. This is based on an assumption that the toxic action of the substances works in the same way. When calculation is based on independent action, it is assumed instead that the substances may have different ways of attaining the same toxic action and the effects are then multiplied instead of being added together. To evaluate the methods, the results are compared with measured values, and the concentration addition method has proved most usable, although it may lead to a more cautious assessment than calculations based on independent action. However, the difference is no greater than 1.5–3 times for studied chemicals.[17]

These two methods are intended to theoretically weigh together the known properties of the individual substances. In reality the chemicals may, in certain cases, further strengthen but also weaken each other's effects compared with what might be expected on the basis of the calculation models. In a mixture where several chemicals occur and the effect is greater than can be calculated using the methods described above, there are said to be synergistic effects. In cases where the chemicals in the mixture reduce each other's effects, there is said to be an antagonistic effect.

## Environmental effects of mixtures

There are various types of mixtures. A detergent consists of around 10–30 different chemicals that have been mixed together. The mixture has a known composition, which has been developed to give the detergent its function. When the detergent reaches the sewer it is mixed again with other substances from different sources to form a new mixture, now with an unknown composition. That is the way it is with all the different chemicals that are used and then reach the environment. For a known mixture, such as the detergent, it is possible to test its properties, e.g. toxicity to fish, and it is also possible to make a theoretical calculation of the effects if the properties of the individual substances are known. With regard to the mixture present in wastewater, it is possible to test the effects of the water on fish, but it is impossible to estimate the toxicity of the mixture theoretically today as the composition is unknown. To enable the contents to be determined by chemical analysis, it is also necessary to know what one is looking for in order to be able to find it.

Large numbers of studies show that many different chemicals that have been manufactured by humans are present in the environment. Even when they have been used as pure substances in a technical process, they are mixed with other substances when they enter the surrounding environment. Just a few examples of studies that have looked at how different animals or plants are affected by a known mixture of chemicals and how well the combination effects can be described are addressed here.

One of the most studied groups of chemicals is that of pesticides, such as plant protection products and biocides. They have been developed to be toxic as they are intended to control microorganisms, animals or plants and are intentionally spread in the environment. Their impact on health and the environment has been the focus of attention over a very long period of time. Test requirements have also been more extensive in Sweden, for example, than for other chemicals.

The concentration addition method works well as a way of estimating the ecotoxicological properties of the mixture for pesticides that have the same mechanism of action. There are, however, mixtures that deviate. If organophosphates and carbamates are mixed with other organophosphates or pyrethroids, the toxicity is higher than when it is calculated by the concentration addition method. This effect is synergistic, meaning that the substances contained in the mixture reinforce each other's toxicity.

Mixtures of the insecticide α-cyper¬methrin and various fungicides exhibit a synergistic action in most cases. A mixture of α-cypermethrin and prochloraz was 12 times more toxic than the concentration addition method could predict. The toxicity of triazoles mixed with α-cypermethrin was 6-7 times higher than calculated, while fenpropimorph mixed with α-cypermethrin showed an antagonistic action, in other words lower toxicity than indicated by the concentration addition method.[18]

Antifouling paints contain biocides that, just like plant protection products, are intended to be toxic, in this case to prevent the growth of organisms on boat and ship hulls. Synergistic effects have been discovered for mixtures that have been studied, just as they have for certain plant protection products, in comparison with theoretical calculations. Only 5% of the individual EC50 for algae was needed to achieve 50% effect for a mixture of Irgarol (which contains copper) and diuron. This means that the mixture is ten times more toxic than could be predicted by the concentration addition method. Mixtures of diuron and zinc pyrithione and of Irgarol and zinc pyrithione also showed synergistic effects. One explanation as to why the mixture of copper and zinc pyrithione shows synergistic effects compared with the concentration addition method may be the rapid conversion that takes place to the more toxic form copper pyrithione.[19] There were also mixtures that showed small signs of the opposite, that is to say lower toxicity than calculated[20].

In the testing of a mixture consisting of three different biocides, zinc pyrithione, diuron and Irgarol, toxicity to the embryo was found to be substantially lower than indicated by the concentration addition method. It appears difficult to estimate the effects of an antifouling paint using the concentration addition method.

How the uptake of copper by crustaceans is affected by the simultaneous presence of carbon nanotubes has also been tested. One nanometre is a millionth of a millimetre, or a billionth of a metre. Carbon nanotubes are only a few nanometres thick, but can vary in length from nanometres to decimetres. Carbon nanotubes are suspected of being capable of having effects similar to asbestos on the lungs. The effects of this mixture too could be predicted by the concentration addition method[21]. This study also suggests that the uptake of nanomaterials may increase the bioavailability of copper, as a result of copper becoming attached to the nanotubes that can then pass through membranes.

Mixtures of medicines may also show greater toxicity than expected. A mixture of fluoxetine, ibuprofen and ciproxfloxacin had a lethal effect on fish[22]. For crustaceans and algae, the concentration addition method has worked well in predicting the toxicity of a mixture of diclofenac, ibuprofen, naproxen and acetylsalicylic acid, all medicines used to treat inflammation)[23]. The same applies to the β-blockers propranolol, atenolol and metoproplol[24].

# 3. Cocktail effects – a threat to health

Foetuses (embryos) and children are particularly sensitive to chemicals, as their bodies have not yet fully developed. This applies in particular to the development of the brain, nervous system, immune system and genital organs[25, 26, 27]. The following sections address known combination effects on the brain, nervous system, immune system and general development in foetuses, in both humans and other species.

## Disruption of development of the nervous system

Three types of chemicals that are each separately known to disrupt the functions of the brain and nervous system are methylmercury[28], polychlorinated biphenyls (PCBs)[29] and polybrominated diphenyl ethers (PBDEs)[30]. Both PCBs and PBDEs exist in many different variants depending on how many chlorine or bromine atoms the basic molecule contains. The different variants are known as congeners. They are common environmental pollutants that often enter our bodies through the consumption of fish and shellfish[31,32]. It is characteristic of these chemicals that they are readily taken up by the body as they are fat-soluble and at the same remain in the environment for a long time. Chemicals with such properties are described as bioaccumulative and persistent. Our bodies contain a large amount of fats, not just pure fatty tissue under the skin and around organs but also in membranes that surround cells, such as in the nervous system and the brain. Methylmercury, PCBs and PBDEs accumulate in those parts of the body in which there is fat and can exert their toxic action there. You can read more about these chemicals in Chapter 7.

Between 90 and 100 per cent of the methylmercury that enters our bodies through food is taken up through the gastro-intestinal system and transported to different parts of the body with the blood[33]. Methylmercury can freely cross the blood-brain barrier[34] – the selective barrier that regulates the exchange of chemical substances and compounds between the blood and the brain – and the placenta from mother to foetus[35]. Children may thus be born with methylmercury in their bodies. The nerve–disrupting properties of methylmercury may lead to hearing and visual impairments and impaired memory, as well as a deterioration of muscle-coordinating capability[36].

PCBs are taken up by the body from food through the gastrointestinal system[37,38]. They can also cross the placenta between the mother and foetus[39], and children may therefore be born with PCBs in their bodies. PCBs disrupt the blood-brain barrier by inhibiting the production of certain structural proteins in this barrier. When the composition of the proteins in the blood-brain barrier changes, patency to various substances increases, which can lead to tumours[40, 41]. There is then a risk of exposure to PCBs leading to unexpected combination effects with many different chemicals that normally cannot cross the blood-brain barrier. PCBs also disrupt the development of the part of the brain known as the cortex[42,43], where auditory information is processed. Several epidemiological studies suggest that exposure to PCBs at the foetal stage, or later in life, my harm reflexes, adversely affect muscle motor response, and lead to reduced capacity in the senses and a deterioration in IQ[44, 45, 46, 47, 48, 49, 50]. Levels of PBDEs in the environment are increasing in many places, and in humans they are now starting to approach the levels of PCBs[51, 52]. PBDEs are taken up in the body from food[53], but may also cross the placenta from mother to foetus[54]. Many different animal experiments have shown that the development of the brain and the nervous system is disrupted by PBDEs[55], and an epidemiological study suggests that PBDEs may cause a deterioration in muscle motor response, reduced verbal capacity and lower IQ in children[56]. The scientific basis for these substances each separately being harmful to the development of the brain and nervous system is extensive, but what do we know about any combination effects, i.e. about the cocktail effect?

Among several others, a research team from Uppsala University has shown that methylmercury, PCBs and PBDEs have combination effects on the brain and nervous system that reinforce each other and are therefore examples of synergistic effects, that is to say combination effects that are greater than additive effects:

- In one study they found that mice exposed to a combination of methylmercury and PCB-153 (commonly occurring in the environment) at individual concentrations that in themselves were harmless showed neurological effects of the same order of magnitude as mice exposed to a ten times higher dose of methylmercury only[57].
- In another study, they found that the combination of PCB-52 and PBDE-99 (commonly occurring in the environment) in individual concentrations that in themselves were harmless gave rise to greater neurological effects in mice than PCB-52 alone at a five times higher concentration than in the combination treatment[58].
- In a further study it was found that PBDE-99 in combination with methylmercury caused structural changes in nerve cells at concentrations at which these chemical compounds each separately do not produce any effects[59].

**Fördjupning: Metylkvicksilver kan ge sämre inlärning**
Epidemiska akuta metylkvicksilverförgiftningar är kända från Japan och Irak under 1950- till 1970-talen, med dramatiska effekter hos både vuxna och barn. Dödsfall och neurologiska missbildningar förekom. Det finns några större befolkningsstudier, så kallade epidemiologiska studier, där man har försökt utvärdera effekter av kronisk exponering för låga halter metylkvicksilver – en normal exponeringssituation för majoriteten av oss. I en välkänd studie från Färöarna fann man samband mellan metylkvicksilverinnehåll i mödrarnas hår och navelsträngsblod och hur barnen vid sju års ålder presterade i 11 olika neurologiska tester[60]. Studien antyder att kronisk exponering för låga halter av metylkvicksilver kan ge små men mätbara utvecklingsstörningar i nervsystemet. Andra studier har gett liknande resultat, men det finns även enstaka studier med motsägande resultat. I en studie av barn från Seychellerna, till exempel, kunde man inte visa något samband mellan metylkvicksilver och hur barnen presterade i sex neurologiska tester[61, 62, 63, 64, 65]. En komplicerande faktor i tolkningen av resultaten från den färöiska studien var att den studerade populationen också exponerades för höga halter av PCB[66]. En samverkan mellan PCB och metylkvicksilver har föreslagits förklara resultaten i Färöstudien [67]. Vidare tycks resultaten från den svenska forskargruppen i Uppsala ge stöd åt att de neurologiska effekter som studerades i den färöiska studien uppkom genom kombinationseffekt – i detta fall en samverkan mellan metylkvicksilver och PCB.

## Disruption of development of the immune system

A functioning immune system is crucial in enabling the body to withstand attacks by bacteria, viruses and parasites and clearing away genetically defective cells that in the longer term can lead to cancer. There are critical periods in the development of the immune system, both at the foetal stage and later in life, when exposure to chemicals that disrupt this development can led to serious deficiencies in the immune system. It is suspected that childhood leukaemia can arise in this way. Childhood leukaemia is on the rise in many parts of the world[68, 69], as are asthma and allergies, which are also due to imbalances in the immune sysem[70, 71]. A cocktail of foreign chemicals in our surroundings and in our bodies may be part of the explanation behind these trends.

A number of studies have demonstrated effects on the immune system when different chemicals interact. The examples below illustrate how chemicals can interact in creating imbalances in the immune system.

- A combination of the semi-metal arsenic and the metal lead is more toxic to certain cell types in the immune system in mice than the sum of the toxicity of the individual substances[72]. This is an example of synergism. Humans have spread arsenic and lead in the environment, and effects similar to those shown by mice cannot be ruled out in humans.

- A study showed that mixtures of organochlorine compounds, from the groups of PCBs and dioxins, produced different types of combination effects (synergism, antagonism and additive effects) than the effect of the individual compounds on the immune system in different organisms[73]. Humans spread dioxins in the environment involuntarily, principally through combustion processes (read more about dioxins in Chapter 7).
- Polyaromatic hydrocarbons (PAHs) are a group of bioaccumulative and, in some cases, carcinogenic organic compounds dispersed in the environment through all kinds of combustion processes such as traffic, burning of coal and oil, forest fires and volcanic eruptions. In a study of the effect of PAHs on the activity of the immune system, mixtures of PAHs gave rise to synergistic combination effects[74]. Another study showed that the metal cadmium and the polyaromatic hydrocarbon benzo[a]pyrene each separately affected the immune system, but when fish already exposed to cadmium were also exposed to benzo[a]pyrene the effect was substantially greater than was expected from the effects of the individual chemicals[75].

### Disruption of foetal development

A growing foetus (embryo) undergoes series of closely coordinated phases of cell growth, cell death and formation of organs. Imbalances in these phases lead to disruption of development, which may result in the foetus being deformed or dying. There are many examples of documented combination effects with respect to foetal development. Some examples follow below:

- In a study of the effects of bisphenol A (BPA), a common raw material in the manufacturing for example of polycarbonate and epoxy plastics and genistein, which is an oestrogen-like compound in soya beans, clear synergistic effects were found in rat foetuses with regard to the proportions of different body parts and to organ development, particularly the spinal cord and the parts of the brain and nervous system associated with vision and smell[76]. The research team that conducted the study believes that there is a risk of similar effects on human foetal development, which is a cause for concern as BPA is widely used, while consumption of soya-based products (vegetarian alternatives to dairy products) is steady rising. In a recently conducted study in the United States on the level of BPA in urine, BPA was detected in 93% of all samples[77].
- BPA and the pesticide pentachlorophenol can occur in the environment as combined pollutants in water[78], which may be harmful to aquatic organisms. Combination effects with respect to embryo death and cardiac oedema in fish embryos exposed to these compounds were demonstrated in a study[52]. The combination effect already arose when the fish were exposed to pentachlorophenol at concentrations that were below the lowest concentration at which an effect can be detected – the LOEC value. The study showed the occurrence of both synergistic and antagonistic combination effects.

The metals iron and aluminium are spread in large quantities in the environment. Some uses with spread to the environment are as precipitation chemicals in sewage treatment plants, dietary supplements and medicines, and industrial processes. These metals in combination may be more harmful to foetal development in certain aquatic organisms that each of the metals separately. Varying degrees of combination effects – from additive to synergistic – between iron and aluminium have been observed in embryos of mussels and sea urchins. The embryos stopped developing, were deformed, or died.

# 4. Endocrine disruptors and reproductive toxicity

An endocrine system that works well is essential for a number of physiological processes in the body, such as reproduction, metabolism and the development of the nervous system. The endocrine system, which actually consists of a number of parallel systems for different functions, is organised into several levels with mutual feedback. To enable a particular physiological function to be maintained, several hormones are generally required to be produced and released and to act in a correct manner. This structure creates many possible "targets" (see figure 1) for endocrine disruptors, which also increases the risk for combination effects as different substances, despite acting at different levels, may disrupt the same process.

Chemical substances that disrupt the functioning of the endocrine system and in so doing cause adverse effects on health are generally known as endocrine disruptors. There are endocrine disruptors in a wide range of products, for example pesticides, plastics, textiles and medicines. They also occur naturally in certain plants and moulds. Endocrine disruptors have a wide geographical spread and can give rise to harmful effects both in humans and in other animal species, including birds, fish and reptiles[79, 80, 81]. Epidemiological studies in recent years have demonstrated correlations between exposure to endocrine disruptors and obesity, diabetes, ADHD and deformities of the urinary tract and genital organs, which has raised the issue of the significance of these substances to public health[82, 83, 84, 85].

The first endocrine disruptors were identified through their similarities to the female sex hormone oestrogen, and this chemical similarity to endogenous hormones, and the ability to imitate these, was long regarded as explaining the endocrine-disrupting effect. As new substances have been identified, more mechanisms have been revealed and it is now known that endocrine disruptors also affect other levels of endocrine systems. This group of compounds also differs in several important respects from other toxic substances. A fundamental concept in toxicology is being able to predict what happens at lower doses on the basis of observations at a particular dose. This has proved particularly difficult for endocrine disruptors, and in some cases the effects are diametrically opposed in exposure to low and high doses. One example is the phthalate DEHP, which at low doses (10 mg/kg) speeds up the development of puberty in experimental animals while high doses (750 mg/kg) instead delay development[86]. The effects of endocrine disruptors are often discovered far below the NOEC values and are therefore missed in traditional test methods.

What effects arise after exposure to endocrine disruptors additionally depends greatly on the time of exposure and the levels of the body's own hormones[87, 88, 89]. Boys with an endocrine disorder that means that testosterone is totally lacking or is prevented from acting will be born with female external genital organs despite having testes, while milder disruption results in a lower degree of feminisation. Many researchers have therefore chosen to study the effects of endocrine disruptors, both individual substances and mixtures, on foetal development in male animals, principally rats. As a result, it has been possible to identify a critical time window (days 15.5–19.5 of embryonic development) in which the exposure must take place for the males to be feminised. The females are vulnerable during the same interval of time, but instead to substances that resemble testosterone and consequently cause undesirable masculinisation[90]. Taking account of human foetal development, this means that the child is probably at its most sensitive during weeks 8-14 of gestation.

## Combination effects on development and reproduction

To identify and grade an endocrine disruption in boy foetuses, as well as measuring testosterone levels two types of deformities or abnormalities in the urinary tract and genital organs that arise in testosterone deficiency are studied: hypospadias and cryptorchidism. Hypospadias is a defect in which the opening of the urethra is on the underside of the penis, while cryptorchidism means that the testis has not migrated down into the scrotum from the inguinal canal or the abdominal cavity. Another common sign of disrupted testosterone function is a reduced distance between the rectum and genital organs (anogenital distance, AGD), which is probably the most sensitive marker of disturbed testosterone function[91].

Combination effects during foetal development have been documented for both compounds in the same chemical group (for example phthalates) and active substances in different product categories, for example plastics and pesticides[92, 93, 94]. Chemicals that have different modes of action or targets can also give rise to combination effects, as can mixtures where the individual substances occur at such levels that they do not cause any harm (No Observed Adverse Effect Level, NOAEL)[95, 96]. These observations contradict the theory previously accepted generally[97] that combination effects can only arise when each substance occurs in doses that exceed its NOAEL and for chemicals that act in the same way. It is usually possible to estimate the effects relatively well using the dose addition model, but there are also examples of mixtures that give rise to synergistic effects, which are more difficult to predict[98, 99, 100].

It can broadly be said that human reproduction can be affected at far lower concentrations than those that produce acute effects in children and adults.

As mentioned earlier, the dose-addition model often works well in predicting combination effects. In an experiment with a mixture of six phthalates and four pesticides, seven out of eight parameters (including defects) followed the calculated dose-addition curve[101]. Another example of dose addition is the inhibition of testosterone production in rat foetuses exposed to a phthalate mixture (DEHP, DBP, BBP, DiBP, DPP)[102].

Combination effects of endocrine disruptors are not limited to foetal development or the processes regulated by testosterone. A cocktail consisting of seven oestrogenic substances was evaluated in a test in which substances with oestrogenic properties were identified by the fact that they increased the weight of the uterus, and a marked combination effect was found. The mixture consisted of nonylphenol, bisphenol A (BPA), methoxychlor, genistein, oestradiol, diethylstilbestrol and ethinyloestradiol, at doses that were each inactive, and it doubled the uterine weight in the treated rats[103]. A mixture of two plant oestrogens (daidzein and genistein) and six synthetically produced compounds (methoxychlor, o,p-DDT, octylphenol, bisphenol A, betahexachlorocyclohexane and 2,3-bis(4-hydroxyphenyl)-propionitrile) also resulted in a significantly higher uterine weight when they were analysed in the same type of test[104]. The effect was dose-additive and arose at as low a dose as 1/10 of LOAEL (for the individual compounds). The development of puberty is another example of a physiological process affected by substances with oestrogenic properties. Simultaneous exposure to genistein and methoxychlor gave the females an earlier and the males a later start to puberty than non-exposed animals[105].

As well as in animal studies, potential endocrine disruptors, and combination effects of these, are often studied in cell cultures, using what are known as in vitro tests. By isolating cells from any of the organs where the hormone concerned acts, it is possible to study in a more direct way than in animal experiments whether a chemical strengthens, counteracts or takes the role of the body's own (endogenous) hormone. The advantage with this type of tests is that they do not necessarily require experimental animals. They are also cost-effective and enable a large number of substance combinations to be analysed. However, cell cultures are only capable of capturing effects at one level of the endocrine system, why a result from tests of this type may need to be supplemented by animal studies. Examples of mixtures that have been shown to give rise to oestrogenic combination effects in cell-based tests are UV filters (synergistic, NOEC), medicines (synergistic, NOEC), plant oestrogens (concentration additive) and parabens (concentration additive)[106, 107, 108, 109]. In a corresponding way antiandrogenic effects have been documented for different mixtures of pesticides[110,111]. The in vitro methodology has greatly advanced in recent times, which will lead to entirely new opportunities for testing and new test strategies.

Although most of the studies that have been published on combination effects of endocrine disruptors have been concerned with sex hormone-regulating functions, there are other interesting examples. An American research team showed in 2005 that a mixture of 18 polyhalogenated aromatic hydrocarbons (including 12 PCBs and 2 dioxins) inhibited thyroid function (release of thyroxine) in rats. The effect was dose-additive at low, environmentally relevant doses, while it was synergistic at higher doses[112].

It is not an easy task to determine what significance endocrine disruptors have for present-day public health problems. However, the studies reported here provide great cause for concern. This is particularly the case as endocrine-related disruptions have substantially increased in recent decades. For example, sperm concentrations were only half as high in 1990 as fifty years previously, and the number of boys born with hypospadias is increasing in both Europe and North America[113, 114, 115]. The substantial change over a short period and the observation that second-generation immigrants follow the statistics of the new homeland indicate strongly that the underlying explanation is one or more environmental factors[116]. Epidemiological research has traditionally focused on individual compounds or groups of structurally similar substances, but a recently published study analysed 121 endocrine disruptors in the breast milk of Danish and Finnish women[117]. Finland has a low and Denmark a high incidence of reproductive disorders, and there was therefore a desire to investigate whether the reason was a difference in chemical exposure. The result was clear: the samples from Denmark contained substantially more of the endocrine disruptors than the Finnish samples. Combination effects thus probably arise between the chemicals we have in our blood, which is then manifested among other things in testicular cancer and urogenital defects. To our knowledge, it has not yet been studied whether other diseases and disorders, such as diabetes and ADHD, can be linked to a generally higher exposure to chemicals, but such studies would, of course, be valuable.

**A closer look – Oestrogens harm the environment**

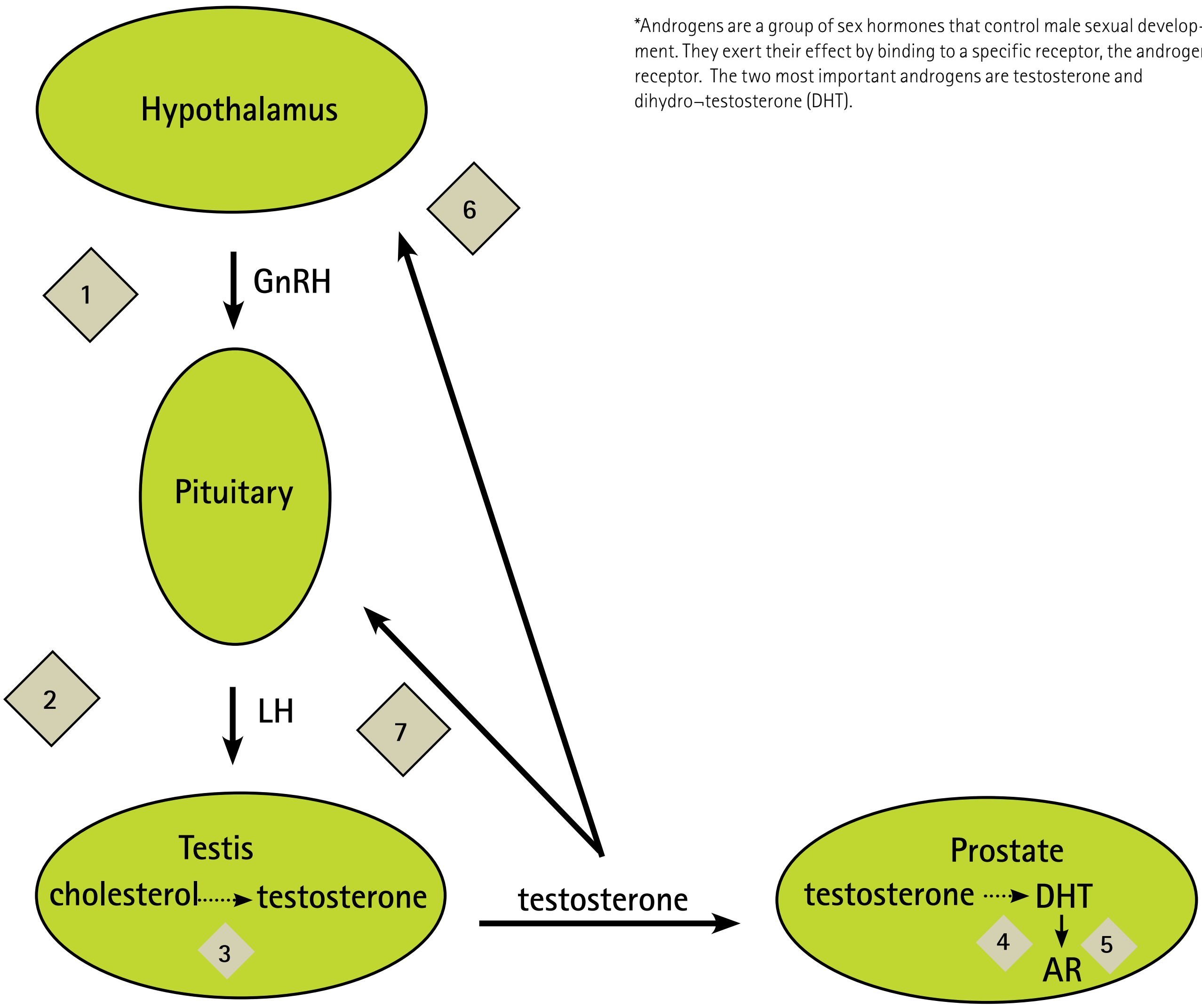
Attention has also been drawn to the environmentally hazardous properties of oestrogens. In the 1990s researchers observed clearly oestrogenic effects in fish downstream of sewage treatment plants in Britain, more recently also documented in Sweden, which has led to increased interest in the issue[118, 119]. The marker used in these studies (as in many others) was the concentration of vitellogenin, a liver protein whose production is strongly linked to exposure to oestrogenic substances. Although the number of studies is limited, it has also been possible to demonstrate combination effects of oestrogenic compounds in fish. A mixture of 17 β-oestradiol (endogenous oestrogen), 17 α-ethinyloestrodiol (contraceptive pill oestrogen), bisphenol A, nonylphenol and octylphenol induced vitellogenin production in a concentration-additive manner in the freshwater species Phimephales promelas (a carp)[120]. In a corresponding way, a mixture of oestradiol, ethinyloestradiol and bisphenol A was found to raise vitellogenin concentrations in sea bass[121]. In this case too, the effect was concentration-additive. As in several other studies mentioned, the oestrogenic effect in the two fish experiments arose at doses where the individual substances were inactive.

**A closer look – Combination effects on male hormones**

A recently published study by Sofie Christiansen and her colleagues at the Technical University of Denmark illustrates several of these aspects well[122]. This study examined a mixture of four chemicals with different uses, namely the phthalate DEHP, the pesticides vinclozolin and prochloraz and the medicine finasteride. All these four compounds are well documented as endocrine disruptors, but with different targets. DEHP reduces the production of testosterone from cholesterol (target 3, see Figure 1), vinclozolin obstructs the action of the androgen dihydrotestosterone (DHT) by blocking its binding to the androgen receptor (target 5), finasteride (a drug used to treat benign prostatic hyperplasia) blocks the conversion of testosterone to DHT (target 4), while prochloraz has several of these steps as targets (3 and 5)[123, 124, 125, 126, 127]. The mixture was found to give rise to both dose-additive and synergistic combination effects on foetal development, depending on which parameter was analysed. The anogenital distance (AGD) in exposed rats decreased in a dose-additive way, while the effect was synergistic with respect to hypospadias. The defect was observed at 3-4 times lower doses than had been calculated in the theoretical model for dose addition. A further interesting result from the study was that AGD was reduced after exposure to a mixture where the doses of each individual substance corresponded to NOAEL. Also other types of mixtures can disrupt foetal development at NOAEL doses (or lower). Exposure to a cocktail of five fungicides, where the doses contained in the mixture were as low as 25% of NOAEL, resulted in a high incidence (>40%) of hypospadias in the male offspring. A significant change in AGD was simultaneously found in both male and female animals[128].

Figure 1. Example of hormonal regulation and possible targets for endocrine disruptors. The hormone GnRH (target 1) is released from the hypothalamus and acts on the pituitary, resulting in release of the hormone LH (target 2). In the testis, LH induces production of testosterone from cholesterol (target 3). In the prostate, testosterone is then converted to dihydrotestosterone (target 4), a more potent androgen*, which acts by binding to the androgen receptor (target 5). Through a feedback mechanism, the levels of testosterone also control how much GnRH and LH is released from the hypothalamus and pituitary (targets 6 and 7). All these steps are potential targets for endocrine disruptors.

*Androgens are a group of sex hormones that control male sexual development. They exert their effect by binding to a specific receptor, the androgen receptor. The two most important androgens are testosterone and dihydro¬testosterone (DHT).



# 5. Politics and legislation in the field of chemicals

Chemicals legislation goes back a long way in time, within the EU to the 1960s. The rules governing industrial chemicals in the EU have recently been revised. A directly applicable Regulation called REACH[129] (Registration, Evaluation, Authorisation and restriction of CHemicals) came into force in 2007. The registration rules set forth requirements on data for substances within particular volume ranges, but the focus is on the individual substances. This means that knowledge about the substances will increase, but it does not automatically provide knowledge about mixtures and combination effects or endocrine disrupting effects. What properties must be tested for registration also depends on how much of the substance is manufactured or imported. The greater the volumes, the more test data are required. For substances manufactured in quantities of between one and ten tonnes, toxicological data have to be produced on skin irritation, eye irritation, skin sensitisation, mutagenicity and acute toxicity. Environmental effects to be studied relate to toxicity in the aquatic environment for crustaceans and algae and degradability. Stricter requirements for data are set for substances manufactured in volumes in excess of 100 tonnes, such as extensive reproduction studies, toxicity to soil organisms, chronic toxicity tests on fish and mapping of dispersal routes in the environment. Conversely there are no requirements for substances in volumes of less than 1 tonne, which in fact means the majority of the substances that may be on the market.

The CLP Regulation[130] on the classification, labelling and packaging of products is also applicable to chemical products. This addresses how mixtures are to be classified and labelled, but in the vast majority of cases is concerned with data for the individual substances. The information produced through REACH is not sufficient to classify the substances correctly for substances in quantities of less than ten tonnes. Mixtures are labelled on the basis of their physical properties (flammability, explosiveness etc.), health effects (toxicity, cancer, adverse effects on reproduction etc.) and environmental effects (principally for aquatic organisms such as fish, crustaceans and algae). It is only for acute toxicity to animals and plants on land or in water that attempts are made in certain cases to take account of how different substances interact in the mixture.

There is other legislation in the environmental area where the status in the environment is looked at instead. Examples are the Water Framework Directive[131], which among other things sets limit values for certain substances in water, and the Industrial Emissions Directive (IED)[132], which sets limits for emissions to air and requirements for best available technology. The Water Framework Directive establishes environmental quality standards for 33 prioritised substances. Mixtures will be addressed in the technical guidance document for environmental quality standards that is being developed. The mixtures of different substances that occur in air and water are all unintentional, and their composition is therefore more difficult to predict.

The legislation on pesticides, the Plant Protection Products Directive (91/414/EC) and the Biocides Directive (98/8/EC), regulates the use of plant protection products (products mainly used in agriculture and in parks, golf courses and domestic gardens) and biocides (which includes other pesticides, for example wood preservatives, antifouling paints, rodenticides and disinfectants). The legislation on plant protection products has recently been revised, and the Directive is being replaced by the Plant Protection Products Regulation No 1107/2009/EC, which is due to come into force on 14 June 2011. This sets expanded requirements for residual levels of several different pesticides in foods or feeds not to have a harmful effect on health. The legislation is also being revised for biocides, and a regulation is on the way there too.

# 6. Ways forward

The Swedish Society for Nature Conservation has been working on chemicals for many years, with analysis and surveying of environmental toxicants in the peregrine falcon, white-tailed eagle and consumer products, the Good Environmental Choice ecolabelling scheme and consumer guidance, and proposals for enhanced legislation at the Swedish and international levels, including proposals for prohibition of individual chemicals such as DDT or techniques such as chlorine bleaching of paper. The Society's policy on environmental toxicants describes objectives, positions and measures to enable the Swedish Parliament's objective of a non-toxic environment within a generation to be attained. The precautionary principle and the responsibility of the polluter are two cornerstones of this policy, meaning that preventive measures must already be taken in the event of uncertainty over threats to the environment and health, and that the polluter has to meet the costs of these measures. A key measure is to require everyone who uses chemicals to replace and search for alternatives to hazardous substances at all times.

The Society makes it easier for consumers to follow the principle of replacement in everyday life through the Good Environmental Choice ecolabelling scheme. Good Environmental Choice sets limits for what properties can be accepted in a chemical on the basis that the less toxic the chemicals are as individual substances, the lower their combined toxicity is likely to be. With strengthened fundamental statutory requirements for better knowledge and data for example on combination effects, advanced requirements on that point can be developed in ecolabelling. It is important to be aware that the purpose of the ecolabelling is to guide consumes towards relatively better products, and that the labelling cannot replace legislation to limit the most hazardous substances or technologies.

This report has described what is known today about the toxicity of mixtures and what gaps exist in present-day legislation. Unfortunately there is great cause for concern. The combination effects observed in animal experiments, for example a shift in the development of puberty and deformities of the genital organs, are the same type of adverse effects that have increased greatly in the population in recent years. The effects additionally already occur at levels measured in nature, or are regarded as safe according to present-day risk assessment methodology. It is particularly alarming that researchers are additionally showing that endocrine disruptors can reinforce each others' effects, particularly when they occur in large numbers and with a wide geographical spread. Urgent action is therefore required to Save the Men, which obviously means also protecting children and foetuses, and consequently also women.

A first measure is to review the system of risk assessments. Despite the great need for data and knowledge there are great deficiencies, for example the fact that combination effects are not assessed despite the research clearly showing that such effects exist. Human blood contains a cocktail of hundreds of chemicals, and it is not justifiable to assess these separately without taking account of combination effects. An argument against including combination effects in the risk assessment has been that there is an infinite number of potential interactions and that there has been a lack of reliable mathematical models. Our review shows, however, that there are now some models that work well and can be applied to endocrine disruptors. The dose addition model was able to predict combination effects with high precision in most cases and proved also to be usable for substances for different mechanisms of action. The independent action model, on the other hand, consistently underestimated the effects[133,134]. The dose-addition model should therefore be introduced as soon as possible in risk assessment contexts, at the same time as the research on new test methods is strengthened.

Another important aspect in the risk assessment of endocrine disruptors is to identify particularly sensitive groups so that they can be protected. Sensitivity varies between different periods of life and with the levels of the body's own hormones. Increased vulnerability can also arise as a result of genetic variation between different individuals or population groups. The properties of the substance are also of key significance. For example, boy foetuses are very sensitive to substances that inhibit testosterone, while prepubertal girls are particularly vulnerable to substances with an oestrogenic action. Increased knowledge of individual chemicals is also essential in making it possible to predict possible combination effects and develop risk assessments models. Further research on endocrine disruptors, both individual substances and mixtures, should therefore be prioritised while also taking action quickly to strengthen protection for those most at risk. The 2009 report that established that Danish two-year-olds are exposed to such levels of endocrine disruptors that their health is at risk indicates the need for rapid action[135].

With regard to the classification and labelling of mixtures, the simple theoretical models should start to be applied quickly so that at least some account is taken of combination effects. It is more difficult in the current situation to see how the unintentional mixtures that are present in water and air should be dealt with. In some cases toxicity can be tested, but this is not always realistic, and in some cases the substances must be assessed on the basis of their inherent properties, in line with the precautionary principle.

Once the substances have been more or less scrutinised, decisions are required on some form of regulation. Even the suspicion of hazardous properties, such as toxicity, endocrine disrupting properties or persistence combined with bioaccumulability should halt the introduction of new substances and lead to the phase-out of existing ones. This in turn requires a reform of chemical legislation. The REACH Regulation, for example, must in general include substances in lower volumes and be modified so that it becomes easier to bring about permit consideration or restrictions.

It is important to focus on four areas in REACH and other chemicals legislation with regard to endocrine disruptors. There are requirements that are backed by environmental organisations throughout Europe, see annex. Firstly it is important to immediately commit more resources to work aimed at identifying known and suspected endocrine disruptors and bringing them within the framework of REACH, particularly in cases where children and women of childbearing age can be imagined to be exposed. Secondly there is a need to tighten up the requirements for substitution of substances in REACH. Particularly on the basis of our understanding of cocktail effects, endocrine disruptors should in future automatically be included among the substances classified in REACH as being of very high concern, and permits should never be granted for such substances if there are less hazardous alternatives. Thirdly, information on such classification should always be transparent and fully available to consumers and companies that use chemicals in their operations. Fourthly, there is a need in future for a radical reform of all rules on chemicals in the EU, so that substances that are endocrine disruptors, according to criteria in line with the precautionary principle, will always be the object of regulatory measures. The Swedish Society for Nature Conservation has presented a number of proposals in various contexts for a policy for a non-toxic environment, which among other things means that male fertility can be protected.

# 7. Facts about various chemicals

**Bisphenol A (BPA)**

**Function:**
BPA is principally used for the production of polycarbonate plastic and for epoxy adhesives. Polycarbonate plastics are widespread and are used in society, for example in water bottles, sports equipment, CDs and DVDs and spectacle lenses.

**Known environmental and health problems:**
BPA has hormone-like properties, which may damage the foetus , have adverse effects on reproduction and affect the immune system, and it is also suspected that BPA is carcinogenic. Based on laboratory experiments and observations of various organisms in the environment, BPA is considered capable of leading to feminisation of males. BPA is classified as harmful to aquatic organisms and can cause long-term harmful effects in the environment.

**Restrictions:**
A risk evaluation of BPA is currently under way in the EU. Denmark and Canada have banned BPA in feeding bottles. The EU has taken a decision that there must be no bisphenol A in feeding bottles from the summer of 2011.

**DDT**

DDT is an insecticide developed during the 1940s. It was commonly used against insect-borne diseases such as malaria and typhus during the Second World War. Commercially available DDT is actually a mixture of several chemicals, the greater part of which consists of p,p'-DDT and o.p'-DDT.

**Known environmental and health properties:**
DDT is an endocrine disruptor, and during the 1950s and 1960s it was found that it interfered with sexual development and caused thinning of the egg shell in birds. It is also persistent, bioaccumulative and classified by WHO (IARC) as "possibly carcinogenic to humans".

**Restrictions:**
There has been a complete ban on DDT in Sweden since 1969. In 1986 it was prohibited in the EU, and in 2001 DDT was one of the twelve original substances placed on the Stockholm Convention list of persistent organic substances requiring far-reaching global measures. However, DDT is still used against malaria by many countries in the South.

**Dioxins**

**Function:**
Dioxins is a collective name for a group of chlorinated combustion products that can be formed when organic matter is burned together with material containing chlorine, for example PVC plastic. Dioxins do not have any uses, but are undesirable environmental pollutants

**Known environmental and health problems:**
Dioxins are soluble in fat and persistent and are therefore readily taken up by organisms and can be spread in the food webs of ecosystems. As they are soluble in fat, they are principally found in animal foods with a high fat content. Several of them can harm foetal development, disrupt the immune system and general metabolism, and lead to DNA damage (mutations), which can result in cancer. The most toxic dioxin is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). TCDD is one of the most potent toxicants known. It is classified by WHO (IARC*) as carcinogenic to humans, and only extremely low levels are considered safe.
Foetal development is particularly vulnerable to dioxin exposure, and the Swedish National Food Administration therefore advises pregnant women not to eat Baltic fish more than two or three times a year. Sweden has an exemption from EU rules which permits fish with dioxin levels in excess of the common limit values to be sold.

*IARC is an abbreviation for International Agency for Research on Cancer, which is WHO's cancer research body.

**Finasteride**

**Function:**
Finasteride is a medicine used to treat benign enlargement of the prostate (prostatic hyperplasia). It acts by blocking the conversion of testosterone to dihydrotestosterone (DHT). DHT is a hormone that stimulates growth of the prostate, there is therefore a desire to stop its production, which can be done with finasteride treatment. On the other hand, DHT is essential during foetal development so that boy foetuses develop naturally, and pregnant women must be very careful not to come into contact with finasteride.

**Known environmental and health properties:**
Finasteride is persistent and bioaccumulates in nature. It is also harmful to aquatic organisms. However, in the human body finasteride is broken down to less active substances before it is excreted.

**Phthalates**

Phthalates are a group of chemicals that are produced in large quantities and occur in a large number of everyday articles. Small phthalates of low molecular weight are found in cosmetics, while larger phthalates of higher molecular weight are used as plasticisers in plastics. It is principally the large phthalates that are associated with negative health effects. These include dibutylphthalate (DBP), die¬thylhexylphthalate (DEHP), benzylbutylphthalate (BBP), diisobutylphthalate (DIBP), diiso¬decylphthalate (DIDP), diisononylphthalate (DINP) och di-n-octylphthalate (DNOP).

**Known environmental and health properties:**
DBP, DEHP, BBP, DIBP, DIDP, DINP and DNOP are endocrine disruptors (to varying degrees) and can adversely affect foetal development and reproductive capacity. Certain phthalates also have environmentally hazardous properties. DBP and BBP, for example, are bioccumulative and very toxic to aquatic organisms.

**Restrictions:**
Four phthalates (DEHP, DBP, BBP and DIBP) are included in the candidate list

for REACH, which means that they have been identified as substances of very high concern. A special permit may in future be required to use these substances. The fact that they are included in the candidate list also means that the seller of an article containing more than 0.1% of any of these phthalates is obliged, on request, to inform his customers of this fact.

Special rules limit how phthalates may be used in toys. DEHP, DBP and BBP must not be present at levels above 0.1% in any toys or child-care articles, while DIDP, DINP and DNOP are prohibited above 0.1% in toys or child-care articles that can be put in the mouth. DEHP is one of the prioritised substances in the Water Framework Directive and is thus to be phased out. In the spring of 2011, Denmark proposed regulation of the phthalates DEHP, DBP, BBP and DIBP based on their combination effects.

**Metal compounds**

**Function:**
Metals have a plethora of different functions in society, but also occur as impurities, for example in motor fuels and commercial fertilisers.

*Aluminium* is principally used for metal alloys, but is also used in cosmetics and medicines.

*Arsenic* was previously used in large amounts as an impregnating agent in the wood industry. It may also be present in alloying metals and is used in glass manufacturing.

*Lead* is used for instance in storage batteries and electronic equipment, cables, paints, weights and ammunition and cut glass and for protection against radiation.

*Iron* is mainly used for the production of steel.

*Cadmium* has previously been used on a large scale in batteries, but its use there is steadily decreasing, in solar panels, as a stabillser in plastics and in pigments. Cadmium is a contaminant in commercial fertiliser.

**Known environmental and health properties:**
*Aluminium* can cross the blood-brain barrier and is suspected of being linked to the development of dementia and Alzheimer's disease, although the correlations have not been entirely clarified. Aluminium is toxic to fish by damaging the gills.

*Arsenic* causes disturbances to the metabolism and is classified as very toxic to aquatic organisms and can cause harmful long-term effects in the environment. Arsenic is readily taken up by organisms, is accumulative and can be spread through the food webs of ecosystems. Several arsenic compounds are additionally suspected of being carcinogenic.

*Lead* can cross blood-brain barrier and cross the placenta from mother to foetus. Nerve damage and damage to the cardiovascular system are the most serious health effects of lead. More and more lead compounds are suspected of also being carcinogenic. Lead is very toxic to aquatic organisms and can cause long-term harmful effects in the environment.

*Iron* is not normally freely present in the cells, but is bound to proteins and enzymes. Iron is often vital to enzyme function. Exposure to other metals may, however, release iron in the cells and cause the occurrence of free radicals that lead, among other things, to DNA damage, which can also increase the risk of cancer.

*Cadmium* amd several of its compounds are classified as carcinogenic, as well as very toxic to aquatic organisms, and can cause harmful long-term effects in the environment. As cadmium is readily taken up by organisms and accumulates in them, the metal is dispersed in food webs of ecosystems. Cadmium crosses the placenta from mother to foetus and damages the kidneys and skeleton.

**Restrictions:**
The use of certain aluminium compounds is limited in cosmetics by the Cosmetics Directive (Directive 1976/768/EC) and in toys by the Toys Directive (Directive 2009/48/EC).

The use of arsenic in the European Union is limited under Annex XVII of REACH, in antifouling paints and for preservation purposes. It is also limited in toys under the Toys Directive (Directive 2009/48/EC).

Lead carbonates and sulphates are prohibited for use in paints in the European Union under Annex XVII of REACH. Lead is additionally regulated in electrical and electronic products through the RoHS Directive (Directive 2002/95/EC), in batteries by the Batteries Directive (2006/66/EC), in cosmetics by the Cosmetics Directive (Directive 1976/768/EC), in toys by the Toys Directive (Directive 2009/48/EC), in motor fuels by the Petrol Directive (Directive 1998/70/EC), in the End-of-Life Vehicles Directive (Directive 2000/53/EC) and some directives concerned with food production and packaging.

Under Annex XVII of REACH, cadmium must not be used in the European Union for paints or types of plastic defined in Annex XVII. It is also limited in toys under the Toys Directive (Directive 2009/48/EC) and in electronic products through the RoHS Directive (Directive 2002/95/EC). The Cosmetics Directive (Directive 1976/768/EC) prohibits cadmium in cosmetic products.

**Methylmercury**

Methylmercury is a highly toxic mercury compound formed in the natural environment from metallic mercury. Methylmercury is a fat-soluble compound and accumulates in the food chain. The principal source of exposure for humans is consumption of fish.

**Known environmental and health properties:**
Methylmercury is transferred between mother and foetus. It also crosses the blood-brain barrier, the function of which is to prevent hazardous substances from reaching the brain tissue. Methlymercury, even at very low levels, disrupts the development of the nervous system in the foetus. In the

case of exposure to high doses the damage is extensive and is manifested in the form of a substantial decline in intellectual and motor capacity, while lower exposure results in more subtle adverse effects such as impaired speech development and memory capacity. WHO (IARC) classifies methylmercury as "possibly carcinogenic in humans".

**Restrictions:**
There has been a general ban on mercury in Sweden, which includes compounds containing mercury, since 2009. This ban is more extensive than the previous one from 1993, but does not encompass certain uses where EU-harmonised legislation prevails. For this reason mercury may, for example, be present in lighting. Despite decades of decreased use of mercury in Sweden, the levels in nature are increasing, which makes clear the need for common international rules and commitments. Emissions of mercury and its compounds have to have ceased completely in 2020 under the Water Framework Directive.

**Nonyl- and octylphenol**

Nonyl- and octylphenol belong to the group of alkylphenols and are formed as breakdown products of nonyl and octylphenol ethoxylate (surfactants used in cleaning products).

**Known environmental and health properties:**
Nonyl- and octylphenol are bioaccumulative and toxic to aquatic organisms (nonylphenol is classified as very toxic). They are also endocrine disruptors.

**Restrictions:**
There is legislation in the EU that very greatly restricts the use of nonylphenol and nonylphenol ethoxylate in industrial processes. However, there is no equivalent legislation for finished products, and imports of articles (for example textiles) containing these substances are therefore permitted. Both nonyl- and octylphenol are included among the prioritised substances of the Water Framework Directive. This means that they have been identified as highly problematic and are to be phased out. Nonylphenol is deemed to be so problematic that emissions to the aquatic environment are to have ceased completely by 2020.

**Parabens**

Parabens are a group of chemical substances that are used as preservatives, for instance in cosmetics and medicines. Some commonly occurring parabens are methylparaben, ethylparaben, propylparaben, benzylparaben and butylparaben.

**Known environmental and health properties:**
Butylparaben can cause allergy by skin contact and is bioaccumulative. Many parabens have also been found to have oestrogenic properties. The strongest oestrogenic effects are shown by butyl- and propylparaben, which have also been found to lower sperm production and testosterone level in male animals.

**Restrictions:**
No parabens have been permitted as preservatives in products such as laundry and dishwater detergents since 1 January 2011. However, parabens are not restricted from use in cosmetic products.

**Pentachlorophenol (PCP)**

**Function:**
PCP has been used as a herbicide and fungicide, to impregnate wood, as a general disinfectant, and as a component in antifouling paints.

**Known environmental and health properties:**
PCP is very toxic to aquatic organisms and can cause harmful long-term effects in the environment. It is persistent in certain environmental conditions and can therefore be found in organisms and sediments. Acute toxic effects of PCP exposure including damage to lungs, eyes, skin, blood and heart, kidneys, liver and immune system.

**Restrictions:**
Under Annex XVII of REACH, pentacholorophenol, and its salts and esters, as pure compounds (100%), are banned on the European Union market, but in a very limited amount may be included in chemical products that are mixtures of different compounds.

**Perfluorinated substances**

Perfluorinated substances have been used since the 1950s for their water- and grease-repellent properties. They can be found for example in surface-treated clothes, fire extinguishers and floor polish. It is common to perfluorinated substances that they break down extremely slowly in nature. As they are extremely persistent, it is important to restrict the use and spread of all perfluorinated substances, even those that have not yet been found to cause adverse health and environmental effects.

**Known environmental and health properties:**
As well as being persistent, some of the perfluorinated substances also have hazardous properties for the environment and health. Perfluorooctane sulphonate (PFOS), which is probably the best known of them, can harm foetal development and breastfeeding infants. PFOS accumulates in the liver and blood. It is also toxic to aquatic organisms. Knowledge of many of the other perfluorinated substances is still very limited.

**Restrictions:**
There has been a ban on PFOS in chemical products and articles in the EU since 2006. The ban includes substances that are broken down to PFOS, but many uses are exempt. In 2009 PFOS was placed on the Stockholm Convention list of persistent organic pollutants that require far-reaching global action PFOS is one of the eleven substances that have been assessed for possible inclusion as in the Water Framework Directive list of "prioritised substances".

**Polyaromatic hydrocarbons (PAHs)**

**Function:**
Polyaromatic hydrocarbons are a large group of combustion products from incomplete combustion of organic matter or can occur as constituents of petroleum products, i.e. the oil produced from mineral oil. PAHs do not, in themselves, have any uses and are undesirable environmental pollutants.

**Known environmental and health problems:**
PAHs are to varying degrees fat-soluble and persistent, and they can therefore be taken up by organisms and dispersed in the ecosystem's food webs, particularly among invertebrates that have particularly great difficulty in breaking down PAHs. They can cause harmful long-term effects in the environment. Many of the breakdown products from PAH cause DNA damage (mutations), which can result in cancer. PAHs are the group of organic compounds with the greatest number of known carcinogens.

**Restrictions:**
In the European Union levels of certain PAHs are regulated in extender oils for car tyres (see Annex XVII to the European chemicals regulation REACH).

**Polybrominated diphenylethers (PBDEs)**

**Function:**
Flame retardants in electronic products, furniture, vehicles, plastic articles and textiles.

**Known environmental and health problems:**
Polybrominated diphenylethers are a group of around 70 different compounds and belong to the group of brominated flame retardants. They are, in varying degrees, fat-soluble and persistent, and some of them are readily taken up by organisms and dispersed in the food webs of ecosystems, where they remain for a long time. There are great gaps in our knowledge of environmental and health effects for several of these compounds. The five PBDE variants (pentabromodiphenylether, octabromodiphenylether, decabromodiphenylether, tetetrabromobisphenol A and hexabromocyclododecane) that have been historically used in the largest volumes have been studied. Many PBDEs are very toxic to aquatic organisms and can cause harmful long-term effects in the environment, some harm the nervous system and octabromodiphenylester is classified as toxic to reproduction.

**Restrictions:**
Penta- and octadiphenylethers above a certain level are banned in chemical products and articles in the European Union (see Annex XVII of the European chemicals regulation REACH). PBDE is additionally prohibited for use in electrical and electronic products under the RoHS Directive (Directive 2002/95/EC).

**Polychlorinated biphenyls (PCBs)**

**Function:**
PCBs are used as electrical insulation fluids in transformers and capacitors, hydraulic oils and cutting oils, may be found in sealants, paints and carbonless paper, and are used as plasticisers and stabilisers in plastics and cement etc.

**Known environmental and health problems:**
PCBs are fat-soluble and persistent, and are therefore readily taken up by organisms and spread in the food webs of ecosystems, where they remain for a long time. PCBs damage the brain and harm its development, have hormone-like properties and can disrupt general metabolism and reproduction and give rise to certain types of cancer. Skin exposure can lead to rashes, known as chloracne, and ulcers.

**Restrictions:**
All new use of PCBs was prohibited in Sweden in 1978, and they have since been gradually phased out, most recently through Ordinance SFS 2007:19. Globally PCBs still pose an environmental problem. In the European Union, the production and use of PCBs is regulated by Regulation (EC) No 850/2004 of the European Parliament and of the Council and exports of them by Regulation (EC) No 689/2008.

**Vinclozolin and prochloraz**

Vinclozolin and prochloraz are fungicides.

**Known environmental and health properties:**
Vinclozolin can harm foetal development and result in impaired reproductive capacity. It is also bioaccumulative and toxic to aquatic organisms, and can cause allergies. In addition, vinclozolin is suspected of being carcinogenic. Prochloraz is persistent, bioaccumulative and highly toxic to aquatic organisms.

Vinclozolin and procholoaz are mentioned in the report principally because of their endocrine disrupting properties. As they disrupt the normal functioning of the body's androgens (male sex hormones), they can harm foetal development of boys.

**Restrictions:**
Vinclozolin is not permitted for use in the EU. Prochloraz is currently being evaluated, and pending a decision it may be used until the end of December 2011. Both vinclozolin and prochloraz are used in many countries outside the EU.

# 8. Glossary

**Androgens**
Sex hormones that control the sexual development in men and male animals. Testosterone and dihydrotestosterone (DHT) are the most important ones in humans.

**Antiandrogenic effects**
This term is used for effects where functions controlled by androgens are disrupted, for example by chemicals. Such disruption may arise as a result of the chemical reducing the production of the hormone (for example testosterone) or blocking its action.

**Bioaccumulative substances**
Substances with properties such that they are stored in tissues and increase in concentration as they are taken up more quickly than they are broken down or excreted.

**In vitro methods**
Tests conducted on cell cultures instead of using animal experiments.

**LOAEL/LOEC (Lowest Observed Adverse Effect Level/ Lowest Observed Effect Concentration)**
The lowest dose/concentration at which no toxic effect has been observed.

**NOAEL/NOEC (No Observed Adverse Effect Level/No Observed Effect Concentration)**
The highest dose/concentration at which no toxic effect has been observed.

**North and South**
North and South today is a generally accepted concept identifying a socio-economic and political demarcation that exists between developed countries (collectively known as the North or "Global North") and developing countries and countries in economic transition (collectively known as the South or "Global South"). It is more common to use these terms today than, for example, the Third World.

**OECD countries**
The OECD is a cooperative organisation, principally for industrialised countries, that mainly concerns itself with economic and development issues. Certain environmental issues are also on its agenda. Members include all the Member States of the EU, the United States, Japan and Canada. Countries such as Mexico, Turkey and Chile have become members in recent years.

**Persistent substances**
Substances that are long-lived or difficult to break down.

**Pesticides**
This is a collective name for plant protection products and biocides. Plant protection products are used to protect plants in agriculture and forestry against attack, while biocides is the name for those pesticides that are used in other contexts, for example antifouling paints and rodenticides.

**Risk assessment**
In order to assess the risks associated with chemical substances, risk assessments are made in which the predicted exposure to a substance is compared with the level at which harmful effects arise. Account is taken both of the inherent properties of the substance (hazardousness), for example whether it causes reproductive effects or allergies, and of what the exposure situation is like, and the risk is described.

**Toxicology**
The science of the properties and actions of poisons.

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## Endocrine Disrupting Chemicals under REACH: Four Priority Areas for Regulation

Endocrine disrupting chemicals (EDCs) have been linked with several health problems including the deterioration of male reproductive health, the increased incidence of hormone related cancers and the increase in cardiovascular disease, obesity and diabetes. Despite this growing weight of evidence, the EU has been very slow in regulating EDCs. We therefore call upon the European Commission, Member States and relevant European institutions to:

### ACT NOW: Expedite the use of REACH to reduce exposure to EDCs

Chemicals with ED properties should be subject to restrictions or authorisation and phased out without delay. Priority should be assigned based on their hazardous properties and the likelihood of coming into contact with the public, particularly with vulnerable populations such as infants, children, women of childbearing age and pregnant women, or the environment. SIN List 2.0 is a good starting point for identifying priority chemicals for stricter control under REACH, as it shows that the Commission and Member States can act now despite the fact that an EU wide approach for identifying EDCs is not in place yet.

### PLAY IT SAFE: Replace EDCs with safer alternatives whenever they exist

The Commission shall review by June 2013 the conditions for granting authorisations to chemicals with ED properties under REACH. Given the possibility of mixture effects, the goal should be the elimination of exposure to chemicals with ED properties. This review should ensure that:

- ED properties are recognised under a distinct and additional criterion in Article 57 for naming a chemical as a SVHC and separated from the Equivalent Concern criterion (57f).
- An authorisation can only be granted for a limited period if no safer alternatives are available and the use is absolutely essential to society.
- CMR chemicals with ED properties be proposed on the basis of both 57c and f.

### PROVIDE TRANSPARENCY for citizens: Disclose information on EDCs

Sufficient information to allow chemical users and consumers to make informed choices must be publicly available on ECHA's website. Member States should make information available about EDCs present in consumer and industrial goods and how citizens and workers can protect themselves from them.

### GET THE CRITERIA RIGHT: Develop comprehensive criteria for identifying chemicals with ED properties to be used across all relevant EU legislation

- Public interest stakeholders must be involved in the development of the criteria currently being elaborated in the EU, which will have implications for several policies.
- The absence of precise scientific knowledge of how a substance with endocrine properties exerts its effects (mechanisms of action) should not hinder or retard the regulation of such a chemical.
- Independent peer reviewed studies (including non-GLP ones) should be considered when assessing whether a chemical has ED properties and its likely effects to humans and the environment.
- Apply the precautionary principle in the identification of ED chemicals.

**We therefore call upon the European Commission, Member States and the relevant European institutions to achieve the above by 2013.**

Chemicals in the environment are attracting increasing attention. The legislation has recently been tightened, and more knowledge is gradually being developed. Despite this, chemicals continue to have an impact on our environment and health. What were previously assumed to be safe levels of chemicals are proving to be capable of harming sensitive processes that are controlled by hormones. These may be vital functions such as the ability to have children and development of the nervous system.

The chemicals that can be found in the environment are often at low levels and in an unknown mixture from the diffuse sources that disperse them. This report addresses what is known about how chemicals affect reproduction and development of other important functions in the body. It also describes simple methods that can be used to estimate the properties of chemicals in a mixture and what gaps there in present-day legislation.

Unfortunately there is great cause for concern. The combination effects observed in animal experiments, for example a shift in the development of puberty and defects of the genital organs, are the same type of disruptions that have increased greatly in the population in recent years. It is particularly alarming that endocrine disruptors can reinforce each others' effects, particularly when they occur in large numbers and with a wide geographical spread. Urgent action is therefore required to Save the Men, which obviously means also protecting children and foetuses, and consequently also women.

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The Swedish Society for Nature Conservation is an environmental organisation with power to bring about change. We spread knowledge, map environmental threats, create solutions, and influence politicians and public authorities, at both national and international levels. Moreover, we are behind one of the world's most challenging ecolabellings,

"Bra Miljöval"(Good Environmental Choice). Climate, the oceans, forests, environmental toxins, and agriculture are our main areas of involvement.

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