



REPORT

FR

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Conservation

Biodiversity

Sustainability

**Endocrine disruptors and biodiversity**  
biological diversity faced with chemical risks :  
the need for a paradigm shift



WWF is one of the world's largest and most experienced independent conservation organizations, with over 5 million supporters and a global network active in more than 100 countries.

WWF's mission is to stop the degradation of the planet's natural environment and to build a future in which humans live in harmony with nature, by conserving the world's biological diversity, ensuring that the use of renewable natural resources is sustainable, and promoting the reduction of pollution and wasteful consumption.

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Minimal number of man-made chemicals found in the blood of 13 families from 12 European countries during WWF's 2005 Detox campaign.



63

Highest number of chemicals, found in the grandmother's generation. However, the younger generation had more chemicals in their blood (59) than their mothers (49), and some chemicals were found at their highest levels in the children.



## SEX RATIO

Recent studies show modifications of the sex-ratio in areas where EDs are concentrated : from 1 boy to 1 girl in 1984, the ratio was of 1 boy to 2 girls in 1999.

Daughter of a Belgian family showing her blood sample in a test tube. As part of its DetoX campaign, WWF conducted in 2005 the first European-wide family bloodtesting survey. For this survey, the blood samples were analyzed for man-made hazardous chemicals in the blood of 13 families (grandmothers, mothers and children) from 12 European countries.

# CONTEXT & GENERAL DETAILS OF ENDOCRINE DISRUPTORS

## Definitions and general context

### What is an endocrine disruptor?

In humans as in the entire living world, the endocrine system is central with highly sensitive mechanisms. The endocrine system (from the Greek : endon “ inside ” and crinis “ secrete ”) is a system of glands and cell groups. Together with the nervous system, it is responsible for maintaining the internal stability of pluricellular animals, managing various cycles and triggering appropriate responses to external stimulations. Many vital functions such as reproduction, growth, development, behaviour and the production, use and storage of energy are entirely dependent on it. The endocrine system is regulated by highly active substances - hormones.

Hormones are characterized by their specificity of action on certain tissues and organs. Hormones act at very low blood concentrations. They degrade, generally in a few hours. Generally speaking, there is no hormonal specificity between the species (with a few exceptions such as the human growth hormone) : human hormones can also affect the endocrine system of other species more or less closely related.

The feminization of communities, flagrant decline in populations and anatomical defects in animals have all been detected over the last decades in parallel with a decrease in male fertility in humans. As early as 1950, an article by Burlington and Lindeman described the harmful effects of DDT on living organisms ; this was followed by numerous publications in subsequent years.

The endocrine system's vulnerability is therefore in question and it is essential we gain a better understanding of the phenomena described. Numerous research projects have therefore been conducted over the last two decades to study this phenomenon of disruption to the endocrine system both in terms of toxicology and ecotoxicology.

### Definitions

The term “ endocrine disruptor ” (ED) refers to a wide spectrum of xenobiotic substances (i.e. foreign to the living organism) which have the capacity to act on the endocrine system of animal and plant species, disrupting its normal function.

The definition of EDs given by the European Union in 1999 is as follows : “ exogenous substances that alter function(s) of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub)-populations ”. Different definitions have been issued by other bodies. The US EPA (Environmental Protection Agency) defines endocrine disruptors more precisely, describing them as “ exogenous agents that interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body which are responsible for the maintenance of homeostasis, reproduction, development and/or behaviour ”. This definition is open for discussion as it only includes exogenous agents, with no mention of internal secretions, linked to metabolization, or to maternal transmission, for example. Aside from the numerous discussions these questions raise, it is clear that as knowledge improves, the semantic scope must adapt to the scientific

# 870

## POTENTIAL ENDOCRINE DISRUPTORS TO DATE ON THE TEDX LIST

reality, particularly in relation to sources of contamination and notions of threshold and low doses.

Given the enormous diversity of molecules and molecular receptors involved in the endocrine system of living species, the definition of ED encompasses a very high number of substances of varying sources and natures. This is why a general classification of EDs is not easy. Thus to this day there are none which can be considered exhaustive. Failing a strict classification, the different types of EDs can be categorized, based partly on their nature and partly on their action mechanisms and targets.

### ED categorization

#### According to nature

The first distinction to be made between the different EDs is based on their origin. Three categories can be distinguished :

- Natural compounds : phytoestrogens, produced by plants, and mycoestrogens, produced by mushrooms and mould ;
- Natural (animal, human and plant) or synthetic hormones ;
- Synthetic compounds.

Phytoestrogens and mycoestrogens have chemical structures that imitate or interact with estrogenic hormones. Over 300 plants from 16 different families producing phytoestrogenic substances have been identified. Furthermore, some mycoestrogens are produced by mushrooms which can contaminate cultures. This is notably the case of zeralenone, a mycoestrogen which can be found in maize used in pig farming and which can have toxic effects at a low dose.

Natural animal or human, or synthetic hormones (e.g. contraceptive pill, therapeutic treatment of endocrine regulation, anabolics) are generally excreted by urine and released in wastewater. These are likely to maintain a certain degree of activity in natural ecosystems and/or be transferred to food chains. Thus the residues of synthetic hormones used in intensive farming may also be found in food such as beef.

Synthetic compounds are products used in the chemical industry and their sub-products, engendered by industrial processes, natural processes or incineration, for example. These compounds include chemical products for industrial use such as phthalates, polychlorobiphenyls (PCB), perfluoros, bisphenol A, etc. Chemical compounds for agricultural or domestic uses, such as pesticides (fungicides, insecticides, larvicides and herbicides) are also to be included in this category. Finally, we mainly find products released by waste incineration such as dioxins and dibenzofurans in the secondary products.

These three types of substance present different problems. The intensity of the effects will vary, as will the management methods aiming to reduce their emissions. Given their relatively recent detection, proportional to the lack of knowledge, attention and concern are focused on synthetic compounds. Furthermore, by their very nature, endocrine disruptors differ in their modes of action and targets. This classification is important to consider if we wish to focus on the disruption of a particular organ or function, or the complex question of “ cocktail effects ” (see page 24).

#### According to mode of action and targets

EDs interfere in the function of hormonal regulation according to the following three modes of action :

- A mimetic effect, imitating the action of a natural hormone and binding with this hormone's target receptor ; it attaches itself to the cellular receptor and engenders a normal response, known as agonist.
- A blocking effect, blocking the action of a natural hormone (for example by saturating



# FINDING ALTERNATIVES

According to the Stockholm Convention on Persistent Organic Pollutants, 9 of the 12 most dangerous and persistent organic chemicals are pesticides. The World Health Organization and the UN Environment Programme estimate that each year, 3 million workers in agriculture in the developing world experience severe poisoning from pesticides, about 18 000 of whom die. According to one study, as many as 25 million workers in developing countries may suffer mild pesticide poisoning yearly.

Some evidence shows that alternatives to pesticides can be equally effective as the use of chemicals. For example, Sweden has halved its use of pesticides with hardly any reduction in crops.

In Indonesia, farmers have reduced pesticide use on rice fields by 65% and experienced a 15% crop increase.



the hormone's target receptor) ; this is an antagonist response.

- A disruptive effect, interfering with the physiological processes of production, transport and degradation of a natural hormone.

The description of an ED's mode of action can be further refined by specifying the hormonal function disrupted by the substance's action. A distinction is therefore made between compounds with estrogenic or anti-estrogenic (disrupting the regulation of female characteristics), androgenic or anti-androgenic (disrupting the regulation of male characteristics), or even thyroid effects (disrupting thyroid gland function).

## A significant environmental challenge

The difficulties in classifying EDs highlight the diversity and complexity of this phenomenon. Although the intensity of these disruptions is currently difficult to measure, the targeted ecosystems are likely to suffer effects and the transversality of their consequences cannot be estimated. This emerging problem of endocrine disruption brings into question the very bases of certain principles of ecotoxicology, such as the notions of threshold, low doses, window of exposure or even impact on an entire trophic chain (*see page 17*).

It is important to assess the scale of the impacts likely to affect ecosystems by taking into account new paradigms and the irreversibility of certain phenomena, to be able to consider appropriately the urgency of analysis, evaluation and then management of this “ new risk family ”.

In addition to the multi-exposure phenomena already mentioned, other processes generally linked to the biosphere come into play. By way of illustration, bioamplification throughout a trophic chain can be cited. Certain pesticides, for example, accumulate throughout the food chain to concentrate in the last links. Carnivores and piscivores located at the top of the chain concentrate pesticide doses which can reach 10 000 times those of the first links.

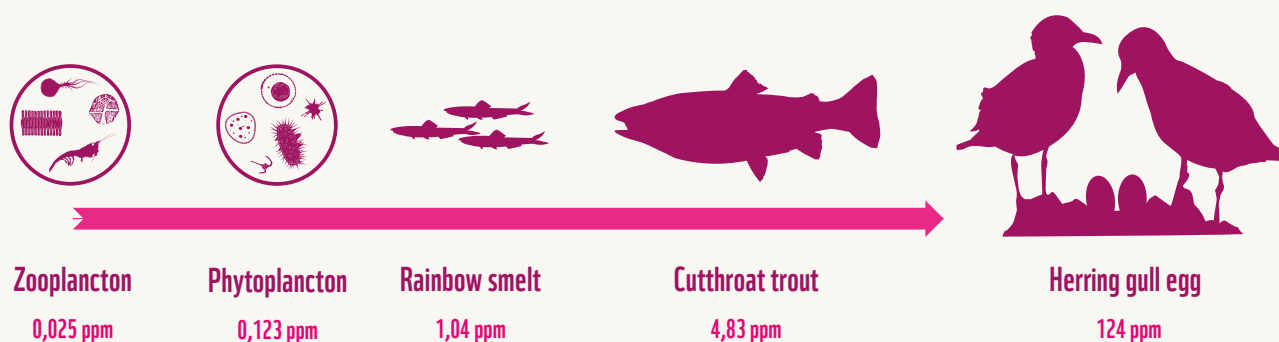


Figure 1 : Explanatory diagram of the bioamplification of a substance (*source: US EPA*)

This example illustrates the globalness of the environmental and health problem posed by endocrine disruptors. When placing man at the top of the food chain, it also illustrates the interaction between the environmental impact and the health impact. Someone who eats fish would be a typical example. This demonstrates all the more the need for strong transversal action.



## A few regulations

With regard to the solutions to be applied, it is reasonable to consider that the regulatory tool is currently insufficient to meet these challenges.

From the health point of view, the European Union has established a classification of chemical substances toxic to reproduction (directive 67/548/EEC modified in relation to the classification, labelling and packaging of dangerous substances). It has three categories, based on the level of knowledge of the substance in question's effects on health. Carcinogenic, mutagenic and reprotoxic (CMR) effects, for example, are covered by the REACH regulations. In France, a decree specific to the professional sphere has been introduced to oblige the implementation of preventive measures. However, other effects relating to endocrine disruption are not covered.

From the environmental point of view, the conclusions are more uncertain, as a classification of endocrine disruptors does not exist per se. However, there are regulations limiting environmental contamination, such as the Framework Directive on Water, for example, which limits the release of certain products toxic to the environment, which in some cases concern endocrine disruptors (such as PCBs, phthalates, etc.).

*Man-made chemicals can be bad for health and the environment. Hazard signs are not enough to protect us from harmful chemicals.*



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It is essential to establish a classification of endocrine disruptors to enable appropriate combined management of human health and environmental health. Regulations must be able to integrate improved knowledge of sources of contamination, effects on ecosystems and biodiversity, and of the notion of low doses and exposure period. The parts below provide an overview of the state of knowledge based on scientific literature and underline the essential elements needed to understand and get the measure of these phenomena.

# ENDOCRINE DISRUPTORS IN THE ENVIRONMENT

## Main sources of contamination

Numerous chemical products are now known or suspected to have endocrine disruption effects. However, the diversity of these products implies a wide variety of sources of contamination to the environment. Thus, if considering an industrial release of PCB into the Rhône or water loaded with estrogens via releases from wastewater treatment plants, for example, their impacts will be different.

To characterize the different modes of environmental contamination, several approaches are possible :

- It is possible to formulate an approach by substrates : water, soil and air. However, after analyzing the literature, it appears that the most contaminated environments are aquatic, so this distribution is inconsistent.
- Reasoning in terms of types of release and whether or not they are industrial may also be considered. However, few studies have addressed the issue of sources with this dichotomy, and justifiably, numerous uncertainties remain to be dispelled with regards to non-industrial releases. Whether accidental or diffuse, industrial releases of chemical products are theoretically quantifiable. Even if this question of industrial or agricultural releases still remains the priority in terms of risk management, interest must not be lost in other types of release. These releases, via purification networks or waste storage centres for example, are currently very poorly quantifiable and therefore extremely little known.
- An approach which addresses both the uncertainties and the reality of the scientific literature on this subject is the approach by family of endocrine disruptors. A few articles regarding this report on knowledge of the sources of contamination by product family. It is this option which has been selected to define the sources of contamination.

### Industrial chemical products

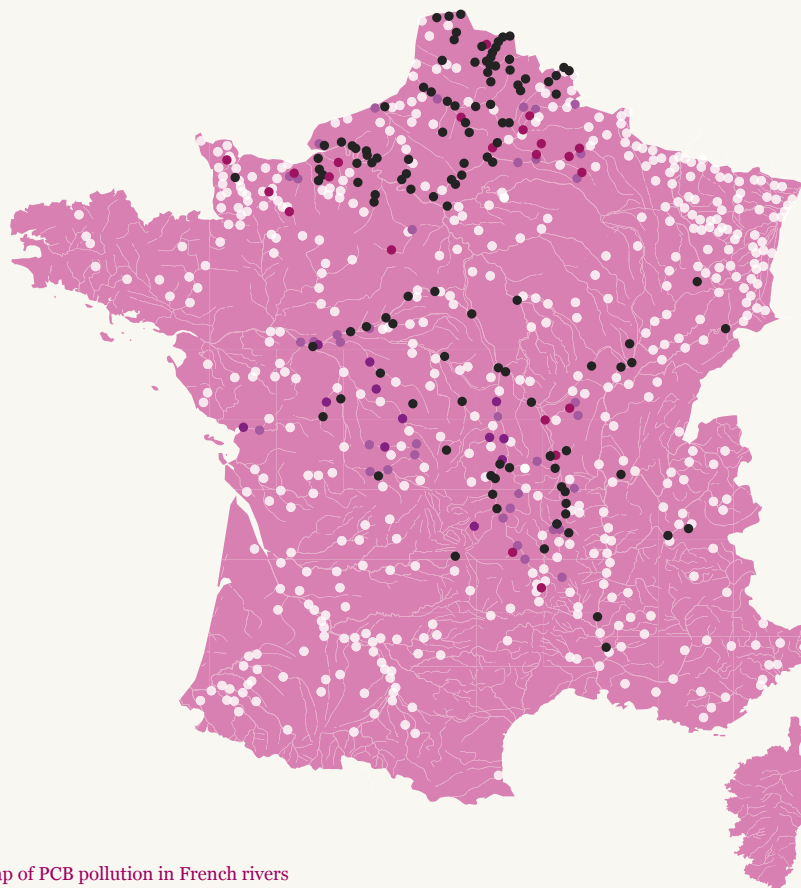
Chemical pollution of the environment related to industrial waste is today a sad reality. Whether accidental or permanent, these releases affect living organisms more or less directly, be it through lethal toxicity mechanisms or through endocrine disruption. It is not possible to put all of these products in one box as their effects are as varied as their sources. It is thus proposed here to review the main families of these products for which the effects in terms of endocrine disruption are known :

- **PCBs (Polychlorobiphenyls)** : This very large family of compounds (209 congeners), manufactured for almost a century as thermal insulators, represents a benchmark in the field of industrial pollution. Their strong persistence, mobility and capacity to become fixed in sediment make them long-lasting and ubiquitous pollutants. Although their production was stopped in France in 1987, emissions continue from old equipment and batteries. Today, practically every study conducted to search for the presence of this type of compound has found it. However, the strongest concentrations are logically found in aquatic environments polluted upstream by this type of industry, particularly where accidental leakages have occurred. The Rhône can be cited as a perfect example. However, transport through the atmosphere and by bioaccumulation phenomena are significant and important to note, leading as they do to widespread pollution.



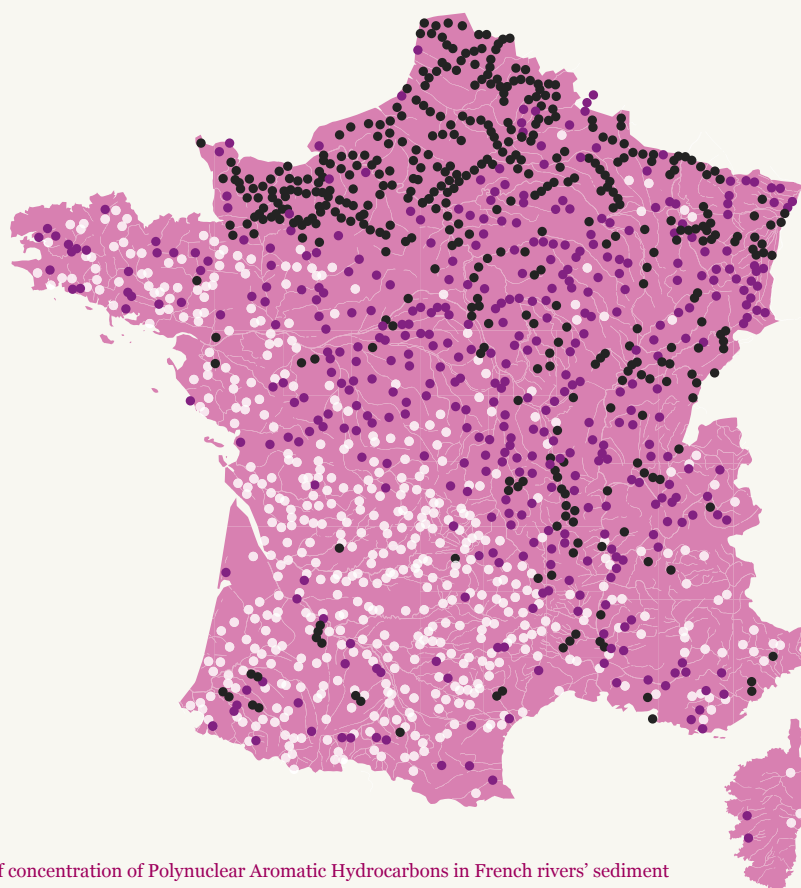
*Leak under an electric transformer containing PCB's, banned world-wide since 2011.*

© THIERRY MEUNIER



Map of PCB pollution in French rivers

*The dots show the concentration of PCB in samples from the sediment of French rivers, a darker color meaning a higher concentration, black being superior to 10 µg/kg. The raw data dates back to 2007 and is useable on the interactive maps of the French website [eau-evolution.fr](http://eau-evolution.fr).*



Map of concentration of Polynuclear Aromatic Hydrocarbons in French rivers' sediment

*The dots show the concentration of Polynuclear Aromatic Hydrocarbons (PAHs) in samples from French rivers' sediment. PAHs are on the priority lists of the EPA US, as well as the World Health Organization and the European Union, due to their toxicity and their presence in all areas. A darker color means a higher concentration here as well, black being superior to 2,000 µg/kg. The raw data dates back to 2007 and is useable on interactive maps on the French website [eau-evolution.fr](http://eau-evolution.fr).*



• **Alkylphenol ethoxylates (APE)** : These compounds, whose annual production worldwide approaches 390,000 tonnes, are used in some industrial and agricultural processes but their main use is domestic in certain household products. However, one of the uses that must be underlined in this report is that as a contraceptive via spermicide applications. It is important to add that these compounds have the capacity to be biologically degraded in wastewater, to form highly toxic metabolites (p-nonylphenol, etc.) with remarkable estrogenic activity. Aside from the use of these compounds in detergents and their release in wastewater, industrial releases into aquatic environments are not insignificant, and regulations vary by country. In Europe, varied sources of contamination are observed. Thus this family of endocrine disruptors differs from the others, on the one hand due to its strong presence in domestic daily uses, which reinforces releases into the environment, particularly through waste water, and on the other hand through its non-negligible presence in the air compartment due to aerosols, among others. Both of these aspects can explain the globalization of environmental contamination.

• **PAHs (Polycyclic Aromatic Hydrocarbons)** : These compounds are generated by incomplete combustion of organic matter (coal, oil, petrol, wood, etc.). The main sources are anthropic, via automobile traffic, heating, cooking and certain industrial processes such as the production of aluminium. However, “natural” sources such as forest fires and volcanoes are not entirely negligible. In the environment, these compounds can be degraded biotically (through the action of biotransformation enzyme systems, for example) or abiotically, and also generate new compounds (epoxides, phenols, etc.). Their omnipresence in the environment and physico-chemical properties make the PAH family a worthy representative of Persistent Organic Pollutants (POPs), as are PCBs. Note that some of them, such as benzo[a]pyrene, are proven carcinogens. PAHs are mostly transported through the atmosphere in the form of particles which are deposited in other environmental compartments. These compounds are therefore found in the environment at very different concentration levels, depending on whether located near to industrial and urban zones or more remote areas.



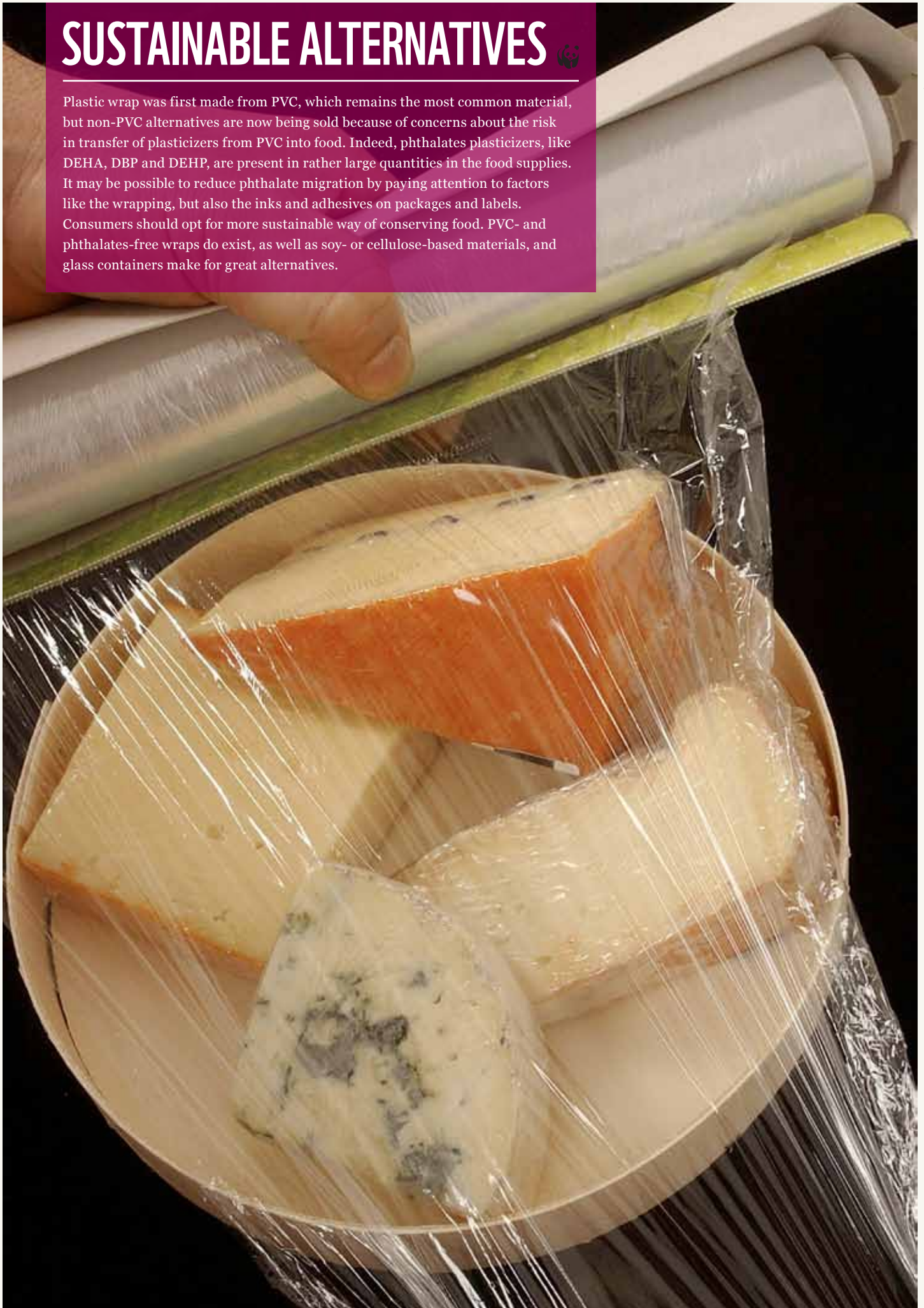
• **Bisphenol A (BPA)** : This compound, which has received wide media coverage in recent years for its ability to disrupt the endocrine system, is one of the most used chemical compounds in the world. However, the first studies to question it date from the 1930s (*Dodds et al., 1936*). It is very widely used today, mainly in certain plastic compounds (hard and translucent plastic), which can be found in food containers and some baby bottles. But if we wanted to be exhaustive, the list is very long (dental prostheses, flame retardants in electrical devices, etc.). In terms of environmental impacts, the main environment concerned is again the aquatic environment, which enables this compound to be transported into all other compartments. Due to its physico-chemical properties, bisphenol is a very persistent compound and in the environment its metabolisation is mainly biotic, notably producing compounds which are then mineralised. Emissions of this compound are today widespread and ubiquitous, with accidental or localised releases being proportionally low. In effect, the quantities released in wastewater by man, or via waste are far from negligible. In some studies, its presence has been revealed in the majority of samples taken, whether from wastewater, water intended for human consumption, untreated surface and subterranean water or even sediment. This can be explained by the large number of products (polycarbonate, epoxy resin, PVC, etc.) that contain it and its consequent worldwide production.

• **Other compounds** : Further product families can be added to the main compounds described above. To this end, we can cite PBDEs (polybromodiphenylethers), fire resistant products used primarily as flame retardants in a large number of commodities from our daily lives (screens, furniture, etc.), and which can be released into the environment either by air emissions or through soil and water via waste. We can



# SUSTAINABLE ALTERNATIVES

Plastic wrap was first made from PVC, which remains the most common material, but non-PVC alternatives are now being sold because of concerns about the risk in transfer of plasticizers from PVC into food. Indeed, phthalates plasticizers, like DEHA, DBP and DEHP, are present in rather large quantities in the food supplies. It may be possible to reduce phthalate migration by paying attention to factors like the wrapping, but also the inks and adhesives on packages and labels. Consumers should opt for more sustainable way of conserving food. PVC- and phthalates-free wraps do exist, as well as soy- or cellulose-based materials, and glass containers make for great alternatives.



also cite certain compounds such as TBT (tributyltin), used in particular in some ship hull paints, which has had significant effects on mollusc populations. TBT is directly released into water and concentrates in sediment. With a concern for exhaustiveness, the list could again be long, but to complete this overview of endocrine disruptor chemical products, we can cite dioxins, one of the most toxic of which, 2,3,7,8-TCDD (2,3,7,8-tetrachlorodibenzodioxin), is used to calculate toxic equivalents. Numerous studies report their presence in sensitive environments (*Fielder et al., 1995*). These compounds, released by incomplete combustion of other substances, especially in old generation incinerators, are currently exhibiting a reduction in their atmospheric release, particularly since the application of environmental standards. However, their presence in soil and aquatic environments is commonplace. Finally, polyfluorinated or perfluorinated compounds such as perfluorooctanoic acid (PFOA), found in non-stick coatings as well as in a wide variety of products due to their waterproofing or anti-stain action, are some of the emerging endocrine disruptor pollutants. With some of them having half-lives of several decades, they are persistent in the environment and are bioaccumulated and bioamplified in trophic networks. Likely to cause developmental and metabolic disorders, they are reprotoxic, carcinogenic and act on thyroid regulation.

#### Steroid hormones

Steroid hormones are a group of biologically active compounds. These compounds are naturally secreted by various organs (cortex, ovaries, placenta, etc.) both in humans and animals and include, among others, progestogens, glucocorticoids, mineralocorticoids, androgens and estrogens (Raven and Johnson, 1999). Estrogens (estradiol, estrone and estriol) are mainly female hormones essential to the regulation of the hormonal and reproductive system. In humans and animals, these compounds are excreted via natural processes and reach environmental compartments through purification networks, waste disposal systems or even through land treatment of waste. Numerous studies report the presence of such compounds at wastewater treatment plant outlets and in surface water (rivers, lakes, etc.) (*Desbrow et al., 1998; Fromme et al., 2002; Ternes et al., 1999*). The compounds that cause the most concern due to their potential for endocrine disruption are estrogens and other contraceptives, including 17 $\beta$ -estradiol (E2), estrone (E1), estriol (E3), 17 $\alpha$ -ethynylestradiol (EE2) and mestranol (MeEE2).

The main sources of contamination of the different compartments are:

- **Wastewater :** The presence of these compounds in the environment is worrying because of the consequences they can have on man, farm animals or fauna in general, due to their strong potential for biological modification which characterizes them by nature. Some of these molecules are naturally excreted and a few studies report indicative values. However, in view of current contraceptive methods, and given existing measures in purification equipment, there is a high probability of finding this type of substance in a large number of water courses. Although significant efforts need to be made in terms of making water clean and potable, greater public awareness of this impact is needed above all.

- **Animal releases :** The other large source of environmental contamination by these compounds is that relating to farm animals. For a number of years, there has been a more or less rational use of veterinary medicines, in particular to control the reproductive cycle of females, causing numerous disorders including abortion (*Refsdal, 2000*). This type of use leads to an increase in the production of these hormones and a multiplication of releases, via land treatment of waste, into the environmental compartments (*Baronti et al., 2000*).



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Over the last years, a few studies have focused on measuring concentrations of these hormones in water. They have reached the same conclusion irrespective of the country, which is that over half of the samples exhibit values above the detection threshold, with wide seasonal variation (*Tabata et al., 2001*), the environments concerned being surface waters and subterranean waters in equal measure. However, these values rarely exceed 5ng/L. Although there is great uncertainty regarding the effects of these compounds, it is worrying that traces of these substances are found quasi-systematically.

### Pesticides

71 600 TONS



France's use of pesticides in 2006, ranked 1<sup>st</sup> in Europe and 4<sup>th</sup> worldwide

Pesticides constitute a large family of chemicals containing a multitude of highly active components. Pesticide use can result in these chemicals being directly discharged into the environment, or indirectly discharged outside the area where they were applied through soil leaching. They can also be ingested by humans through food ; herbivores also accumulate pesticides in their meat, which is then eaten by humans.

Their presence in the environment is disturbing, as is their longevity and mobility, which explains why they are found in the Arctic and Antarctic. As these products have been in use for many years, they have been thoroughly studied from a toxicological and ecotoxicological standpoint, and evidence points to their having great endocrine disruptor potential.

However, considering the fact that this family of chemicals is very large, there are certain pesticides that are not considered to be endocrine disruptors, in particular organochlorine pesticides.

- **DDT and its metabolites** : this compound was first produced over 60 years ago and was used intensively as an insecticide, in particular on mosquitoes and other insects carrying diseases such as typhus and malaria. Despite the fact that it was banned in the 1970s in developed countries, this compound can still be found in substantial quantities in the environment. Some researchers estimate that more than 2 million metric tons of this product have been discharged into the environment. Its presence can be explained in large part by the fact that this compound does not biodegrade easily. Moreover, its metabolites, a result of changes in the environment, add an extra burden that can be even more toxic and persistent than the original compound. Its main metabolite is DDE, known for its ability to damage the endocrine system of certain mammals.

- **Methoxychlor and its metabolites** : this cousin of DDT, having the same insecticide properties, was put on the market just after the Second World War. After DDT was banned, it had wide commercial success, positioning itself as the ideal replacement. This compound is less active and lasts for a shorter time than DDT, but its metabolites are much more worrisome, and traces can still be found in both carnivorous marine species and birds (*Tullner et al., 1961*). Other organochlorides were widely used for “ phytosanitary treatments ”. Most, like dieldrine and aldrine, were banned in the 1980s, others were taken off the market more recently, such as lindane, which was banned in 1998. However, they are still a concern due to their longevity and the persistence of residues in the environment. A recent report on the health impacts of chlordecone (banned in 1993) in the French Antilles underscores just how current those concerns are.

- **Urea substitutes like inuron, diuron and their metabolites** : these herbicides were widely used up until 2008 on vineyards, produce, and cereal crops. Diuron was also used for non-agricultural uses such as playing fields and freeway



and train track maintenance. This type of use is considerably more troubling in terms of impact area, as it diffuses the product over long distances. Annual production of these products is estimated to be around 45,000 metric tons per year. Recent studies have also illustrated the capacity of these two products to form metabolites and intermediary products when linked with other chemicals such as medicines.

- To this list of pesticides that are known to be endocrine disruptors, we can unfortunately add many others, as well as their metabolites. Vinclozolin, atrazine, trifluralin, and endosulfan would come under this heading. Each of these pesticides has unpredictable characteristics, and each has been searched for and found in ecosystems.

#### Pharmaceuticals products

Pharmaceuticals place on the list of products that have the capacity to disrupt the endocrine system. Many research teams have shown the presence of active ingredients in sufficient concentrations in the environment to provoke adverse effects in marine organisms (Guehlstorf et al., 2004). They originate from hospital or urban waste. Part of this waste comes from excretions by humans or animals (livestock or pets) containing medical drugs. These compounds and their metabolites are subject to being diffused into aquatic environments. These drugs have been detected in soil, sediments, the sludge in sewage treatment plants, surface and underground water, as well as in the tissue of aquatic organisms that make up the food chain (Halling-Sorensen et al., 1998; Heberer, 2002; Porter & Janz, 2004; Enick et al., 2007). Some of these products are even directly discharged by fish farming).

Even if it is reasonable to assume that pharmaceutical products are less present than the compounds cited above, these types of compounds are relatively atypical and deserve special attention for the following four reasons:

- The use of medicines has become widespread and some environmental measurements have shown concentrations equivalent to those of some pesticides (Jones et al., 2002).
- Some of these medicines, by their inherent composition, are subject to having substantial effects on biological functions. Included in this group would be hormonal treatments and antibiotics, as well as cytotoxics (anticancer treatments).
- Regarding human medications, despite ample evidence that they can have harmful effects, both short and long term, on living organisms, their environmental impacts are not taken into consideration when they are authorized for sale on the market (Enick et al., 2007)
- Current installations in sewage treatment plants are not capable of filtering out these drugs, and these products are thus discharged into the environment.

*In the early 1990s Indian farmers treated their cows and oxen with diclofenac, a popular anti-inflammatory. When they died, they were traditionally sent to special dumps where flocks of vulture picked them clean. But diclofenac devastated the vultures, and the population declined by 40% a year between 2000 and 2007, killing 95% of Indian gyps vultures and 90% of Pakistan's.*



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## How endocrine disruptors function in the environment, today and in the future



Urban and industrial runoff is one of the leading sources of water pollution in streams, lakes, rivers, and reservoirs.

To understand the impact of the above-described substances, several aspects must be taken into consideration, aside from the large quantities that are produced, their geographic diversity, and the diversity of daily uses. What is important to underline here is the large number of ways that these substances can be transmitted into different environmental compartments, depending on the type of compound examined. That said, the milieu that is the most contaminated, according to existing sources, is clearly the aquatic environment. Other milieus can be considered as conduits for pollution towards water : soil via drainage or runoff, air via deposits. As described above, all chemical pollutants do not move through the environment in the same manner, and their presence in different milieus (air, water, or sediments) influences the way they spread. Therefore, not only are there geographic factors at work, but also the way each substance diffuses in the air, its duration, its solubility during the degradation process (biotic or abiotic), and its capacity to be bioamplified. Other factors, mostly local, also influence environmental behavior. For example, pluviometry, which draws runoff into aquatic environments, or the location of the contamination vis-à-vis the hydrologic basin. The presence of rivers and streams, the composition of sediments, or whether or not the local flora stimulates bioaccumulation also play a role. These contaminants' degradation process is above all microbiological. However, abiotic processes such as photolysis, hydrolysis, or oxidation can lead to the formation of metabolites.

Another important point that needs to be raised is universality. The presence of certain pollutants such as PCBs in Antarctica or above the Arctic Circle illustrates the pervasiveness of the contamination, as well as its ability to endure and to move from one place to another. Some studies show a relationship between these “ long-distance ” transports and the transoceanic transport of DDT (*Hill et al., 1995*) or the transit of PAHs or PCBs from the Mediterranean to the North Sea.

At this point, it is necessary to better understand the amplitude of this phenomenon and its contamination of the environment by analyzing the many compounds as well as elements such as means of transit in the environment. It is important to underscore the global aspect of this phenomenon, as well as the uncertainty that surrounds some types of contamination. The following section addresses effects on the living world, highlighting the great diversity of impacts and other causes for uncertainty.

A new breed of pesticide called neonicotinoids and widely used in the early 2000s, is believed to be responsible for the collapse of honeybee population. In Germany, France, Italy and Slovenia, beekeepers' concerns about neonicotinoids have resulted in bans on the chemicals.



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# THE EFFECTS OF ENDOCRINE DISRUPTORS ON LIVING BEINGS

## How much we know and where to go from here ?

The problems raised by endocrine disruptors and their effects on biodiversity are not new. As we mentioned above, they were first brought to light in Rachel Carson's *Silent Spring*, in 1962. Even if the term "endocrine disruptor" was not used at the time, the book raised the controversy concerning DDT, which is now classed as an ED. Subsequently, similar examples made a strong

impact on public opinion, due to their effects on wildlife, as well as the nature of the effects that these products can have on exposed organisms.

Over the last two decades, numerous scientific studies have been conducted to measure the effects of EDs, especially on organisms or populations. The conclusions of these studies are eloquent, particularly regarding three issues. First of all, the number and the nature of the compounds that have been identified as EDs. These products, most of which come from the chemical industry, are of highly varied usage and nature (*see page 10*). Secondly, the fact that examples of EDs can be found in almost all families of multicellular animals : mollusks, insects, vertebrates, and even in some plants. No family of multicellular living beings seems to be exempt. Finally, the diversity of the effects that EDs can have on exposed organisms : anatomical, reproductive, immunological, and behavioral. Below we will describe a few examples that illustrate the diversity of compounds, organisms, and effects that surround the problem of EDs.

Scientific studies on EDs have often been conducted using reductionist methods, *in vitro*, which have made it possible to define the modes of action, establish the scale of toxicity, and to analyze, among other things, the effects of chemical inductors or inhibitors. However, as we will see, this type of method does not seem to be suitable for studying EDs *in natura*. If the effects of EDs are well documented on an individual and population level, their effects on a more global level are still not sufficiently known. Scientists have rarely taken into consideration the effects of EDs on the level of communities, ecosystems, or ecospheres. Considering recent assessments of EDs' role in biodiversity erosion, additional research programs must be put in place, despite the difficulties faced conducting experiments *in situ*.

## The extent of the endocrine disruptor problem

### An example : prosobranchs and TBT

Prosobranchs represent about half of all mollusk species, or around 60,000 species (including whelks and snails). They can be found in most ecosystems, where they play an important role due to their presence on many trophic levels. They are food for a large number of fish, bird, and mammal species. However, mollusks and prosobranchs are especially threatened by the contamination of the aquatic environment. Their metabolic capacity to eliminate chemical pollutants is very limited.

In the 1980s, mass extinctions of prosobranchs began to be observed in port zones. Laboratory experiments as well as *in situ* studies quickly pointed to a culprit: a chemical substance found in paint used on boat hulls called TBT (Tributyltin). This substance has a masculinization effect on female prosobranchs. Even in very weak doses, such as 0.1 ng/L (*Oehlmann et al., 2007*), an "imposex" phenomenon can be observed where females develop penises and a sperm canal. At stronger doses (around 1 to 10 ng/L), the effects of TBT are even more obvious because exposed individuals

# STUDYING & MONITORING ED'S

Many pollutants from earlier decades remain in streambeds, building up in the bodies of fish and birds. These pollutants include heavy metals, DDT, dioxin, PCB's, pesticides and fertilizers, all of which can have endocrine disrupting effects. Most of the industrial and pharmaceutical chemicals we use in our daily lives will eventually find their way to streams, and most of it will remain in the sediments of the floodplain, further poisoning the ecosystem.

The International Chemical Secretariat (ChemSec), based in Sweden and supported by many NGO's, has recently added 22 more substances to its Sin list (<http://www.sinlist.org/>), reaching 378 substances of very high concern, in an effort to speed up the european REACH legislative project, provide progressive companies with a list of chemicals to avoid and challenges chemicals companies to change.





have a deformation in their shell. More recently, studies have shown that TBT also has an effect on the immune system and the development of larval embryos. Even if how TBT's hormonal disturbance mechanisms work on prosobranchs is not yet entirely understood (researchers are divided between several hypotheses), the decline of prosobranch populations is an established fact. In Germany, 60% of sea and land mollusk species are considered to be threatened or extinct. Currently, the case of tributyltin and prosobranchs is scientific literature's most striking example of the effect that endocrine disruptors can have on wildlife on the scale of an entire population.

#### Range of affected species

One of the unique features of endocrine disruptors is that there is an extremely wide spectrum of species that are sensitive to them. Among multicellular organisms, for example, cases of endocrine disruption have been found in the majority of taxonomic branches.

#### Vertebrates

Another example of endocrine disruption after contamination by an organic pollutant concerns reptiles, specifically the alligators of Lake Apopka. In the 1990s, this lake was subjected to an accidental contamination by organochloride insecticides (DDT in particular). The effect of these insecticides on the alligator population was a significant reduction of the size of the penis, preventing any reproduction, and going as far as to lead to a population decline.

Harmful effects after exposition to endocrine disruptors have been reported in all five classes of vertebrates. We just gave an example of reptiles. In mammals, endocrine disruptor effects have been observed even in animals in zones that are supposedly not impacted. In certain islands off of Norway, high concentrations of PCB and PBDE have been observed in polar bears. These high concentrations have been linked to a decrease in the size of reproductive organs in both sexes (Sonne *et al.*, 2006).

Amphibians, with their permeable skin, are a prime target for endocrine disruptors. It has been shown, for example, that a pesticide, atrazine, can disrupt the development of frogs. In birds, numerous chemicals can alter the reproduction or behavior of adults, or development in chicks (see table page 21).

Finally, the presence of endocrine disruptors in almost every aquatic milieu (see above) makes fish an ideal model for studying their effects. An English study dating from 2006 is eloquent on the size of the problem. Gross-Sorokin *et al.* have evaluated the anatomical effects of disruption due to estrogenic steroids in roach fish, effects found in over 50 sites where risk of contamination existed. About a third of the males collected had a phenotype that was in between male and female (intersexual phenotype), and this phenotype was found in 86% of the sites sampled, including sites where the risk of contamination was low. Researchers also found that these induced effects were highly correlated to the concentration of estrogenic steroids. Finally, the study showed that feminized males were less fertile than healthy males. Spermatozooids in the most impacted fish were 50 to 75% less mobile.

#### Invertebrates

Though they represent around 95% of all animal species, invertebrates seem to receive less attention from researchers when it comes to endocrine disruptor phenomena. Though we gave a detailed example above of prosobranchs and the decimation of their populations in port zones, considering their numbers and diversity (especially for insects), invertebrates have not been widely studied. In 2007, Soin and Smagghe only found 15 scientific studies on endocrine disruptors and their potential effects on insects. Moreover, none of these studies was conducted on site, all drew their conclusions from experiments conducted in controlled environments. According to Soin and Smagghe, considering the fact that a very large number of insect species have at least one aquatic phase (often the larval phase), and that the aquatic environment (water,



Agricultural pesticides have been of primary interest to researchers due to frequent reports of malformations from agricultural sites where pesticides are likely to have been used.

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sediment) is easily contaminated, we can expect significant results regarding endocrine disruption in arthropods.

It is important to stress, however, that if studies on pollution-induced endocrine disruption in insects are rare, there has been abundant research conducted on using insect hormones to control selected insect populations that wreak havoc on crops.

### Plants

Plants (especially those that produce phytoestrogens) have been studied as possible endocrine disruptor sources. For example, soy has recently received a lot of attention, particularly in relation to young children's diets (Bar-El and Reifen, 2010).

However, though the phenomenon has not been thoroughly investigated, plants can also be the target of endocrine disruptors. Recent work conducted in vitro has shown, for example, that at high levels of concentration, bisphenol A can have an endocrine disruptor effect on kiwis (Speranza et al., 2011).

#### The diversity of induced effects

The examples described above give us an idea of the wide diversity of ways in which EDs can affect living organisms. Their effects can be grouped in five categories : effects on development, anatomy, reproduction, behaviour, and finally, the immune system.

A well-known rule in toxicology and ecotoxicology is that the effects of a toxic substance are more intense in a juvenile than in an adult. This rule applies to EDs as well. Certain substances are thus capable of disturbing an organism's development. That is the case, for example, of atrazine, which slows or inhibits the metamorphosis (the transformation from the larval phase to the adult phase) in frogs (Hayes et al., 2006). Disturbances in developmental phases can then affect the adult in diverse ways. Most obvious are the anatomical consequences of disturbances in developmental phases. This is what we have seen in mollusks, in the deformation of their shells after TBT exposure. This is also the case with trifluralin, an herbicide that can cause deformation of vertebrae in many fish species.

Exposure to EDs, in any developmental phase or even during adulthood, can also have repercussions on an organism's capacity to reproduce. We have seen examples of this in fish, where intersexual phenotypes between male and female appear, or in polar bears and alligators, where individuals have been observed with atrophied reproductive organs. This phenomenon clearly has an impact on the fertility of the individuals concerned. It has been generally observed that males exposed to estrogenic substances have reduced fertility, an observation that holds true for all vertebrates.

One of the roles of the endocrine function is to regulate behaviour, which is why ED exposure can also have an impact on the reproductive level. PCBs, for example, can alter marine bird's behavior towards their young (feeding, in particular). In the same vein, it has been observed that ibis exposed to mercury exhibit homosexual behavior (Frederick and Jayasena, 2010).

Finally, by miming the effects of thyroid hormones, some substances can disturb thyroid gland function. In vertebrates, this gland is responsible for, among other things, the maturation of immune system cells. In this way, exposure to EDs can also have an impact on the entire immune system, especially if exposure occurred during a juvenile phase, when the immune system is being developed.

We have already noted the diversity of chemicals that can have a disruptive effect on the endocrine system. Substances used in agriculture are only one group of chemicals that have disruptive effects. That said, in this one group, we can see a very wide variety of induced effects (see table page 24).



Normal male whelk (*Buccinum undatum*) with large curled penis clearly visible below the shell.



Female whelk with small penis homologue on the side of the body ('imposex')

Substance	Effect
Herbicides	
Trifluralin	Vertebral abnormality within fish
Atrazine	Induction of premature metamorphosis and alteration of the immune system within the salamander
Fungicides	
Benomyl	Alters growth within fish ; reduced survival at the embryonic stage
Iprodione	Modification of birds behaviour, reduced production of their eggs, reduced weight of chicks at birth, alteration mysidace reproduction
Mancozeb	Alters birds reproduction, delayed laying
Metiram	Alters bird reproduction, reduces production of eggs, reduces fertility, embryo mortality
Tributylétain	Imposex within snails, growth abnormality for oysters
Vinclozolin	Alters birds reproduction, reduces production of eggs, reduces fertility, testicle development disorders
Tetraconazole	Alters the reproduction of mammals and birds
Insecticides	
Carbaryl	Alters the reproduction of birds and fish
Azadirachtine	Inhibits the metamorphosis of arthropods
Diflubenzuron	Reduces testosterone within birds ; disrupts the formation of cuticle for arthropods
Fenoxycarb	Inhibits the metamorphosis of arthropods
Malathion	Reduces growth of fish
Methomyl	Alters the reproduction of birds
Methoxychlor	Alters the reproduction of birds and fish, reduces successful hatching
Parathion	Alters the reproduction of birds and fish, diminishes laying, reduces body weight for adults, vertebral abnormality, reduces the growth of mysidace
Pyrethroids	Alters the reproduction of birds and fish, thinning of egg shells

## Towards a new approach of ED

Efforts in research for the last twenty years have succeeded in demonstrating the width and the diversity of the problems related to ED. However up till now, the emphasis on these problems was generally limited to a reductionist approach : researchers would study the effects of a single substance on a specific species and in a defined or controlled environment. Yet given the specific action mechanisms of ED, this approach does not always seem realistic. Moreover by restricting their study to only one species, scientists can neglect potential disruptions which can extend throughout a trophic chain or modify the trophic links and thus threaten the stability of an entire ecosystem. As regards to the adding up of several substances the potential, synergy or antagonism of its effects is rarely addressed. Finally it is important to put this issue of EDs in a global context which includes the other pressures which threaten global biodiversity.



# ALTERNATIVE ENGINEERING



Endocrine disruptors flush into lakes and streams worldwide, and studies have shown them to interfere with reproductive and immune function in both humans and wildlife. They have been found so far in water and sediment, and recent research reports that endocrine-disrupting chemicals might accumulate as well in the greenish-brown slime, called biofilm, that coat streams and lake bottoms. These biofilms could absorb as much as ten times more ED's than sediment. Fish and aquatic insects feed on this biofilms, and the buildup of EDs in this central source of food could lead to serious problems in the food chain. But we could also imagine a way to use this absorbing capacity in wastewater treatment plants, to remove endocrine disruptors and pollutants from the sewage water before releasing it into the environment.

## The need for a paradigm shift

In a publication from 2009, a group of experts met at the initiative of the Endocrine Society and listed 5 major points that should be at the heart of research on EDs in order to apprehend the action mechanisms and consequences related to EDs, as much from an ecological as a human health standpoint.

### The diversity of induced effects

Being exposed to EDs at an adult age has very different consequences from those at a younger age. Indeed, most organisms have a higher sensitivity during their growth phase. Thus being exposed in prenatal period (in utero for mammals, in the egg for ovipars) or perinatal disrupts all the steps of the immune system by limiting its efficiency (production of immune cells, maturation, etc.). Yet these steps of growth no longer exist at an adult age, at which the immune system is final. This is why scientists now talk about foetal origin (or more largely speaking growth) of the adult disease. By only considering exposure at an adult age scientists have probably neglected many existing effects over a long period of time (*Rodney et al., 2006*).

### Latency period

The equivalent of the window of exposure is the notion of latency period. Indeed if an organism is more sensitive to an exposition during its growth phase, the effects of this exposition are generally delayed, and more often impact the organism at the adult stage. We will need to wait several years to observe the effects of EDs' exposure regarding species with a long life expectancy, including man. It is necessary to consider this latency period for a adequate evaluation of the effects of a substance. Regarding human health, one can question the effects of a former exposure of adult populations to forbidden chemical products after several years of use. Among the most known examples here are two : in France, PCB was forbidden in 1987, Atrazine in 2003. The latter substance is, however, still in use in the USA.

### The cocktail effect

The conventional approach in toxicology and ecotoxicology is to only study the effects of one substance, separately from the other exposures. Yet, in practice the organisms are exposed to multiple substances, potentially capable of synergy. Thus substances which are considered independently as non-toxic can when in conjunction with one another render harmful effects. This is what we call the cocktail effect. A study by Hayes and al (2006) has demonstrated that within amphibians, a herbicide that alone has no effect, the S-metolachlore, can multiply its harmful effects if in synergy with atrazine. In practice, these two substances are often mixed together in industrial products.

Given the enormous diversity of endocrine disruptors, one can easily imagine the problem related to the notion of the cocktail effect : the number of combinations possible seems endless. Faced to this challenge, the most coherent is maybe Hayes and al approach : to not limit research to effects of pure substances, but to start from the combinations which are the most often found in nature, that is the ones organisms are exposed to in their natural environment.



*Daphnia, or water flea, is used widely for testing purposes, and suffered no adverse effects when submitted to low doses of endocrine disruptors, but their sex ratio skewed when exposed to a cocktail of three different EDs.*

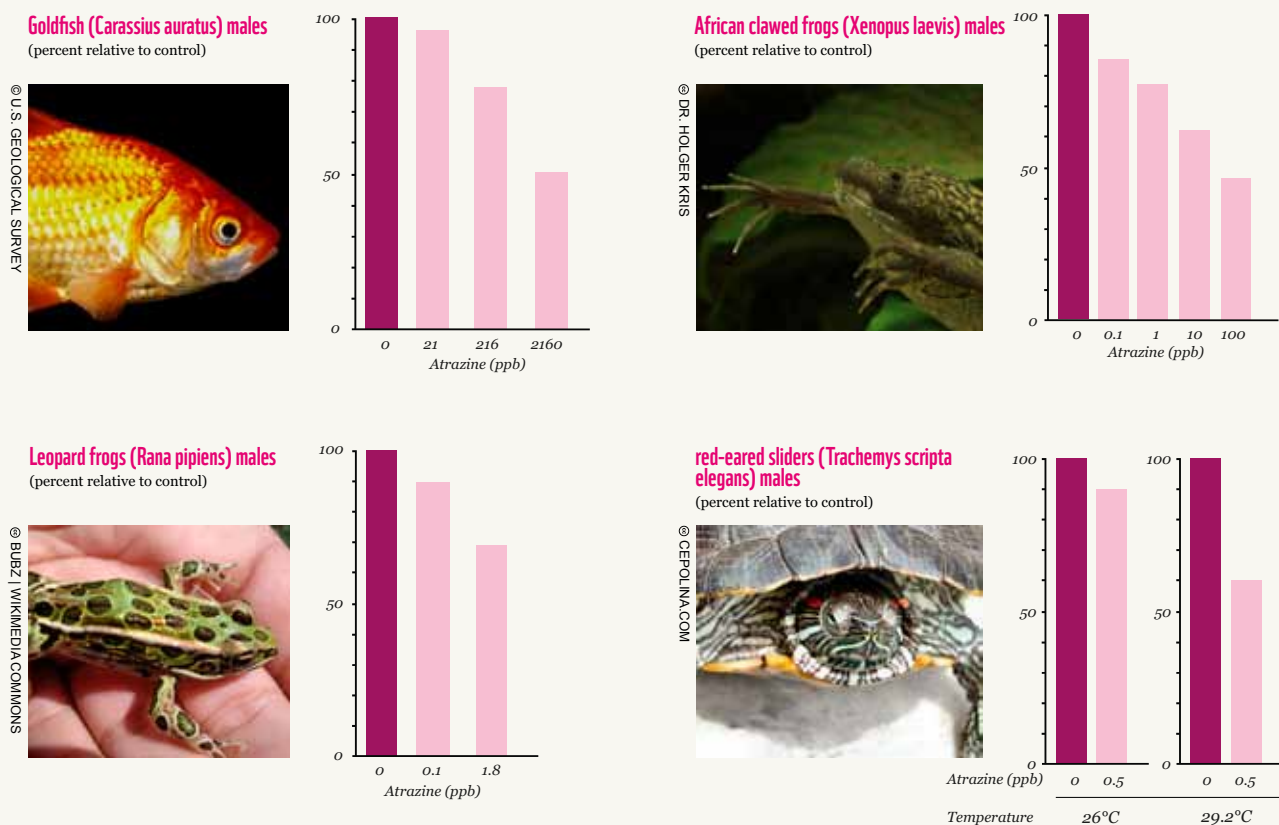
### Absence of maximum measure & measure/classic response curve

The measure/response curves that define ED can be quite surprising : for example there can be curves in bell shape, which means that the effects rendered by average measures can be more important than effects rendered by stronger measures. Moreover, one of the main characteristics for endocrine disruptors, is that there is no minimal measure of exposure without any effect. If one takes the opposite of the



Paracelse principle according to which “ everything is a poison, nothing is poison, it is the dose that makes the poison ” one must consider that “ it is the period that makes the poison ”. Consequently, even extremely small doses have effects, in particular if the exposition to these doses occurred during the growth or gestation period. Study has thus shown that by studying the phenomenon of gender inversion rendered by oestradiol within turtle embryo, there was no minimal dose under which the phenomenon was no longer found (Seehan *et al.*, 2006). This study illustrated quite well the limits of the idea that smaller levels of exposition eliminate the risks.

These aspects have only been accepted by the scientific community in more recent years. It is of course necessary to include them in the regulatory and legislative domain.



### Complete sex reversal by atrazine in vertebrates

Atrazine exposure causes a loss of males in exposed fish, amphibians, and reptiles at low doses, as shown in a recent study by Hayes *et al* from 2011.

(source : *Journal of Steroid Biochemistry and Molecular Biology* 127 (2011))

### Transgenerational effects

EDs are not only potentially capable of having an effect on the generation which is exposed, but also on the descendants of this generation. This has been observed (Crew *et al*, 2006) within rats which were exposed to a fungicide, the vinclozolin. Males were exposed as well as their descendants of 3 generations (which were not exposed themselves) experienced lower reproduction success rates than the control group. Other studies (Anway & Skinner, 2008) suggest that pathologies due to endocrine disruptors, such as prostate problems, kidney, and spermatogenesis abnormality or cancers can also be transmitted beyond generations, affecting the genetic mechanisms (epigenetics).

## Considering the global context

Research about EDs must overcome another challenge, that is to consider the current global context, that biodiversity is subject to multiple pressures. We now know that not a single species is completely dependent of other species which surround it, whether in its close environment or at the biosphere level. This is why the reductionist approach that consists in only studying the effects of one substance over one isolated species is not satisfactory.

The EDs are not the only environmental pressure that affect today's ecosystems. Other threats exist, global warming in the foreground. Norway's Bjorn Jenssen developed this theory in 2006 by giving the example of arctic ecosystems, which are the most threatened by global warming. We know since the 1990s that even these ecosystems, however remote, are contaminated by persistent organic pollution of anthropic origin. Jenssen explored the effects that these pollutants, specifically the endocrine disruptors, can have on arctic organism adaptation capacity to climate changes. He explains that EDs, that affect the neuro-cognitive development within polar bears, could diminish their learning and cognitive capacities. Yet these capacities are very important in order to evolve in an environment which is rapidly changing, due to global warming. As such, EDs are suspected of disrupting the behaviour of arctic birds, in particular their migration or fasting periods and thus lead to a less than optimal behaviour, whilst these birds already have to face a great deal of stress due to the quick variations of their environment. Jenssen considers, on the basis of these two examples, that global warming combined with exposition to EDs could constitute a worse scenario for the arctic ecosystems. As in Jenssen's study, to best assess the effects of EDs is to keep studying them within their geoclimatic context.

These few examples show that it is no longer sufficient to study the effects of EDs, if limited to an organism or population scale. We have already stated the historical example of contamination of port areas by TBT, which impacted and destroyed entire populations of sea mollusks. However these mollusks represent an essential trophic link in their ecosystem : then what about the interrelations between trophic chains? Given the capacities of bioaccumulation of a great number of EDs, one is entitled to believe that the disruption can be observed at all levels of this chain, and thus impact the entire ecosystem.

To consider the effects of EDs on entire ecosystems, even at the biosphere level, is of course not easy or even illusory. However it is one of the goals that scientific research should turn to. The development of modeling methods, combined with data collection at the level of several species of the same ecosystem, could be one approach.

*Over the past four decades, the Arctic became threatened by long-range atmospheric transport of man-made chemicals. Endocrine disruptors were detected in endemic Arctic species, such as polar bears (Norheim et al. 1992).*



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## CONCLUSION

This report is not intended to overview exhaustively all the issues related to endocrine disruptors.

We hope however to heighten decision makers' awareness of the complexity of this issue, by presenting the main substances, their origins and behaviour in the environment. We also tried to illustrate the multiplicity of their effects on a wide range of living species.

However the consequences of the disruption of ecosystems by these substances on a larger scale remain widely unknown. This is why we believe that current research should integrate the paradigm and interpretation shift that comprises the specific issue related to EDs. This condition is necessary to accurately assess ED threat over wild fauna and flora, and to consider measures to control this risk.

There is however one aspect which we intentionally eluded in this report : the impact of endocrine disruptors on human health. The threat presented by the direct exposure of man to these substances has been at the heart of a collective expertise by the INSERM in 2011.

Yet, we would like to emphasize how much human health is dependent on the good health of all ecosystems and biodiversity. The WWF Living Planet Report 2010 has contributed to bringing this message across : it is impossible to live a healthy life on a planet that is not. This is the reason why it is urgent to find solutions to the issue of endocrine disruptors.

*The Doñana National Park in Andalusia, Spain, celebrated the 40th anniversary of its creation in 2009, and is a prime example of a healthy ecosystem.*



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100%  
RECYCLED



90 %

Percentage of human background exposure to dioxins that occurs through the diet, essentially with fats from animal origins

1/100th

Since DDT and PCB ban in 1972, the PCB body burden is 1/100th of what it was in the early 1980s



90 %

Percentage of pesticide missing their goal when dispersing. Those pesticides end up in the soil and ground, where they are transferred, immobilized or degraded

553 SUBSTANCES

Number of man-made chemicals, with 9 synthetic hormones, on the EU ED's priority list of substances to be evaluated



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