

A black and white microscopic image of numerous sperm cells. The sperm cells are elongated with a distinct head and a long, wavy tail. They are scattered across the frame, with some in sharp focus and others blurred in the background.

Endocrine disruptors: an occupational risk in need of recognition

—

Marie-Anne Mengeot, journalist

with Tony Musu and Laurent Vogel, ETUI

etui.

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Contents

05	Introduction
07	Chapter 1
	Observing nature to understand what is happening to humans
07	Rachel Carson, the toxicity of pesticides and the right to know
10	Three generations marked by the “miracle drug”
12	Workers made sterile
13	Theo Colborn and the concept of endocrine disruption
16	The link between humans and wildlife
19	Chapter 2
	The endocrine system: a complex and fragile mechanism
19	A true “orchestra conductor”
22	Disruptions of the endocrine system caused by chemical substances
24	The effects of endocrine disruptors on humans
31	Traditional toxicology put to the test
35	Chapter 3
	Exposure to endocrine disruptors
35	Europe still waiting for identification criteria
36	The costs of endocrine disruptors
36	The many lists of endocrine disruptors
38	Bisphenol A (BPA)
41	The agri-food sector
47	Chapter 4
	European legislation and endocrine disruptors
48	The REACH Regulation
49	The Plant Protection Products Regulation
50	The Biocidal Product Regulation
51	The Cosmetics Regulation
52	The Water Framework Directive
53	Legislation on medical devices
55	Chapter 5
	20 years of European policy on endocrine disruptors
56	1999: an innovative and ambitious strategy for the time
58	Identification of endocrine disruptors
59	Regulation of endocrine disruptors
60	The Commission chooses to violate EU law
62	The criteria proposed by the European Commission
65	Conclusions

Acknowledgment:

The authors would like to thank Lisette van Vliet for her careful reading of the text.

Introduction

Since the second half of the 19th century and the rapid expansion of the chemical industry, tens of thousands of chemical substances have been created, produced and used. They have greatly changed our whole environment and forms of consumption, sometimes for the better, sometimes for the worse.

In the 1880s, doctors observed that workers exposed to certain chemicals (aromatic amines) were more likely to develop cancer of the bladder than those who were not exposed. Despite this, bans and preventive measures were taken only slowly.

The list of carcinogens has since increased and now, at the start of the 21st century, nobody can ignore the role played by chemicals in the increase of cancer. The second greatest cause of death worldwide, cancer has become the primary cause of death in western Europe, and its prevalence is growing rapidly in developing countries. Throughout the world, it tends to hit economically disadvantaged groups the hardest, perpetuating social health inequalities despite improvements in living standards.

While the responsibility of chemical substances for reproductive disorders (sterility, miscarriages and congenital defects) is now acknowledged, it has been more difficult to establish as the disorders concerned are often seen as a concern of the private family sphere.

Over the past twenty years, the issue of certain chemical products – so-called “endocrine disruptors” – having a negative effect on hormonal activity in the endocrine system at doses previously considered safe has gained increasing attention in the public debate. These chemical substances with their hormonal effects have the potential to cause not just cancer and reproductive disorders, but also subtle disruptions to the way an organism works, in turn another cause of illness. Observations of their effects are upturning the precepts of conventional toxicology, as well as our understanding of ways to protect the public and workers.

Labour cannot remain indifferent to this problem. It urgently needs to take a stance in the public debate. Occupational exposure affects a wide range of sectors: hairdressers subject to a whole cocktail of dangerous cosmetics, cleaning staff, workers in the pharmaceutical and plastics industries and in agriculture, to mention just a few. As with other toxic chemical products, exposure is linked to the social division of labour. Low-skilled workers, often in precarious employment, are the ones most exposed to risks.

In most cases, such occupational exposure takes place invisibly: there is no specific labelling, nothing is mentioned on safety factsheets, there is no specific screening of exposed workers, etc. When health problems arise, whether in the workers themselves or in their children, the connection is almost never made to occupational exposure to such substances.

The aim of this brochure is to inform people, helping them to better understand this complex issue and to know what is at stake. It also intends to show that this is a major political issue, requiring European policies to be greatly modified in order to ensure more effective prevention. In various countries, national strategies for fighting endocrine disruptors are being blocked at EU level. However, the wide media coverage of European policy on endocrine disruptors in 2015 and 2016 is creating opportunities for mobilising workers and building alliances.

Endocrine disruptors also constitute an important issue for trade unions. Through taking up this issue, the trade union movement can establish a link between mobilising for better work-related risk prevention and challenging the policy choices that sacrifice health and the environment for the sake of industry profits.

Chapter 1

Observing nature to understand what is happening to humans

This first chapter retraces the major steps forward in raising our awareness to the risks linked to endocrine disruptors, thanks to the perspicacity and obstinacy of two scientists.

1.1. Rachel Carson, the toxicity of pesticides and the right to know

In 1962, US biologist Rachel Carson listed the risks associated with the massive use of man-made pesticides since the Second World War in a book entitled *Silent Spring*: “There was a strange stillness. The birds, for example – where had they gone? Many people spoke of them, puzzled and disturbed. The feeding stations in the backyards were deserted. The few birds seen anywhere were moribund; they trembled violently and could not fly; it was a spring without voices ... Only silence lay over the fields and woods and marsh.” In the view of Rachel Carson, birds and humans shared the same environment, meaning that they also shared the same threats.

1.1.1. DDT, a “slumbering volcano”

In her book, Rachel Carson questioned the use of organochlorine pesticides and especially dichloro-diphenyl-trichloroethane, better known as DDT, a substance first synthesized in 1874 in the era of the rapid expansion of organic chemistry. In 1939, the insecticidal properties of DDT were discovered by the Swiss chemist, Paul Müller, who went on to be awarded the Nobel Prize in Physiology or Medicine in 1948. DDT proved to be very effective in curbing a typhus epidemic that

broke out in Naples in 1943 and in fighting malaria in South Africa from 1946 onwards. At that time DDT was considered a “miracle pesticide”, as witnessed by the growth in its production: 125 million tonnes of DDT were produced in 1947, increasing to 638 million tonnes in 1960. Other organochlorine pesticides (chlordane, heptachlor, dieldrin, aldrin, etc.) were similarly increasingly used in agriculture. Unfortunately, there were two sides to the story.

When Rachel Carson’s book appeared, the disappearance of spring birds had just been reported in several US regions. Residues of man-made pesticides had been measured in the soil and rivers, as well as in animals and human beings. The biologist explained how organochlorine pesticides and DDT, substances soluble in fat, came to be present in the tissues of all living creatures, discovering a tendency for them to accumulate in such organs as adrenal glands, testicles and the thyroid. In her view, they constituted a latent threat similar to a “slumbering volcano”, as they had the potential to interfere with a body’s vital functions and to weaken its defence mechanisms.

Rachel Carson described how DDT and other organochlorine substances affected the nervous system, observing that their effects were not limited to acute poisoning but also had consequences which only appeared over time, especially in reproductive functions. She also noted that mosquitoes exposed to DDT for several generations mutated into strange creatures, half male, half female. She also looked at the growing occurrence of cancer, especially among children. At that time, scientists had already started positing that a number of these cancer forms could be related to a mother’s exposure to carcinogens during pregnancy. Rachel Carson also stressed that exposure to multiple toxic substances, what we now call the “cocktail effect”, increased the risks and that, with regard to carcinogens, there was no such thing as a safe dose.

Rachel Carson wanted to make her findings known. The second chapter of *Silent Spring* highlights a quote from the French biologist Jean Rostand: “The obligation to endure gives us the right to know”. Dedicating ten years of her life to writing it, the book turned out to be a true eye-opener for the public at large and for politicians on the effects of what she called the “elixirs of death”. In the United States, the shockwave was similar to that caused by *Uncle Tom’s Cabin*, a book which, appearing in the 19th century, had condemned slavery and the living conditions of black slaves. Greatly impressed by Carson’s criticism, President Kennedy ordered his Science Advisory Committee to investigate the misuse of pesticides. The Committee ruled in favour of Rachel Carson, stating in a report published in 1963 that until *Silent Spring*, people were generally unaware of the toxicity of pesticides.

Despite the huge success of her book, Rachel Carson remained vulnerable: she was not part of the scientific establishment, she wrote books for the general public and she was a woman. Industry started attacking her, spending large amounts of money on persuading the public that pesticides were beneficial, risk-free and of vital importance for the development of US agriculture. A press campaign aimed to denigrate her, portraying her as hysteric, a romantic speaking out on a subject which exceeded her intellectual capabilities. Worse still, she was accused of having hindered the fight against malaria, making her responsible for millions of deaths. Even so, her observations and arguments were not questioned.

Rachel Carson died in 1964 from the consequences of misdiagnosed breast cancer. Eight years later, DDT was banned in the United States, with many other countries following in its footsteps. It is however still used in India and several African countries, in

particular to fight malaria¹. Other organochlorine pesticides have since also been banned, though much too late for the planet and its inhabitants, as these substances are for the most part persistent organic pollutants, i.e. they degrade extremely slowly and remain in the environment for decades (DDT for more than 100 years). Their presence in soil, in river mud and in the sea, together with their ability to accumulate in the fatty tissue of living organisms throughout the food chain, mean that the risks they pose have not disappeared.

In June 2015, the insecticide DDT was classed by the International Agency for Research on Cancer (IARC) as a Group 2 (probably carcinogenic) carcinogen on the basis of sufficient evidence, showing that it induces cancer in lab animals and limited evidence of carcinogenicity in humans. Epidemiological studies reveal positive associations between exposure to DDT and non-Hodgkin's lymphoma, testicular cancer and liver cancer. The IARC also has experimental data proving that DDT weakens the immune system and disrupts sexual hormones.

Humans in contact with toxic substances from the moment they are conceived to their death

"For the first time in the history of the world, every human being is now subjected to contact with dangerous chemicals, from the moment of conception until death. In the less than two decades of their use, the synthetic pesticides have been so thoroughly distributed throughout the animate and inanimate world that they occur virtually everywhere. They have been recovered from most of the major river systems and even from streams of ground-water flowing unseen though the earth. Residues of these chemicals linger in soil to which they may have

been applied a dozen of years before. They have entered and lodged in the bodies of fish, birds, reptiles, and domestic and wild animals so universally that scientists carrying on animal experiments find it almost impossible to locate subjects free from such contamination. They have been found in fish, in remote mountain lakes, in earthworms burrowing in soil, in the eggs of birds – and in human beings. For these chemicals are now stored in the bodies of the vast majority of human beings, regardless of age. They occur in the mothers' milk, and probably in the tissues of the unborn child."

Extract from Carson, R., *Silent Spring*, p. 31.

1.1.2. PCBs even in the waters of northern Europe

Pesticides are not the only problematic substances. In 1966, the Swedish researcher Sören Jensen, concerned about marine fauna contaminated by DDT, investigated a fish eagle (an animal at the top of the aquatic food chain), discovering in its tissues not just DDT, but also other chlorinated substances he knew nothing about. It took him two years to find out that the substances concerned were polychlorinated biphenyls (PCBs). PCBs, a chemical family made up of more than 200 different compounds, have been marketed since the 1930s and used in many industrial applications. Thanks to their heat resistance and non-flammability, they were used *inter alia* in electric transformers and capacitors.

PCBs are present everywhere in the environment, contaminating wildlife and in particular the fish on which fish eagles feed in the Baltic Sea. In the years following

1. DDT remains one of the products whose use the WHO allows inside homes under certain conditions in the context of fighting malaria, a disease transmitted by mosquitoes. In 2013, India was the only country still producing DDT, and it is also its largest user. In 2015, an agreement was reached between the United Nations and India for the latter to stop using DDT by 2020.

Jensen's discovery, a decline in the fertility of three species of seals found in the Baltic Sea was registered and a clear link established between PCB concentrations in female seals and malformations of their genitalia.

Though production of PCBs was stopped in the European Union in 1986, they continue to contaminate rivers, lakes and seas, as is the case with DDT. An assessment conducted in 2005 estimated that 350,000 tonnes of PCB were still present in electrical equipment.

In 2015, a British study² revealed that PCBs were responsible for very low fertility rates among porpoises populating the European shores of the Atlantic. Of the 329 female porpoise corpses stranded on British shores between 1990 and 2012, 47% had a rate of contamination higher than the threshold above which PCBs have adverse health effects on marine animals. Among sexually mature females, some 20% were sterile and 16.5% suffered from infections or tumours of the genitalia. The rate of PCB in their fatty tissue was directly linked to their gestational status.

Although the UK banned PCBs in 1981, the rate of contamination in porpoises only started going down in 1998.

DDT and PCBs are now acknowledged as endocrine disruptors. The list of their toxic effects on wildlife is very long, while more and more observations are being made regarding their effects on human beings (see p. 24 *sqq.*).

1.2. Three generations marked by the "miracle drug"

At the same time that the toxic effects of DDT and PCBs on wildlife were being discovered, a new "miracle drug" appeared on the market. Diethylstilbestrol (DES), a drug marketed under the brands Distilbène and Stilboestrol, is a synthetic hormone which acts like an oestrogen (female hormone). In the United States and several European countries, including France, the Netherlands and Belgium, it was prescribed for pregnant women to reduce the risk of a miscarriage. In 1971, a Harvard University doctor established the link between several cases of vaginal cancer in adolescent females (a rare disease at this age) and the fact that their mothers had been prescribed DES during pregnancy. The mother of one of the young girls had put him on the track. Occurrence of this particular cancer is fortunately relatively rare: about one in a thousand girls who have been exposed *in utero* (in their mother's womb). Estimates put the number of occurrences in the United States at around 600 and at more than 100 in France.

Some years later, a new publication pointed to a high prevalence of anomalies of the uterus among girls exposed *in utero* to DES, causing difficulties in getting pregnant and infertility. The risks of complications during pregnancy are also much higher: ectopic pregnancy (a sixfold risk), late-term miscarriages (tenfold risk), premature births, etc.

In boys exposed *in utero*, an increase in certain anomalies of the urogenital tract was also observed, including testicular hypotrophy, cryptorchidism (when one or both testicles have not descended) and hypospadias (when the opening through which urine passes is not located at the tip of the penis, but on its underside).

The consequences of DES are difficult to bear, especially as this drug, advertised as a "miracle drug" and routinely recommended for all pregnancies, was in fact useless. Though a study conducted in 1953 showed that it was ineffective in preventing miscarriages, it

2. Murphy S. *et al.* (2015) Reproductive failure in UK harbour porpoises (*Phocoena phocoena*): a legacy of pollutant exposure?, PLoS ONE 2015; 10 (7): e0131085.

continued to be routinely prescribed until 1971 in the United States and at least until 1983 in Europe.

The ability of certain natural substances to interfere with the reproductive system has been known for a long time. But, from the 1920s onwards, scientists sought to isolate and reproduce natural hormones (oestrogen, progestin and androgen) and ended up successfully producing synthetic hormones. Testosterone (the male hormone) was isolated in 1935, and a synthetic testosterone produced in 1951. Discovered in 1923, the active substance that precedes and accompanies ovulation was named estrone. Its copy, ethinyl oestradiol, was produced from 1950 onwards. Progesterone (the female hormone) was isolated in 1934 and synthesized in 1949.

At the same time, British chemists discovered the oestrogenic properties of certain synthetic substances, leading to them conducting systematic research which resulted in the isolation of particularly active compounds. These they called stilbestrols, a family that included the DES discovered in 1938. While these synthetic compounds had a chemical formula that actually had little in common with natural oestrogens, the ease of synthesizing them and their low cost led many pharmaceutical companies to market them.

From the end of World War II, DES was prescribed not only for reducing the frequency of miscarriages but also to treat acne, stop growth in girls afraid of becoming too tall, or as a morning-after pill, as well as for treating prostate cancer.

DES was also used, together with other hormones, in breeding animals, for example to boost growth in chickens and to fatten calves. Its use was banned in the European Union in 1981.

Testimonial of a "DES daughter"

"I was born in 1961. At the age of 27 and after two years of assisted reproduction, I was told that I had a T-shaped uterus (typical abnormality in girls exposed to DES *in utero*). I was also told that I had been exposed to Diethylstilbene as a foetus. I have now been married for 26 years. I have had six spontaneous miscarriages, as well as many attempts at artificial insemination, in vitro fertilization (IVF) and other treatments, all without success. My body is inflated by hormones and I'm ridden with doubt about their future undesirable effects (...)

I have only told you the medical side of my story,

omitting the consequences that all this has had on my relationship with my mother and on the management of her guilt, on my relationship with my husband, my family, my friends, and with society (...) So much grief to cope with: that of my desire to have children, that of the spontaneously aborted babies, (...) the break in the generational chain ... The least that I can hope for is that our collective experience of DES and its effects on our day-to-day lives can help others and future generations to be more discerning."

Testimonial in the journal *Prescrire* in 2010.

Children exposed *in utero* – the so-called "second generation" – are not the only victims of DES. All generations are affected. The first generation, i.e. the mothers who took DES during pregnancy, have a high risk (about 30%) of developing breast cancer. The third generation, i.e. the grandchildren of the women who took DES during pregnancy, are also affected. According to French studies, third-generation boys have a five times higher risk of hypospadias. The association of French victims (*Réseau DES*) has pointed to an increase in the number of children with cerebral palsy linked to a higher rate of premature and very premature births.

As regards the second generation, now quite old "DES daughters", studies conducted in the United States show that they have a two times higher risk of developing breast cancer

after reaching the age of 40 and a three times higher risk after 50, and that their risk of contracting vaginal cancer constitutes a second peak around menopause. A study conducted in 2015³ in France confirms the twice higher risk of breast cancer vis-à-vis non-exposed women.

DES is now considered as an “involuntary human experiment” and as the paradigm of the toxic effects of endocrine disruptors.

1.3. Workers made sterile

In the aftermath of the 1972 ban on DDT in the United States, several pesticide scandals rocked the scientific community and the media.

1.3.1. Chlordecone

The first scandal concerned two related chemical compounds produced from the 1950s onwards: mirex, marketed as Dechlorane, and chlordecone, sold under the name of Kepone.

Mirex was used as a fire retardant, but also as an insecticide against ants. It was banned in the United States in 1976 due to its toxic effects on aquatic animals and its carcinogenic and teratogenic (toxic for the foetus) properties observed in lab animals.

Chlordecone was used as an insecticide in tobacco, banana and citrus plantations. When the “affair” exploded in 1975, the only company to produce it on a global scale was the Life Science Products Company, whose factory was located in the state of Virginia. A doctor discovered that one of his patients, a worker at the company suffering from severe tremors, had been intoxicated by Kepone. A factory inspection conducted by the Virginia Department of Health revealed massive workplace contamination and a high incidence of a hitherto unknown disease among workers. Of 133 workers affected by the production of chlordecone, 76 (57%) showed symptoms of the disease: tremors, weight loss, pains in joints, oligospermia (a deficiency of sperm cells in the semen) and in certain cases a loss of libido and infertility. Two wives who washed the work clothes of their husbands also suffered from tremors. The severity of the symptoms was related to the level of chlordecone measured in the workers’ blood.

In lab animals, exposure to chlordecone led to neurological and testicular effects similar to those observed in humans. Studies have unambiguously shown that chlordecone has oestrogenic hormonal properties.

Following the ban on the production and marketing of chlordecone in the United States in 1976, the substance continued to be used elsewhere in the world, in particular in banana plantations in the French Antilles until 1993. In 1999, French scientists started work on assessing the impact of exposure to it, leading to an action plan published in 2008, 30 years after the US scare. A 2010 study showed that the use of chlordecone in the French Antilles was responsible for a significant increase in the risk of prostate cancer, a form of cancer accounting for 50% of cancer cases in Guadeloupe and Martinique. The risk of developing prostate cancer in Guadeloupe is 2.5 times higher for those most contaminated.⁴

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3. Fenichel P. (2010) L'exposition au distillibène: une expérimentation humaine involontaire riche en enseignements, in Levadou A. and Tournaire M. (eds) DES (Distillibène – Stilboestrol). Trois générations: réalités – perspectives, Mont de Marsan, Réseau D.E.S France.
 4. Multigner L. *et al.* (2010) Chlordecone exposure and risk of prostate cancer, *Journal of Clinical Oncology*, 28 (21), 3457-3462.

Generations of Antilleans will have to live with this substance because it will take hundreds of years for chlordecone to be spontaneously eliminated from soils and rivers. The health risk is highest for the poorest, the ones growing their own vegetables in contaminated soil, and for the workers, often black, employed in the plantations. A 2014 study revealed a link between chlordecone contamination and an increased risk of premature births.

1.3.2. DBCP

The discovery that a further pesticide, dibromochloropropane (better known as DBCP), was responsible for serious alterations to semen dates back to 1977. At that time, some thirty US workers employed by the Occidental Chemical Company Western Division in California were affected by the production of DBCP. This pesticide had been used since 1955 in fruit plantations, especially citrus fruits and bananas as a nematocide (worm killer). Confiding in each other, the workers, most of them quite young, found out that many of them were unable to have children. Through contacts with scientists from the local university, they learnt that, in experimental studies, DBCP was mutagenic and carcinogenic and had even shown serious effects on the reproductive function of rodents (reducing testicle size and sperm quality).

Several workers decided to have their sperm tested. The results revealed azoospermia (the lack of sperm in one's semen) or oligospermia (a very low sperm count), and hormonal disorders. These initial observations were confirmed by studies involving other groups of workers exposed to DBCP. In 1977, the US Environmental Protection Agency (EPA) suspended the sale of DBCP throughout the United States. The ban on the use of DBCP for all types of cultures became permanent in 1979, with the exception of pineapple plantations in Hawaii, where it was not banned until 1985.

The use of DBCP by US companies continued in the Philippines and Latin America until the mid-1980s, especially in banana plantations.

In 1992, 4,000 farm workers in Costa Rica who had been made sterile by DBCP withdrew their lawsuit against several US companies in exchange for compensation. In 2007, a Californian jury sentenced Dole Food Company, the largest producer of fruits in the world, to pay \$2.5 million to six banana plantation workers in Nicaragua who had become sterile.

Both DBCP and chlordecone have toxic effects on workers' reproductive systems, but they act in different ways. While chlordecone, due to its oestrogenic properties, is considered as an endocrine disruptor, DBCP is not generally classified as an endocrine disruptor, but as being reprotoxic.

1.4. Theo Colborn and the concept of endocrine disruption

In the aftermath of the publication of Rachel Carson's *Silent Spring*, observations of reproductive disorders in wildlife, and especially aquatic animals, increased significantly, and scientists started questioning the chronic or accidental pollution of the waters in which these phenomena were observed.

1.4.1. The masculinisation of females and feminisation of males in aquatic animals

In the coastal waters of various parts of the globe, female marine gastropods (a variety of molluscs) with male sexual characteristics, called imposex, have been observed since 1971.

This phenomenon was attributed to tributyltin (TBT), a class of organotin compounds used in anti-fouling paint for boats. An anti-oestrogen, TBT has led locally to major declines of certain species, and even their extinction. The effects of TBT observed in nature have been reproduced in the laboratory (see Box).

In Florida, Lake Apopka, already polluted by agricultural effluents, was widely contaminated in 1980 by an accidental inflow of pollutants, including DDT. Three years later, a significant decline in the number of young alligators in the lake was observed, although numbers were rising or remaining stable elsewhere. The decline was explained by an endocrine disruption impacting the hormonal system, linked to the combined effects of substances in the lake. There was a lot of data to back up this theory, including a twofold concentration of oestradiol and ovarian malformations in female alligators, and abnormally small penises in the males, together with a concentration of testosterone precursors equal to that of the females.

In several places on the West Coast of the United States, feminisation of gulls was observed and attributed to environmental pollution by DDT. Through injecting DDT into gulls' eggs at doses comparable to those measured in the environment, scientists were able to reproduce what they had observed in nature.

During the 1960s and 1970s in both the United States and in the United Kingdom, populations of various birds (pelicans, cormorants, falcons) declined on account of incubation failures due to abnormally thin egg shells. This phenomenon is attributed to DDT, the presence of which was particularly high in the environment at that time. Experts were able to demonstrate that DDE, the metabolite⁵ of DDT most often found in several bird species, inhibited the synthesis of prostaglandins⁶, in turn inhibiting the transport of calcium.

The TBT saga

Tributyltin (TBT) is a case study for the realisation of the effects of hormonally active substances. TBTs constitute a group of chemical compounds known for their high level of biocidal action. First used as fungicides and bactericides, from the 1960s onwards they were greatly used in anti-fouling paint (bottom paint) for ships, as they prevented the growth of organisms on a ship's hull able to slow it down. In 1970, scientists in the United States and the United Kingdom observed that some female molluscs had a sort of penis, called imposex. The phenomenon was more frequent in areas close to ports.

In the Bay of Arcachon in France, it had led to the virtual disappearance of oysters. The high losses incurred by the oyster industry helped accelerate research, and

the culprit was soon found: TBT. In 1982, France became the first country to ban the use of paint containing TBT on boats less than 25 metres long. Later studies demonstrated that the development of an imposex could occur in certain species at pollution levels in the order of 0.1 – 1 nanogram per litre of water. TBT acts as an anti-oestrogen and helps increase testosterone, the main male sexual hormone.

The use of TBT in paint has been banned in Europe since 2003 and throughout the world since 2008. Nevertheless, it continues to pollute certain coastal areas and ports. In the Bay of Arcachon, the speedy ban of TBT led to stocks of oysters returning to normal levels from the mid-1980s onwards. Consumption of shellfish and fish containing TBT has certainly infected humans, though the effects remain unknown.

5. A metabolite is what results from transforming a chemical substance in a cell, tissue or blood, in the case of DDT.
6. Prostaglandins get their name from the fact that, on discovering them in sperm, they were thought to be produced by the prostate gland. The substances are produced naturally by the body and are involved in several physiological and pathological processes.

1.4.2. Mammals have not been spared

In Europe, the otter population was decimated between 1960 and 1980, a phenomenon attributable to reproduction disorders associated with water pollution due to PCBs. Numbers of otters and mink in the Great Lakes region of North America have similarly declined due to PCBs and dioxin. Mink given food containing PCB at levels comparable to those measured in nature have been shown to cause reproductive disorders (foetal death, malformations, reduced survival and growth rates).

A masculinisation of female bears has been observed in Canada, as well as in European polar bears at the top end of the aquatic food chain. They are being contaminated by organochlorine products, including PCBs.

All these facts are leading scientists to consider that certain chemical substances act like hormones, changing natural parameters. Comparable effects to those produced by DES in humans, and confirmed in lab animals, have been reported with regard to PCBs and DDT in wildlife.

Piece by piece, scientists are putting together the jigsaw puzzle, backed by their observations of wildlife, the consequences of occupational exposure, and the rise in concern sparked by the increase of cancer in humans. In line with what Rachel Carson wrote about 30 years earlier, (*"Our fate is connected with the animals"*), more and more scientists are seeing animals as models for understanding what is happening in humans; the zoologist Theo Colborn is among them.

1.4.3. "We know enough to take action"

Theo Colburn, who died in December 2014, restarted studying late in life, gaining a PhD in zoology in 1985 at the age of 58. Her research focused on the effects of chemical pollution on the wildlife of the Great Lakes in the north of the United States.

In a report published in 1988, she described not just the reproductive disorders found in fish living in polluted waters (decrease in sexual functions, the demasculinisation of males, hermaphroditism), but also immune problems, behavioural modifications, hormonal and metabolic changes, deformities, tumours, etc.

She established a link with the illnesses affecting humans, themselves also the victims of pollution in the Great Lakes. Theo Colborn had several intuitions, all of which have now been confirmed. She realised that even very low levels of exposure can have profound and long-term effects on health, that the point of time at which contamination actually occurs plays a key role in the development of these effects, that environmental exposure can affect several generations, and that the severity of the effects is not necessarily linearly linked to increases in doses.

Theo Colborn considered that she knew enough to take action. However, she also knew that, as long as she was on her own, the impact of what she had found out would be limited. In 1991, she got a number of scientists from various disciplines to come to a series of conferences in Wingspread in Wisconsin to discuss the presence in the environment of hormonally active substances capable of disrupting the endocrine systems of animals and humans⁷. These meetings, soon to become known as the Wingspread meetings, ended with

7. In 1996, Theo Colborn published *Our stolen future*, a book now considered as just as important as that of Rachel Carson. In 2003, at 76 years old, she founded the Endocrine Disruption Exchange (TEDX), an NGO focused on researching and disseminating knowledge on endocrine disruptors (www.endocrinedisruption.org).

the publication of a document outlining for the first time the concept of endocrine disrupting chemical substances.

1.5. The link between humans and wildlife

In the 1991 Wingspread meetings, the scientists gathered together by Theo Colborn stated that they were certain of the following facts:

- A large number of man-made chemical substances released into the environment are able to interfere with the endocrine system of living organisms (animals and humans).
- Many wildlife species are already affected by these chemical substances in the form of thyroid malfunctioning, a drop in fertility and the number of broods, deformities, feminisation, masculinisation and immune system deficiencies.
- Although there are common features, effects vary depending on the species concerned and the type of chemical substance: effects on embryos and fetuses are different to those in adults; effects are more frequent among offspring than among parents; the point of time at which exposure occurs determines the character of the effect and its future development; although exposure may take place during embryonic development, the effect may possibly only manifest itself in adulthood.
- Laboratory studies confirm the observations made in nature and enable us to understand the biological mechanisms explaining such phenomena.
- Humans can be impacted by the same substances, as seen with DES, the synthetic oestrogen.
- Concentrations of the same chemical substances measured in humans are at levels comparable with those measured in wildlife.
- The effects observed in wildlife also concern humans, as the latter share the same food resources (e.g. potentially contaminated fish) with certain animal species, especially birds.
- For the scientists gathered together in Wingspread, the issue of a common danger to both wildlife and humans presented itself, which they termed the “*Wildlife/Human Connection*”.

1.5.1. The decline in sperm quality

In 1992, one year after the declaration of Wingspread, a study published by Danish scientists highlighted the deterioration of sperm quality over the past 50 years. Elisabeth Carlsen and her colleagues based this finding on a series of studies published between 1938 and 1991 and covering a total of 14,947 men. The Danish team considered that this development, occurring in just a short space of time, was probably due to environmental rather than genetic factors. According to the scientists, a common cause, occurring in the prenatal phase, could explain this drop in sperm quality and the parallel increase in deformities of the male sexual organs (hypospadias and cryptorchidism), as well as the rise in testicular cancer observed in many countries. Again, the effects of DES pointed the scientists towards chemical substances with hormonal action that permeate the environment and contaminate the food chain. The Danish scientists came up with the “oestrogen hypothesis”, stating that, even at the low doses present in the environment, oestrogenic substances could be behind such disorders when contamination occurred *in utero*, especially at the point in time when sexual differentiation occurs. Exposure of animals (rats and mice) to oestrogen

in utero or during the period immediately following birth led to a reduction in the size of their testicles and in sperm quality in adulthood.

1.5.2. The “testicular dysgenesis syndrome”

In 2001, again in Denmark, scientists developed the hypothesis that low sperm quality, testicular cancer and male genital deformities (hypospadias and cryptorchidism) were symptoms of the same underlying factor. This they termed the *testicular dysgenesis syndrome* (TDS).⁸

The scientists demonstrated that the various TDS components were interlinked and originated at the very beginning of foetal development. In their opinion, epidemiological studies confirmed that TDS was caused by environmental factors acting separately or in association with genetic factors. For example, the rate of testicular cancer was lower in Finland than in Denmark, but its rise in both countries took place at the same time, suggesting factors linked to the environment or lifestyles.

The Danish team’s publication prompted many reactions and intensive research activity, though without establishing conclusive proof of the existence of TDS as a single widespread pathology. The Danish scientists behind the concept of “testicular dysgenesis” stated that the TDS hypothesis did not mean that men affected by testicular development disorders would necessarily develop afflictions linked to TDS. According to the 2012 WHO report, foetal exposure to substances influencing the production of testosterone in lab animals caused a range of TDS symptoms, as did oestrogenic substances.

Low sperm quality in a large proportion (over 40%) of the population of young men and the rise in genital deformities in boys and in testicular cancer are realities that are not contested (see also Chapter 2).

In 2009, the Endocrine Society, an association with 18,000 members from more than 120 countries, made a statement saying that the accumulated data on the effects of endocrine disruptors was sufficient to call for the precautionary principle⁹ to be applied and for reduced exposure, especially during and immediately after pregnancy. The effects studied by the Endocrine Society refer more to the male reproductive system, yet women are equally affected. Moreover, it is not just the reproductive system that is affected (see Chapter 2).

In 2015, it confirmed the contribution of chemical substances with hormonal action to the rise of chronic diseases linked to obesity, diabetes, reproduction, cancer, and thyroid and neurological functions. The Endocrine Society again called for the application of the precautionary principle, which would mean that chemical substances are tested for their hormonal action at low doses before being placed on the market. A number of its members have stressed the importance of providing all necessary information before including a new chemical compound in food packaging, hygiene and beauty products, as well as in household products.

8. Dysgenesis refers to organ or tissue deformities occurring during embryonic development, i.e. during the first eight weeks of pregnancy.

9. The precautionary principle enables rapid response in the face of a possible danger to human, animal or plant health, or to protect the environment. In particular, where scientific data do not permit a complete evaluation of the risk, recourse to this principle may, for example, be used to stop distribution or order withdrawal from the market of products likely to be hazardous. (Source: European Union – EURLex)

Read more

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Chapter 2

The endocrine system: a complex and fragile mechanism

In this chapter, we will be seeking to describe the endocrine system, how certain synthetic chemical substances are capable of disrupting it and the consequences this has on human health. We will see that research into endocrine disruptors is revolutionising the toxicology, forcing us to review the rules on the protection of the public at large and workers.

2.1. A true “orchestra conductor”

The human body is made up of billions of individual cells, small factories ceaselessly producing the molecules responsible for such different functions as thinking, movement or controlling temperature. These biological processes allow the body to adapt to ever-changing circumstances and continue to function properly. They are all interconnected, permanently sending out and receiving messages to start or stop any one process. They are regulated by such systems as the nervous system or the endocrine system.

From the moment a living being is conceived, the endocrine system regulates a large number of biological processes including growth, maintaining homeostasis¹⁰ and reproduction. All vertebrates (from fish to mammals) have an endocrine system which works hand in hand with the nervous system.

10. The term “homeostasis” refers to the tendency of an organism to seek and maintain a condition of balance or equilibrium within its internal environment, even when faced with external changes.

2.1.1. Glands, hormones and receptors

The endocrine system is a complex communication network involving hormones, the endocrine glands which produce them (the hypothalamus, thyroid, liver, pancreas, ovaries, testicles, adrenal glands, etc.), and specialized cells. The hormones released into the blood stream generally act remotely on cells via receptors that recognize and react to them. The hormones get bound to the receptors, rather like inserting a key into a lock to open a door. Sometimes, the process only takes just a few seconds, for example when reacting to stress; while at other times it can last many years, as in the case of sexual differentiation.

Some fifty different hormones have been identified in human beings. The main ones are the sexual hormones (androgens, oestrogens, progesterone), corticosteroids and thyroid hormones.

Certain hormones – insulin, adrenalin or the growth hormone – are molecules soluble in water. They bind with the target cells via receptors located on the surface of the latter, as they are unable to cross the fatty membrane surrounding the cell. Steroid hormones, including the sexual hormones and the corticosteroids produced from cholesterol, are soluble in fat. They act via receptors located inside a cell, the walls of which they can easily get through. Thyroid hormones also have an aversion to the aqueous medium.

A hormone's affinity to an aqueous or fatty medium determines the way it circulates in the body. Hormones soluble in water have no problem circulating as they are "like" water. To reach their target, fat-soluble hormones have to hook on to water-loving transport proteins. Certain transport proteins are very selective and will only transport steroid or thyroid hormones.

The same selectivity characterises the relationships between hormones and their receptors. Oestrogens bind with oestrogen receptors, androgens with androgen receptors, etc. Several receptors can exist for one and the same hormone. The action triggered in the various receptors leads to different responses.

Once the target cell has responded to the request transmitted by the hormone to the cell, it in turn sends a message back to the cell which secreted the hormone. Many activities in the endocrine system are thus governed by a complex series of *feedback loops*, working like a thermostat which responds to a change in temperature through sending a signal to start or stop a heating system.

Such regulation is supported by the action of specialised enzymes. Present in various tissues, these are involved in the synthesis and elimination of steroid hormones.

2.1.2. Sexual hormones and reproduction

Sexual hormones – androgens, oestrogens and progesterone – are present in both sexes but at different levels.

Androgens are mainly produced in the testicles, but also by the ovaries and adrenal glands. Following sexual determination, androgens take control of growth and the development of male sexual organs. Later on, they trigger puberty and confer masculinity (a deep voice, muscle mass, behaviour, etc.).

Oestrogens by contrast are produced mainly by the ovaries and in low quantities by the testicles, as well as by adipose tissue and the adrenal glands in both sexes. Oestrogens are involved in the formation of the female reproductive system, and during puberty in the development of secondary sexual characteristics (breasts, pubic hair, etc.). Acceleration of bone growth is first stimulated then stopped by oestrogens. Oestrogen production in the

ovaries fluctuates over the ovarian cycle. In men, oestrogens influence fertility through their action on the prostate gland, testicles and on sperm maturation. During puberty, they also regulate boys' growth and determine their final height.

Progesterone, the main progestin, is called the "pregnancy hormone" because it prepares the female body for pregnancy and acts throughout the nine months of gestation. In women, it plays a crucial role in ovum maturation.

Sexual hormones ensure gender differentiation in the embryonic phase. Disruptions can occur when the cascade of masculine development events does not occur normally (risk of feminisation) and when a feminine embryo is exposed to a high rate of androgens (risk of masculinisation).

2.1.3. Corticosteroids and stress

Corticosteroids are non-sexual, supporting the same functions in both sexes: reaction to stress, vitality, temperature control, etc. Produced by the adrenal glands (glands on top of the kidneys), there are two types: glucocorticoids and mineralocorticoids. Glucocorticoids (called such because they are involved in the production of glucose) are principally known as stress hormones. They transform the sugar, fats and proteins stored in the body into energy for use in combating emotional and physical stress including fever, illness or injury.

To generate this energy, glucocorticoids act on the liver, causing it to release stored glucose into the blood stream and transform proteins and fats in the muscles into glucose. Glucose is then delivered mainly to the brain and to the heart to fuel the response to stress. Cortisol is the most powerful glucocorticoid. Too much or too little cortisol can cause severe illnesses: overproduction can cause Cushing's syndrome, characterised by weight loss and changes in appearance due to abnormal fat distribution; while underproduction can cause Addison's disease. Malfunctions in the production of glucocorticoids are also linked to certain types of diabetes.

Mineralocorticoids such as aldosterone are there to manage such minerals as salt or potassium which play a role in regulating blood pressure.

In toxicology, the adrenal glands producing corticosteroids are considered to be extremely sensitive to endocrine disruption. However, there is little information on the effect of endocrine disruptors on the adrenal glands of human beings. In theory, endocrine disruptors can alter our responses to stress and modify cognitive functions. *In utero*, they can impact the normal functioning of the adrenal function, causing disorders which can persist into adulthood.

In animals, exposure to PCBs has been linked with particularly low levels of glucocorticoids observed in polar bears, fish and birds. Disorders resembling Cushing's syndrome in human beings have been identified in three species of seals found in the Baltic Sea, and linked with their exposure to PCBs and DDT. Since the decline in the levels of such pollutants, seal populations have recovered.

Arsenic, a natural pollutant of many sources of water throughout the world and widely used as a wood preservative, can interfere with the complex relationship between glucocorticoids and their receptors; this explains the carcinogenic effect of this metalloid.

2.1.4. Thyroid hormones and the proper development of the brain

Thyroid hormones support virtually all vital systems: the functioning of the blood, the heart, the lungs, bone growth, etc. They ensure the proper development of the brain, bones

and organs. Deficiencies or excesses can derail their delicate balance, causing development disorders and illnesses. They are mainly produced by the thyroid gland at the end of a long and complex process. The main thyroid hormone is thyroxine. Alone or in association with other hormones, thyroid hormones play a crucial role in reproduction and growth and can even influence behaviour. No vertebrate can live without them.

Concentrations of thyroid hormones must be sufficient *in utero* and immediately after birth to ensure the proper development of the brain, bone maturation and an adequate level of the growth hormone. A deficiency can impact not just growth, but also the hearing, motor skill and intelligence of new-borns and children.

Throughout life, thyroid hormones, in combination with oxygen, ensure a body's energy balance. Hyperthyroidism, i.e. the excess production of thyroid hormones, can cause weight loss, rapid heartbeat and irritability, while hypothyroidism is associated with weight gain, apathy and a slowing down of heartbeat.

Numerous chemical substances, including dioxins, PCBs and DDT metabolites, interfere with the functioning of the thyroid, modifying the quantity of hormones produced or altering their distribution to the various organs and tissues.

2.2. Disruptions of the endocrine system caused by chemical substances

Chemical compounds interfering with natural hormonal functions have been called different names, but the most usual are Endocrine Disrupting Chemicals (EDCs).

EDCs vary by origin, capabilities, life cycles and effects. Many chemical substances are produced for specific uses, for instance in pesticides, plastics, cosmetics and many other products. Certain EDCs are generated during the production or decomposition of other chemical substances. There are also plants with oestrogenic properties (so-called phytoestrogens) such as soya beans.

EDCs act at different levels in the endocrine system. They can bind with hormone receptors, imitate them, block them or modify their action. They can alter signals, or send non-standard responses which are without effect or can lead to a lower, higher or totally different effect than that of natural hormones. They can act indirectly through altering the way in which natural hormones, transport proteins and receptors are produced, used and eliminated. An EDC can have several different actions at the same time.

2.2.1. At receptor level

Scientists initially thought that just one particular hormone could stimulate a specific receptor, like a single key opening a single door. They then realised that the reality was not so simple and that non-hormonal molecules could also exploit the system. Acting like natural hormones, a whole range of man-made compounds, although different in form and structure, are capable of finding their way into the blood stream, contacting and penetrating a cell and binding with a receptor – like impostors manipulating the lock, opening the door and deceiving the receptor. Once bound to the receptor, the intruder can cause a variety of events: it can provoke a normal or abnormal hormonal response, or rather elect not to respond by blocking the receptor and thus preventing natural hormones from binding with the receptors.

The synthetic oestrogen ethinylœstradiol, used in contraceptive pills, is one such substance imitating the natural hormones capable of producing a normal hormonal response.

DDT and its metabolite DDD, or alkylphenols used as detergents, are among the chemical compounds provoking an abnormal hormonal response. In both sexes, these substances can produce an oestrogenic response, but at the wrong moment or in unforeseen proportions. Such behaviour can cause feminine characteristics to grow in males, cause deformities in offspring, and endanger reproduction and the ultimate survival of a species.

Certain disruptors adopt an antagonistic attitude, blocking the receptor and preventing it from responding to a signal from a natural hormone. Chlordecone and DDD are for instance capable of blocking progesterone receptors, impairing the capability of sperm cells to fertilise the ovum. Administered to rats during gestation, the fungicide vinclozoline caused anomalies in the male reproductive system. Among the substances capable of blocking the hormonal receptors, we find an anti-oestrogenic drug, tamoxifen, used in the treatment of certain forms of breast cancer.

2.2.2. At transporter level

Certain endocrine disruptors interfere with the transport of a hormone to its receptor by binding with the proteins used for conveying steroid and thyroid hormones. Either the disruptor ejects the natural hormone, preventing it from joining its receptor and provoking its elimination via the liver or the kidneys, or, by attaching itself to the transporter protein, it modifies the latter, destroying its ability to bind with other molecules. Another possibility is for the disruptor to modify the speed at which the transport protein releases the hormone at the level of the target cell. Pentachlorophenol (PCP), an organochlorine compound used as a herbicide and pesticide, significantly slows down the binding process between testosterone and its receptors. Several chemical substances, in particular phenols and phthalates, compete with oestradiol and testosterone to bind the transport proteins of steroid and sexual hormones.

In all cases, the consequences are the same: too few hormones reach the target cell. The body senses a deficiency and the hormone-producing gland starts to produce increasing amounts of a hormone which never reaches the target cell it is designed for. For instance, the thyroid gland compensates for the destruction of thyroid hormones by producing excessive amounts, putting the organism at risk of developing a goitre. This was the case with the trout and salmon exposed to PCB pollution in the Great Lakes in the 1970s and 1980s. Lab experiments showed that rats exposed to PCBs developed the same symptoms.

2.2.3. Endangering hormonal balance

The mechanisms and workings upon which hormonal balance depends are fragile. Certain specialised enzymes maintain the balance of steroid and thyroid hormones through contributing to the natural production and degradation of hormones, facilitating their elimination. They are also capable of destroying alien substances, many of which are potentially toxic. Any interference with the action of these enzymes through endocrine disruption can make toxic a substance that up to then had been without effect. Certain PCBs can thus be transformed to compete with the proteins transporting thyroid hormones, thereby dangerously destabilising the balance of this hormone in the body, leading to either its over- or underproduction. Excessive levels of thyroid hormones cause irritability, while deficiencies cause apathy and weight gain.

2.3. The effects of endocrine disruptors on humans

Initial research into the effects of chemical substances on hormonal action focused on the reproductive system.

2.3.1. Men

Development of the male reproductive system is regulated by sexual hormones, for the most part androgens. It is becoming increasingly evident that chemical substances disrupting the endocrine system, and in particular those with an anti-androgenic effect, play a key role in the disorders affecting the development and maintenance of men's health.

Lower sperm counts

Alarming us to the drop in sperm quality, the data from Elisabeth Carlsen's study (see Chapter 1) has since been re-examined by other scientists. In the United States, sperm counts declined at a rate of 1.5% a year between 1938 and 1988, while in Europe they dropped at a rate of 3.5% a year between 1971 and 1990. In France, a 2012 study covering more than 26,000 men revealed a decline in sperm quality between 1989 and 2005. Such decline in sperm quality makes it impossible to conceive children or at least delays it.

Other studies conducted in various parts of the world have come up with diverging results. Several indicate time variations in the decline of sperm quality, at least in certain regions, while stressing that this is not an overall phenomenon.

Genetic or ethnic factors have been put forward for explaining these marked geographical differences. Environmental factors have also been blamed.

Investigations in the early 2000s showed that sperm quality varied greatly from one state to another in the United States. Further studies showed that sperm quality was linked to the level of contamination by pesticides used in agriculture.

The relationship between declining sperm quality and contamination through PCBs, DDT and dioxin has been observed in several countries.

Imbalance in the sex ratio to the disadvantage of boys

The sex ratio is measured through dividing the number of male births by the number of female births. The "natural" sex ratio is in the order of 1.05, i.e. 105 male births for every 100 female births. This can also be expressed as a population having a male proportion of 0.515. Deemed stable over time, the sex ratio declined in several European countries between 1970 and 1990. An analysis of birth statistics in Japan (1970-1999) and the United States (1970-2002) revealed a 127,000 deficit in male births in Japan, and a 135,000 deficit in the white US population. The proportion of male foetal deaths also increased during the same period in the two countries. The study's authors raised the question of the role played by endocrine disruptors in this evolution of the sex ratio in industrialised countries.

A deficit of boys has been observed in the offspring of workers exposed to DBCP in the United States, in workers exposed to pesticides in the Netherlands, and in Russian workers involved in the production of the herbicide 2,4,5,-trichlorophenol (or 2,4,5 T).

In the aftermath of the Seveso accident, the number of female births surpassed that of male births among the population most exposed to the dioxin. The effect persisted over time, especially among men exposed before the age of 19. Among these fathers, the number

The Seveso dioxin footprint

At midday on 9 July 1976, a red cloud escaped from the chimney of the ICMESA chemical plant located close to the town of Seveso, 25km north of Milan, after a safety disc in a reactor producing trichlorophenol (used in the manufacture of herbicides and antiseptics) broke. The leak lasted one hour. The toxic cloud settled over several hundred hectares of land, burning vegetation and affecting birds and farm animals, many of which died in the following days. Humans intoxicated by the chemical cloud suffered from headaches, nausea and eye irritation. Several children were hospitalised for burns on exposed parts of their bodies.

The ICMESA plant belonged to Givaudan, at that time a subsidiary of Hoffmann-La-Roche. Ten days later, the company announced that the toxic cloud had contained 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), since known as Seveso dioxin. The massive concern shown by the population was justified by the fact that TCDD was highly toxic and had proved to be carcinogenic in animal studies. Its effects on humans are little known, especially in the case of environmental exposure*.

Monitoring of the contaminated Seveso population showed that men exposed in boyhood (at the age of 1-9) had lower sperm counts and lower sperm mobility in adulthood. The opposite effect was registered when exposure took place between 10 and 17. Exposure in these two age brackets led to long-term hormonal disruptions.

The results of the Seveso catastrophe suggest that the same substance may act in opposite ways depending on a person's age at exposure, and can brand its victims for life. These disruptions appeared at exposure levels comparable to the dioxin levels observed in industrialised countries in the 1970s and 1980s. This could partially explain the decline in sperm quality observed in young men in industrialised countries.

Published in 2011, a second study monitoring people affected by the Seveso accident looked at the effects of prenatal TCDD exposure on adult sperm quality. It sought to distinguish between the effects of solely *in utero* exposure and those of cumulative exposure *in utero* and during breastfeeding.

This second study analysed the sperm of 39 men aged 18–26, whose mothers had lived in the area most polluted by TCDD in 1976. 21 had been breastfed, while 18 had been fed with powdered milk. The results were compared with the data of other men of the same age and socio-economic status (the case control cohort), but whose mothers had not lived in the areas contaminated by the TCDD.

50% lower sperm counts were observed in the exposed breastfed sons compared to the case control cohort. The same gap was observed among the exposed children between those breastfed and those fed with powdered milk. No difference was found between the latter and the case control cohort.

These studies back the hypothesis of a link between dioxin and the decline in sperm quality in several industrialised countries in young men born in the 1970s and 1980s and whose mothers were born in the 1950s and 1960s, the period with the highest level of pollution by dioxins and equivalent substances.

Since the late 1990s, dioxin contamination in women aged 20–40 has decreased greatly in Europe and the United States. Concern is now focused on high-growth regions where widespread environmental contamination by endocrine disruptors such as dioxins and equivalent substances has been registered.

* In 1997, the International Agency for Research on Cancer (IARC) classified 2,3,7,8-TCDD as a Group 1 substance (carcinogenic to humans).

of girls born was significantly higher than that of boys, with a sex ratio of just 0.380. According to a 2015 US study, a child's sex can be influenced by its parent's exposure to bisphenol A (BPA) and to phthalates. In fathers, contamination by phthalates was linked to a very high number of female births, while in mothers it was linked to a very high number of male births.

Deformities of male genitalia

Much scientific literature is dedicated to deformities of male genitalia following exposure to oestrogenic or anti-androgenic substances during the critical phases of an embryo's development. The former can cause a reduction in testicle size, as well as an increase in the volume of the prostate gland. The latter are responsible for a decrease in anogenital distance (a sign of feminisation) and hypospadias.

Several reports have highlighted an increase over time in the incidence of deformities of male genitalia in human beings, in particular cryptorchidism and hypospadias (see Box).

Deformities of male genitalia

Cryptorchidism refers to the absence of one or both testicles in the scrotum. Epidemiological studies conducted in environments greatly exposed to pesticides have shown a heightened incidence of deformed male genitalia and cryptorchidism. A Danish study (1997-2001) highlighted a relationship between the rate of polybrominated diphenyl ethers (PBDE) in a mother's milk and cryptorchidism.¹¹

A case-control study, conducted between 2002 and 2005 in two maternity hospitals in southern France, identified 15 compounds known for their anti-androgenic and/or oestrogenic effects in the milk of breastfeeding mothers. All the samples of breast milk tested were contaminated, in particular by a "cocktail" of PCBs, DDE (a DDT metabolite), phthalates and hexachlorobenzene (HCB). Concentrations of this cocktail were higher in the cases of cryptorchidism. The risk of cryptorchidism was 2.5 times higher among the children exposed to PCBs *in utero* than in those least exposed. The results of this study point in the same direction as comparable studies conducted in Spain and Scandinavia.

Since 1994, the US National Cancer Institute has been tracking all cohorts of men and women exposed to DES *in utero*. A 2009 publication pointed to a 2 times higher risk of cryptorchidism and a 2.5 times higher risk of testicular pathologies (inflammation and infection) in those exposed. When exposure to DES started

before the eleventh week of pregnancy, the risk went up to 3 times higher.

In the early 2010s, a Danish study and a Dutch study observed a relationship between mothers taking paracetamol (a much-used painkiller) at the beginning of pregnancy and an increase in the risk of giving birth to a boy with cryptorchidism.

Hypospadias is a deformity where the opening of the urethra is on the underside of the penis rather than at its tip. An increase in the incidence of this deformity has been reported in Australia, Europe and the United States. This could however also be due to better reporting. Environmental causes have also been mentioned.

Between 2009 and 2014, a French team¹² compared 400 boys suffering from hypospadias (excluding cases of a genetic origin) with 300 others without any deformity. The risk of hypospadias was 3 times higher when the parents' work exposed them to endocrine disruptors present in paint, solvents, detergents and pesticides. Among the sectors most affected were, among mothers, cleaning work, hair and beauty salon work, and laboratory work; among fathers it was agricultural work.

Studies have shown a higher risk of hypospadias in the sons of women exposed to DES *in utero* (see Chapter 1). In this case, possible transgenerational effects via epigenetic mechanisms¹³ were also mentioned.

11. PBDEs are used a lot for fireproofing plastics and textiles. Some are regulated and/or in the process of being banned, while others are already banned.

12. Kalfa N. *et al.* (2015) Is hypospadias associated with prenatal exposure to endocrine disruptors? A French collaborative controlled study of a cohort of 300 consecutive children without genetic defect, *European Urology*, 68 (6), 1023-1030.

13. Epigenetics refers to the study of changes in the activity of genes capable of being transmitted during cell division, without modifying DNA. The mechanisms behind the intergenerational transmission of changes in gene activity are still unclear (Source: www.inserm.fr).

Testicular cancer

In the industrialised countries with cancer registers going back to the middle of the 20th century, a major rise in the incidence of testicular cancer has been observed. In Sweden, this increase was 2.4% a year between 1984 and 1993 and 1.4% between 1994 and 2003. According to data gathered in nine northern European countries, testicular cancer is the most frequent form of cancer among young men, with its incidence peaking between the ages of 25 and 34.

Variations in the incidence of testicular cancer between the countries give credit to the assumption that environmental factors have a role to play. According to several studies, though first-generation immigrants have a testicular cancer rate comparable to that of their countries of origin, their children have an incidence comparable to that of the country in which they were born and grew up.

Testicular cancer seems to have a prenatal origin. No chemical substance has yet been identified as causing it, as it is difficult to trace parental exposure 30 years later.

Prostate cancer

The prostate gland is a hormone-dependent structure. With increasing age, the increase in hormonal disorders is well-known as one of the factors contributing to the rise in prostate problems. Endocrine disruptors are capable of disrupting the functioning of the prostate gland in many ways, supporting the hypothesis of a link between the increase in the incidence of prostate cancer and exposure to such substances.

Prostate cancer is the form of cancer most often diagnosed among men in developed countries. In the United States, it is the second most common cause of death by cancer. One of every two American males older than 60 suffers from a benign prostatic hyperplasia. Several factors heightening the risk of prostate cancer have been identified: genetic, ethnic and dietary. Steroid hormones play a crucial role in triggering prostate cancer and in its development. Steroid hormone regulation disorders in the foetal stage would seem to be a predisposing factor. Looking at the population in general, a direct link between environmental endocrine disruptors and prostate cancer has not (yet) been established, though certain data points in this direction. The most convincing data comes from studies carried out in rural and industrial areas.

A US study conducted from 1993 to 1997, the Agricultural Health Study, looked at the relationship between 45 often used pesticides and the incidence of prostate cancer in a cohort of 55,000 people working with pesticides. A slightly higher (but statistically significant) risk of developing prostate cancer was established, compared to the population in general. The only substance for which a dose-response relationship¹⁴ was observed was methyl bromide, a fungicide.

Among users with an incidence of prostate cancer in their families, an increased risk was correlated with several substances, suggesting an interaction between the environment and genetics. Four of these substances are thiophosphates. Though these substances do not show any oestrogenic and anti-androgenic properties, they are capable of inhibiting certain enzymes, thereby interfering with the hormonal balance and contributing to an increased risk of prostate cancer.

14. The dose-response relationship is the relationship between exposure to a toxic substance and the number of persons showing a given response; generally speaking, the proportion of persons affected by a given dose increases when the dose is raised (Source: Commission des normes, de l'équité, de la santé et de la sécurité au travail, www.cnesst.gouv.qc.ca).

The oestrogenic and anti-androgenic properties (see p. 9-10) of PCBs and their ability to accumulate in the human body over time make them potential disruptors of the prostate gland. A study of Swedish men suffering from prostate cancer showed a significant link to PCBs in the most contaminated quartile compared to a case-control group. A 2006 US study of more than 14,000 workers producing electric transformers and potentially exposed to PCBs showed a major correlation between the cumulative exposure dose and death from prostate cancer. This correlation had also been observed previously in groups of workers in the electricity sector.

The use of chlordecone as an insecticide for more than 30 years in the French Antilles caused a rise in the incidence of prostate cancer among the population and exposed workers (see Chapter 1).

2.3.2. Women

Though the effects of DES were first observed in girls exposed *in utero*, research into the environmental causes of these afflictions of the female reproductive system didn't start until quite late. Due to the lack of studies, the role of endocrine disruptors in the occurrence of several female diseases is as yet little documented.

Early puberty

In humans, there are wide variations in the age at which puberty sets in. These are not solely explained by genetic factors. In girls, the age of puberty dropped in the second half of the 20th century in the United States and several other industrialised countries, with breasts appearing on average between 9 and 11, and girls having their first periods between 12 and 13.5. In developing countries, the age at which a girl gets her first period is 13–16. For the specialists, this variation is an indicator of how environmental factors influence the age at which puberty sets in.

The development of secondary sexual characteristics before the age of 8 for girls and 9 for boys is a criterion used in diagnosing early puberty, with girls affected more than boys.

A Belgian team looked at the high proportion of immigrant children (28%) in a series of children showing signs of early puberty. The blood dosage of eight organochlorine pesticides revealed the presence of DDE, a DDT metabolite¹⁵, in the immigrant children and its quasi-presence in the Belgian children.

In vitro and *in vivo* tests on rats¹⁶ conducted at a later date revealed a complex mechanism of endocrine disruption due both to the children's exposure to DDT and DDE in their country of origin and to the end of their exposure after arriving in Belgium.

In the United States, several chemical substances found in household or body-care products have been associated with early puberty. By contrast, exposure to lead is associated with late puberty.

A number of studies conducted on animals have shown that exposure to synthetic and natural oestrogens during embryonic and neonatal periods can accelerate puberty.

15. A metabolite is what results from transforming a chemical substance in a cell, tissue or blood.

16. Krstevska-Konstantinova M. *et al.* (2001) Sexual precocity after immigration from developing countries to Belgium: evidence of previous exposure to organochlorine pesticides, *Human Reproduction*, 16 (5), 1020-1026.

Breast cancer

In the last decades of the 20th century, the incidence of breast cancer increased greatly throughout the world, though with geographical variations. Even in countries with a low incidence, it is the top-ranked form of female cancer. In the industrialised countries, some 10% of all women can expect to develop breast cancer during their lives.

The development and evolution of the mammary gland during life are today well known. The most important transformation phases (embryonic development, pre-puberty and pregnancy) are the ones in which ovarian and pituitary hormones play a key role. They are also periods of heightened susceptibility and vulnerability. The known factors indicating greater risk of breast cancer (age at one's first period, first pregnancy, menopause, etc.) are associated with exposure to ovarian hormones over the course of life.

The influence of endocrine disruptors on the occurrence of breast cancer has been highlighted in several studies.

Studies published in 2006 and 2007 revealed that the risk doubles after reaching the age of 40, and triples after reaching 50 for women exposed to DES.

A 1993 study reported a positive link between DDE, the main DDT metabolite, and the risk of developing breast cancer. Other studies did not reveal any such risk. One explanation could be that, at the moment the disease occurs, the presence of DDT or other carcinogenic substances is no longer detectable.

To avoid this pitfall, a study conducted in 2007 in the United States measured the DDT exposure of the enrolled young women from 1959 to 1967 (the years in which DDT usage peaked) in a series of studies on reproductive health (the Child Health and Development Study). The study showed an increase in the risk of developing breast cancer or of dying from it before the age of 50 among women exposed to DDT before the age of 14.

Continuing their work, the study authors looked at the risk of developing breast cancer in relation to *in utero* exposure to DDT among 9,300 women whose mothers had been enrolled in the programme. Published in 2015, the results show that, in 25% of the women whose mothers were most exposed to DDT, the risk of developing breast cancer was 3.7 times higher.¹⁷ In the view of the study's author, these results need to be taken into account in assessing the use of DDT in countries in which it is still used, such as India or South Africa.

Bisphenol A (BPA) is a chemical substance produced in large amounts and used in the production of many things in daily use (see Chapter 3). The fact that bisphenol A is present in the urine of nearly the whole population of the industrialised world, and in higher proportions in children and adolescents, has led to a number of experiments being conducted on animals. In a study of rats, 33% of animals exposed to 250 µg of BPA per kilo of body weight between the 9th day of pregnancy and birth developed cancer of the mammary gland in adulthood. No cancer developed in non-exposed animals.

DES, DDT and BPA are not the only chemical substances with hormonal action involved in the increased risk of developing breast cancer. According to a 2015 report of a philanthropic organisation, the Breast Cancer Fund, other chemical substances are also under suspicion (solvents, pesticides, PCBs), as are circadian rhythm disorders related to night work.

17. Cohn B.A. *et al.* (2007) DDT and breast cancer in young women: new data on the significance of age at exposure, *Environmental Health Perspectives*, 115 (10), 1406-1414; Cohn B.A. *et al.* (2015) DDT exposure in utero and breast cancer, *Journal of Clinical Endocrinology and Metabolism*, 100 (8), 2865-2872.

Impact on fertility and fecundity

In the industrialised world, a growing number of couples are finding it difficult to have children. In Denmark, 8% of pregnancies leading to the birth of a child are now achieved through assisted reproductive technology. Low sperm quality is seen as a contributory factor, with 20–40% of young Danish men not having an optimal sperm count. However, young men are not the only ones with problems; reproductive disorders in young women are contributing just as much to the decrease in fecundity, though the reasons are less well known.

The difficulties encountered by young couples can be partly explained by the higher age at which they decide to start a family. But this sociological reality is not enough to explain the infertility encountered in young women under 25.

Specialists have established a link between the fertility problems of young women and their exposure to such substances as DES, cigarette smoke, atmospheric pollution, DDT, PBA or PCBs. Several studies of groups of female workers employed in industrial agriculture and workers exposed to pesticides have revealed a higher risk of infertility and difficulties in conceiving children related to the level of exposure. However, though a link to endocrine disruption is plausible, it has not yet been clearly established.

Other disorders

The reproductive system is not the only target of endocrine disruptors. Other functions are also targeted, including the thyroid function.

For several decades, thyroid-related diseases have been on the increase and now affect some two billion people worldwide. They affect children and adolescents in particular, though 6–10% of adults are also affected. Affecting women more, hypothyroidism is the disorder encountered most often. In the long term, it can lead to heart problems and diabetes. Genetic and also environmental factors can influence thyroid health. Observations of lab animals and wildlife show that endocrine disruptors could play a role in thyroid disorders. The link between PCBs, PBDEs, organochlorine pesticides and thyroid disorders in marine mammals, fish and birds has been established in several regions of the world: the Great Lakes in the United States, the Barents Sea and the bays of Tokyo and San Francisco.

Many chemical substances are capable of interfering with thyroid functions and acting on thyroid hormones. However, few of the substances have been tested for this. The most conclusive studies involve PCBs. These reduce the levels of thyroid hormones available in the body, with the potential of impacting brain development. In several studies, an inverse link between the degree of PCB contamination and levels of children's cognitive performance have been demonstrated. Similar to PCBs, certain phthalates can diminish the level of thyroid hormones present in the body. The WHO sees an urgent need to know more about the potentially high impact on populations and their considerable economic cost.

Endocrine disruptors are also used to explain the increase in behavioural disorders in children over the past twenty years, for instance the rise in autism and hyperactivity. Such an assumption is plausible, given the knowledge on the neurological and behavioural effects of exposure to lead, methylmercury¹⁸ and PCBs. A Canadian study has revealed behavioural disorders typical of autism in rats exposed *in utero* to a cocktail of phthalates

18. Mercury released into the environment by human activities changes, in water or in sediments, into methylmercury which is easily absorbed by the body. Methylmercury is toxic for the central human nervous system, particularly during exposure *in utero* or during early childhood (Source: Anses, www.anses.fr).

and bromine compounds used as flame retardants at levels similar to human exposure. Males were affected more than females.

Over the last thirty years, the prevalence of obesity and diabetes has increased. These diseases originate in endocrine disorders and are particularly sensitive to the action of endocrine disruptors present in the environment. Animal studies suggest that exposure to certain endocrine disruptors during gestation can influence the metabolism of cholesterol, leading to weight gain and type 2 diabetes.¹⁹ Several studies have reported excess weight following exposure to substances with oestrogenic action during gestation. The opposite effect is seen when adults are exposed to them. This all confirms the importance of the point in time at which the effects of the endocrine disruptors are assessed.

In human beings, *in utero* exposure to persistent organic pollutants (POPs) has been linked to excess weight during the first years of life. In adults, exposure to dioxin and POPs is linked to type 2 diabetes.

The hypothesis of “obesogenic” substances explaining the increased incidence of various metabolic diseases needs to be the subject of further research. A 2012 study underlines the possible role of endocrine disruptors, and especially BPA, in the human obesity epidemic observed over the last twenty years. This is based on observations of rodents where *in utero* exposure to levels of endocrine disruptors comparable to human exposure leads to changes in the control system needed to maintain normal weight throughout life.

The main function of the immune system is to provide protection against infectious agents. Oestrogen and androgen hormones, in addition to their reproductive role, are also involved in the way the immune system functions. It has been proved that the PCBs in the Baltic Sea have a harmful effect on the immune system of marine animals, reducing their immune defences and making them more vulnerable to infectious agents and to developing cancer.

In human beings, allergies, asthma, respiratory disorders and autoimmune diseases²⁰ of the thyroid could possibly be caused by exposure to endocrine disruptors.

2.4. Traditional toxicology put to the test

The results of the work conducted since the early 2000s on endocrine disruptors have led researchers to question the traditional toxicological approach.

2.4.1. Does the dose always make the poison?

According to traditional toxicology, the higher the dose of a substance is, the greater its effects are. This linear dose-response relationship is termed “monotonic” and dates back to Paracelsus, the Swiss doctor and alchemist who died in 1541 (“Everything is poison, there is poison in everything. Only the dose makes a thing not a poison”). All students of

19. Type 2 diabetes is the most common form of diabetes (90%). The disease is characterised by chronic hyperglycaemia, an excess of glucose (sugar) in the bloodstream. The disease generally affects adults older than 40 and is more likely to occur in overweight or obese people. For several years now, its incidence among increasingly young people has been growing (Source: Inserm).

20. Autoimmune diseases are the result of a malfunction of the immune system, leading to it attacking normal body constituents. This is for example the case with type 1 diabetes, multiple sclerosis or rheumatoid arthritis (Source: Inserm).

toxicology learn that sugar, salt and even water can be poisonous. Everything is dependent on the dose.

University researchers working on endocrine disruptors are now questioning this principle. They have observed that certain natural hormones produce different responses dependent on the dose, and that responses can sometimes be more intense at lower doses. In such a case, the dose-response relationship does not follow a continuous monotonic pattern, but develops in a discontinuous, non-monotonic manner. A “non-monotonic dose-response relationship” has been reported for at least a dozen natural hormones and for more than 60 endocrine disruptors, including DDT and dioxin.

In establishing reference values for endocrine disruptors which would allow exposure norms at work and in daily life to be defined, university researchers found the “monotonic dose-response relationship” to be all the more inappropriate insofar as these substances could have opposite effects at low or high doses. For instance, they observed that low doses of certain chemical compounds could induce endocrine disruption, while a high dose could inhibit it.

2.4.2. The effects of low doses are not properly taken into account

The toxicological reference values for chemical substances are, both in Europe and the United States, determined on the basis of toxicity studies conducted on rodents. These studies follow OECD guidelines, the so-called “OECD Principles on Good Laboratory Practice (GLP)”, for assessing the toxicity of chemical substances.

“GLP studies” allow the calculation of the tolerable daily intake (TDI) and the presumably reliable toxicological values for human exposure. The implementation conditions and requirements for GLP studies make them very expensive, and they are thus generally financed by the producing companies.

In the view of many researchers, the tests carried out on animals do not reflect chronic human exposure and take no account of the effects of low doses of contaminants such as endocrine disruptors. Indeed, these tests normally involve exposing the animal to generally high doses for a short period. However, experiments on animals have demonstrated that several substances cause endocrine disruption at low or even very low doses.

In assessing the risks associated with the use of BPA, researchers criticised US and European health agencies for not taking sufficient account of research work that is independent from the industry. Researchers are saying that this work is being rejected because it does not meet the requirements of GLP studies, which are not designed to demonstrate oestrogenic effects observed at very low doses.

The industry’s influence on the agencies responsible for assessments and regulation is not to be neglected. According to the authors of an article written for the European Environmental Agency, of the 21 experts sitting on the panel of the European Food Safety Agency (EFSA) tasked with examining the BPA case before 2013, nine had links to industrial companies.

The authors of a list of BPA studies published before 2005 found that 90% of state-financed studies had reported harmful effects, while none of the industry-financed studies had come up with any.

Admitting that the effects of certain substances follow non-monotonic curves implies a need to develop new approaches to assessing the health risks linked to endocrine disruptors. Moreover, it also means that it is impossible to determine a reliable dosage level for certain substances.

At the end of 2011, the authors of a report for the European Commission's DG Environment acknowledged that the internationally accepted and validated methods for identifying endocrine disruptors only took account of a limited range of known effects. According to them, the defined threshold values were in many cases arbitrary and not scientifically justified.

Since then, several scientific conferences have been held by the EFSA on non-monotonic dose-response relationships. Critical examination of the data available has been entrusted to specialised institutions in several European countries. Other questions related to assessing risks remain on hold, including the concept of "noxiousness". Certain experts are of the opinion that, just because a response is observed, this does not mean that it is necessarily harmful. Instead, it may just be an organism's adaptive response, without any repercussion on health.

2.4.3. The point in time determines the poison

The scientific community now admits that the period of exposure is a parameter influencing a substance's toxicity. Exposure at the same dosage level can lead to greater or different effects during a susceptible period (*in utero*, postnatal, puberty) than during a different period, as was the case among those exposed to dioxin in Seveso (see p. 25). In animals, exposure to BPA during a susceptible period caused irreversible effects dependent on when exposure occurred. Moreover, certain effects only show up long after exposure, sometimes only in adulthood, i.e. the moment of exposure is not necessarily the moment when the effect is detected.

Criticism has also been levelled at the failure to take account of traditional toxicity studies conducted in periods of heightened susceptibility. For instance, the OECD guidelines for cancer studies do not provide for exposing animals *in utero* and then tracking them their whole lives. Fertility studies do not provide for monitoring the subsequent litters of mothers exposed *in utero*. Similarly, traditional toxicological tests do not include detailed examinations, such as looking for modifications to the prostate or mammary gland, or for neurological or behavioural anomalies.

The OECD has started developing and harmonising tests that take better account of susceptibility windows and of organs or tissues likely to be affected by endocrine disruption induced by chemical substances.

2.4.4. The cocktail effect

It is quite complicated to assess the impact of endocrine disruptors as we have not all been exposed in the same way to the hundreds of substances which may, at work or in our daily lives, impact our health. Specialists are of the opinion that we are on the wrong track if we just examine single substances likely to produce an endocrine effect. In their view, research needs to focus on "mixtures". In their daily lives, human beings are exposed to numerous substances which, when looked at separately, will not reach a measurable threshold effect, but which, when looked at together, can have a negative impact. This is what is called the "cocktail effect". For a long time, the effects of very low doses of endocrine disruptors causing oestrogenic action were refuted, because scientists thought they were too low to have an impact. We now realise that, considered together, these very low doses can indeed have an effect, sometimes even greater than that of the natural hormone. It is therefore crucial

to understand the mechanisms behind the cocktail effect and to evaluate the bad cocktails to which humans are exposed.

A team of French researchers carried out laboratory tests on the action of 40 chemical products, selected singly, then in pairs, etc. on PXR, a cell nucleus element responsible for detoxifying the organism. They observed, for instance, a cocktail effect between two molecules: ethinylœstradiol (the hormone found in contraceptive pills) and chlordane, a persistent pesticide banned in the early 1980s but still detected in the population. “Looked at separately, high concentrations of these two substances are needed to activate PXR. However, when mixed together, they activate the receptor at concentrations 10–100 times lower”, the researchers told the French newspaper *Le Monde* in October 2015²¹. In the view of the French researchers, the work has only just begun; 48 hormonal receptors have been identified in the cell nucleus and there are more than 150,000 chemical substances present in the environment.

Read more

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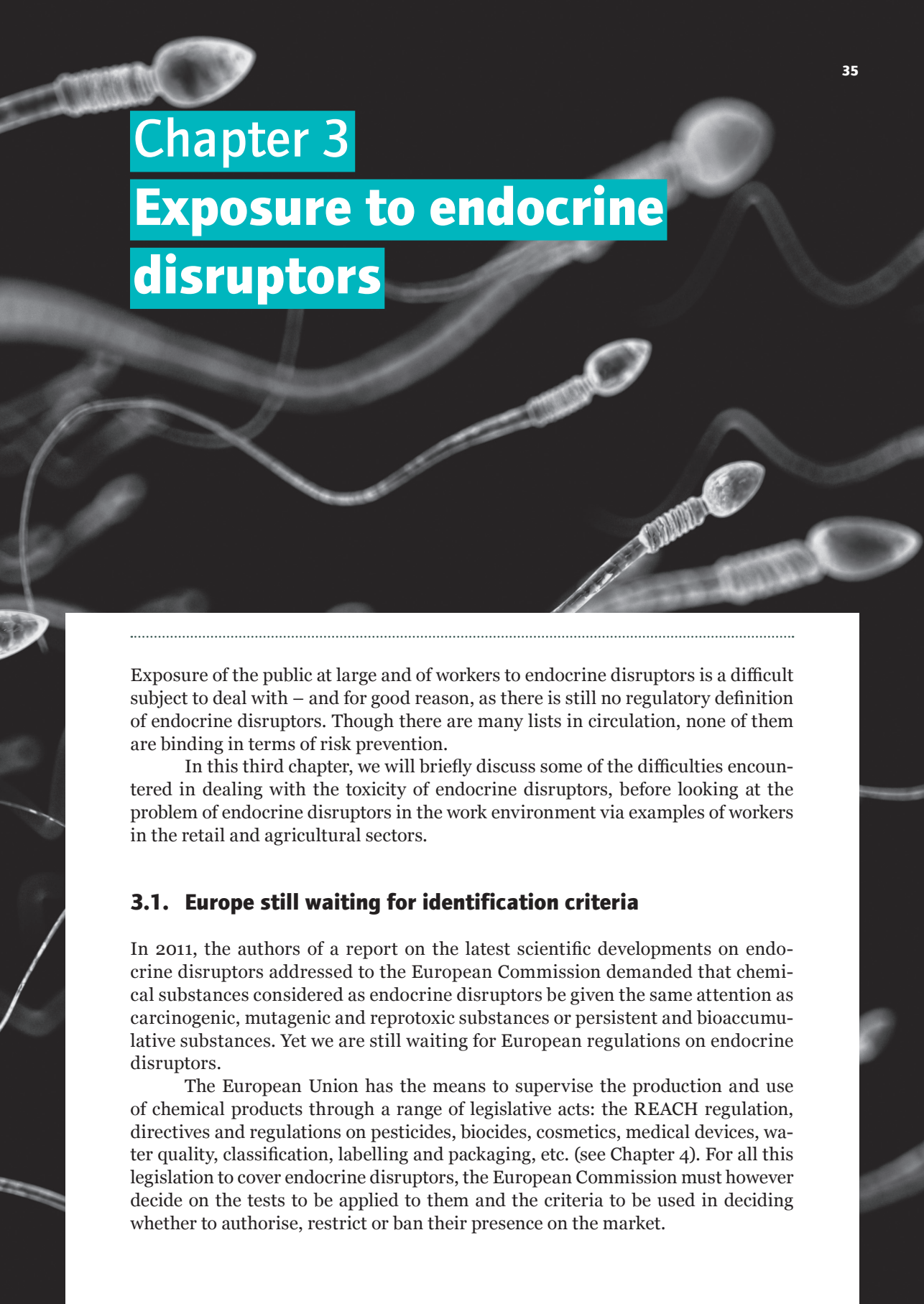
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21. Des enfants qui naissent “prépollués” (Children “pre-polluted” at birth), *Le Monde*, 1 October 2015.

A background image showing several sperm cells in motion, with their heads and long, wavy tails visible against a dark background.

Chapter 3

Exposure to endocrine disruptors

Exposure of the public at large and of workers to endocrine disruptors is a difficult subject to deal with – and for good reason, as there is still no regulatory definition of endocrine disruptors. Though there are many lists in circulation, none of them are binding in terms of risk prevention.

In this third chapter, we will briefly discuss some of the difficulties encountered in dealing with the toxicity of endocrine disruptors, before looking at the problem of endocrine disruptors in the work environment via examples of workers in the retail and agricultural sectors.

3.1. Europe still waiting for identification criteria

In 2011, the authors of a report on the latest scientific developments on endocrine disruptors addressed to the European Commission demanded that chemical substances considered as endocrine disruptors be given the same attention as carcinogenic, mutagenic and reprotoxic substances or persistent and bioaccumulative substances. Yet we are still waiting for European regulations on endocrine disruptors.

The European Union has the means to supervise the production and use of chemical products through a range of legislative acts: the REACH regulation, directives and regulations on pesticides, biocides, cosmetics, medical devices, water quality, classification, labelling and packaging, etc. (see Chapter 4). For all this legislation to cover endocrine disruptors, the European Commission must however decide on the tests to be applied to them and the criteria to be used in deciding whether to authorise, restrict or ban their presence on the market.

In 2012, the Commission undertook, in the context of revising its strategy on endocrine disruptors and adopting the Regulation on Biocidal Products²², to define the scientific criteria for identifying substances with endocrine disrupting properties by 13 December 2013 at the latest.

It did not fulfil its commitments until June 2016, under pressure from certain Member States wanting to better protect their populations from this major health risk (for more details, see Chapter 5).

3.2. The costs of endocrine disruptors

An international team of university researchers conducted a quantitative assessment of the costs associated with the exposure of the EU population to endocrine disruptors. They focused on five health-related problem areas: neurodevelopmental pathologies, obesity and diabetes, changes in human reproductive capabilities, breast cancer and female reproduction disorders. In March 2015, the experts publicised their estimate for the first three problem areas²³, coming up with a figure of €157 billion a year, equivalent to 1.23% of EU GDP. The estimate takes account of both direct costs (hospitalisation, medical costs, drugs) and indirect costs related to disease-induced productivity losses.

The authors say that they deliberately underestimated the economic impact of endocrine disruptors by only basing their figures on highly-proven data covering just a small proportion of diseases related to these substances.

Apart from the costs associated with exposure to endocrine disruptors, the diseases and suffering they cause, the most worrying data concerns the loss of IQ points (some 14 million) and the cases of mental retardation (more than 62,000) attributed to prenatal exposure to polybrominated diphenyl ethers (PBDEs) and organophosphates.

3.3. The many lists of endocrine disruptors

Several lists of potential endocrine disruptors have been compiled over the last few years by governmental agencies and NGOs.

3.3.1. 109 substances under surveillance in the United States

In 1996, the US Environmental Protection Agency (EPA) was tasked with implementing a programme for assessing chemical substances susceptible of causing endocrine disruption.

In 2009, it published an initial list of 67 pesticides. In 2010, a second list of 134 substances, made up of pesticides and other chemical substances considered as priorities in the context of drinking water regulations, was submitted to public consultation. Following this, in 2013 the EPA published a list of 109 substances, the assessment of which was given priority. This list is made up of pesticides, solvents, plasticizers, body-care

²². Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products (JO L 167, p. 1).

²³. Trasande L. *et al.* (2015) Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European Union, *Journal of Clinical Endocrinology and Metabolism*, 100 (4), 1245-1255.

products and drugs. It includes such substances as benzene, styrene, tetrachlorethylene, polychlorinated biphenyls (PCBs), ethylene glycol, etc.

In the United States, not one of the substances listed has yet become the subject of regulation on the sole basis of its endocrine disruption activity.

3.3.2. The European list

In 1999, on adopting an EU strategy on endocrine disruptors, the European Commission decided to compile a priority list of substances likely to produce such effects. This work was done in several steps. The substances selected were classified into three categories, by descending order of concern: category 1: at least one “*in vivo*” study of an animal providing proof of endocrine disruption; category 2: suspicion of such on the basis of “*in vitro*” lab data; category 3: non-proven or missing data.

Between 2000 and 2005, 194 substances from a list of chemical substances suspected of being endocrine disruptors were classified as category 1 substances and 126 as category 2 ones. The list contained a number of substances already banned or subject to restrictions under existing European legislation, though not necessarily for their endocrine effects. Others were not subject to any restrictions or were not listed in any existing legislation.

3.3.3. The TEDX list: 1000 “potential” endocrine disruptors

The Endocrine Disruption Exchange (TEDX)²⁴ is an organisation founded by Theo Colborn (see Chapter 1) for the purpose of preventing health and environmental problems caused by exposure, at low or very low doses, to chemical substances interfering with the development and functioning of the body. According to its sponsors, this database was developed because the protocols of traditional studies use high doses on fully developed individuals, and thus take no account of the effects chemical substances may have on organisms still in the development stage.

In 2015, some 1,000 potential endocrine disruptors belonged to the TEDX list. The organisation uses the term “potential” because, in its view, nobody up till now has defined how much scientific proof is needed for a chemical substance to be considered an endocrine disruptor. Each new entry in the list is justified by at least one verified and referenced citation. The TEDX List, accessible online, classifies the substances by wide categories of use.

3.3.4. The SIN list and the trade union list

The large number of lists of proven or potential endocrine disruptors and the size of certain lists can be overwhelming and encourage complacency. This is why the NGO ChemSec decided to focus on the substances “of greatest concern”. In 2008, the NGO drew up a list of substances of major concern in line with the criteria defined by the EU REACH regulation, the so-called “SIN List” (short for “Substitute it Now”). The list covers substances acknowledged as being carcinogenic, mutagenic and reprotoxic (CMR), substances considered as

24. www.endocrinedisruption.org

persistent, bioaccumulative and toxic, and substances considered as of great or very great concern, but not included in the previous two categories.

ChemSec did not wait for the European Commission's criteria (see p. 62), instead relying on available scientific publications to enter endocrine disruptors into its list. In 2015, the SIN List contained 57 substances with proven endocrine disrupting activity. The NGO considers that 32 of them require immediate action. For each one, the list contains the form of action and the main uses.

In 2009, the European trade union movement also published its own list of extremely worrying substances, calling for their priority inclusion in the list of substances subject to REACH authorisation. This list of 568 substances widely used in workplaces includes 54 proven or suspected endocrine disruptors²⁵.

3.4. Bisphenol A (BPA)

Bisphenol A (BPA) was first synthesised at the end of the 19th century. Its oestrogenic properties were discovered in 1936 in tests on animals, but it wasn't until the late 1950s that this chemical was produced on a large scale. The plastics industry uses it in the manufacture of many artefacts of everyday life.

It was only by chance that the risk associated with BPA was “rediscovered”. In 1993, a group of endocrinologists from Stanford University in the United States were intrigued by the fact that a substance with hitherto unknown oestrogenic properties was contaminating their tests. They finally identified it as the BPA in the polycarbonate boxes used for cell cultures.

This product has now been added to the list of potential endocrine disruptors and has become the subject of many debates in scientific circles. It is steadily becoming the most striking example of the action of an endocrine disruptor.

3.4.1. A much-used chemical substance

Two-thirds of the global production of BPA (some four million tonnes) are used in the manufacture of polycarbonate products including reusable containers (baby bottles, beverage bottles), food packaging, electrical and electronic components, building materials, household appliances, audio and video media, and vehicle components. Polycarbonates are also used to produce medical equipment (blood oxygenators, dialysis machines, incubators, respirators, etc.), optical equipment (contact lenses, glasses, frames) and some composites for dental care.

The second use of BPA is in the production of epoxy resins. Epoxy resins are used in many products to protect them against corrosion and give them thermal stability: protective layers, insulating coatings, the lining of containers, cans and tins, household appliances, composite materials, electrical and electronic applications (boards and printed circuits), paints, printing inks, adhesives, etc.

BPA is also used in the manufacture of flame retardants, able to prevent plastics and textiles catching fire. These substances are found in computers, televisions, dishwashers, etc.

²⁵. The trade union list can be downloaded from: www.etui.org/en/Publications2/Guides

They are also to be found in certain types of thermal paper used for labels, badges, cash register receipts, etc., as well as in hydraulic fluids and cosmetics. BPA was also used in the production of PVC for water pipes; though, according to the manufacturers, this was stopped in 2005.

3.4.2. BPA in the environment and in food

Throughout the lifecycle – from production to final disposal – of the materials of which it is one of the components, BPA is liable to be released into the environment, ending up in the air, water, soil and dust. For instance, between 1999 and 2000, BPA was detected in more than 40% of 139 rivers in 30 US states.

Traces of BPA have been measured in drinking water samples in Germany and Canada. The quantity of BPA released into drinking water that passes through pipes containing BPA, especially in the case of repairs using epoxy resins, rises in line with water temperature.

Via food packaging, BPA contaminates the food chain. French and European data has shown that the migration of this substance from packaging to food is dependent on the packaging categories and the food product in question. The highest levels measured were for tinned meat.

Contamination of children is greater than that of adults, with babies particularly affected. According to a report published jointly by the FAO and WHO, babies under six months who have been fed with infant formula via bottles made of polycarbonate have a 6–10 times higher exposure to BPA than breastfed babies. This contamination of babies has led to BPA being prohibited in baby bottles throughout Europe.

3.4.3. Exposure at work

Workers are at risk of exposure through inhalation and skin contact, whether during the production of BPA itself or in the manufacture of products containing BPA.

Previously considered as negligible, exposure via the skin has gained greater attention since 2010 after a US study reported that the BPA contamination of people working in the retail sector was higher than that of other workers and that of the public at large. For instance, each cash register receipt can contain up to 2% BPA.

A Swiss study estimated that handling thermal paper for a period of 10 hours a day can cause skin contamination. The study also showed that washing one's hands did not fully get rid of the BPA. Another study calculated that 10% of the BPA was absorbed by the skin. Later studies even suggest that this rate of absorption could be much higher. A study conducted in 2015 showed that the BPA absorbed while handling cash register receipts was measurable in cashiers' blood and urine two hours after finishing work.

Though exposure through inhaling BPA-contaminated dust has as yet hardly been looked at, an analysis of the dust in 260 Canadian homes detected the presence of BPA in 99% of them. A Belgian study looking at 18 randomly selected homes and two offices showed that household dust often contained more than 15 milligrams of BPA per kilogram of dust. This amount was five times higher in the dust collected in the offices. According to the study's authors, the use of electrical and electronic equipment, as well as the materials used to make office furniture, could account for the high level of BPA measured in the dust of the two offices.

3.4.4. Contrasting assessments

Since the early 2000s, BPA has been the subject of several (reproductive) health risk assessments conducted at the request of various health agencies in Europe and North America.

In 1988, the US Environmental Protection Agency (EPA) established a BPA reference dose for chronic oral exposure of 50 micrograms per kg of body weight per day.

In the context of a re-assessment of BPA in 2008, US experts from the Center for the Evaluation of Risks to Human Reproduction, expressed moderate concern for its effects on the prostate gland, the brain and behaviour in the case of prenatal and childhood exposure to the levels of BPA observed in the population; minimal concern for the effects of perinatal and childhood exposure on the mammary gland and an earlier age for puberty; and negligible concern for exposure in adults (whether male or female) and for pregnancy.

In the European Union, the regulation on the classification, packaging and labelling of chemicals and their mixtures, which came into force in January 2009, classified BPA as “reproductive toxicant category 2”, i.e. a substance that “may impair fertility” or “may cause harm to the unborn child”.

The European Food Safety Agency (EFSA) completed its full risk assessment of BPA in 2006 and set a Tolerable Daily Intake (TDI) of 0.05 mg/kg body weight/day for this substance, a rate identical to the US one. Invited to re-examine this intake value, the EFSA confirmed in 2010 that this amount of BPA could “be ingested daily over a lifetime without appreciable risk”, while also finding that “intakes of BPA through food and drink, for adults, infants and children ... were all well below the TDI”.

3.4.5. France calls for tougher measures

In December 2012, the French parliament adopted a law suspending the production, import, export and marketing of food packaging containing BPA. This legislation entered into force on 1st January 2013 for containers of food for children under three years old. Two years later it was extended to cover all food containers²⁶.

The conclusions of the French environmental agency Anses (*Agence française de sécurité sanitaire, de l'alimentation, de l'environnement et du travail*) confirm the health risks associated with BPA, in particular for pregnant women and their offspring. The effects identified by Anses relate especially to modifications in the structure of the mammary gland in the unborn child, with the potential to promote the development of tumours in adulthood.

Alongside food exposure, which accounts for more than 80% of the population's exposure, Anses also highlights other forms of exposure, in particular those associated with handling thermal paper (cash register receipts, credit card receipts, etc.) in an occupational capacity. The French agency considered that it could lead to a risk of other health effects for the unborn child, concerning the brain and behaviour, metabolism and obesity or even the female reproductive system.

Anses recommends reducing the exposure of the whole population, and especially pregnant women, and is calling on the European Chemicals Agency (ECHA) to review the classification of BPA, and on the European Food Safety Authority (EFSA) to lower the admissible daily intake.

26. In September 2015, the French Constitutional Council partially censured the law of 2012, ruling that the manufacturing in France and export of food containers containing BPA should be maintained.

France also submitted to the ECHA a proposal for banning BPA in cash register receipts, as well as a proposal for re-evaluating the substance.

In March 2014, the ECHA's risk assessment committee came out in favour of the French proposal to reclassify BPA as a Category 1B (reproductive toxicant with adverse effects on sexual function and fertility or on development) substance, thereby obliging countries to introduce tougher prevention measures regarding the occupational use of BPA and to force its substitution.

In January 2015, the EFSA reduced the Tolerable Daily Intake (TDI) of BPA from 50 micrograms per kg of body weight to just 4 micrograms, considering that, at this level, it would not constitute a health risk. Taking all sources into account, it stated that the contamination of the population was "considerably lower than the danger level (i.e. the Tolerable Daily Intake (TDI)". This statement was strongly contested by the *Réseau Environnement Santé*, a French NGO very active in the field of endocrine disruptors. It questioned the EFSA's credibility, given that the latter had in the past underlined the harmlessness of BPA at doses twelve times higher.

In February 2016, in the context of the CLP Regulation, EU Member States voted in favour of classifying BPA as a Category 1B reproductive toxicant substance. This harmonised classification becomes obligatory throughout the European Union as of March 2018.

3.4.6. Unsafe substitutes

BPA is not the only substance with oestrogenic properties present in food packaging. A US study tested several hundred types of plastic food packaging, showing that nearly all of them could release substances with oestrogenic properties once they were exposed to boiling water, ultraviolet light or microwaves. Paradoxically, certain forms of packaging, while labelled as "BPA-free" (including baby bottles), release more oestrogenic substances than packaging containing BPA.

Research into BPA substitutes has highlighted the fact that bisphenol A and bisphenol F, two substances seen as potential substitutes or already used as replacements, have properties and effects comparable to those of bisphenol A and that they are thus no viable alternative. A French team which had already demonstrated BPA toxicity on human testicular cells and especially its effect on inhibiting the production of testosterone observed the same effect with bisphenols S and F.

In 2014, the US Environmental Protection Agency (EPA) analysed 19 possible alternatives for use in thermal paper, coming to the conclusion that none could be considered as a safe alternative to BPA. The majority of the substitutes presented risks classed as moderate to high for human health and the environment. The use of BPA in thermal paper is to be banned in the EU as of 2019.

3.5. The agri-food sector

Of all the occupational sectors confronted with endocrine disruptors, agriculture is the one in which the situation gives greatest cause for concern, given the use of pesticides at different stages. The threat covers pesticide production plants, as well as a whole range of professional users: farmers and agricultural workers; staff working in greenhouses, orchards and vegetable plots; gardeners; but also many other workers involved in the maintenance

of roads and railways, public spaces and amenity areas, in disinsectisation, wood preservation, the handling of treated wood, etc.

Pesticides are chemical substances used mainly to kill organisms considered as pests (animals, plants, fungi). They can be grouped by their main targets: herbicides, fungicides, insecticides, miticides, rodenticides, nematocides (against worms), etc. But they can also be classed by their usages: crops, green space maintenance, ornamental plants, roads, wood treatment, livestock, etc.

The generic term “pesticide” thus covers a wide range of substances with different physicochemical properties and mechanisms. This makes it difficult to characterise forms of occupational exposure, as does the permanent evolution of the number of substances since the 1950s, with new products hitting the market and others being banned.

Their form of presentation and type of packaging often depend on their use: soil treatment (sprayed by hand, tractor or plane), the treatment of storage facilities, etc. For workers, the form of usage has a great influence on the conditions of exposure and contamination.

The marketing of the large majority of agricultural pesticides in the EU is governed by Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market, which came into force on 14 June 2011. The use of several hundreds of pesticides and biocides is approved in Europe. Classified as biocides under European legislation, pesticides used outside agriculture (i.e. to protect humans, animals, materials and other articles from pests) are covered by a specific regulation that came into force in September 2013.

3.5.1. Millions of workers affected

Millions of workers throughout the world (5.6 million in agriculture and viticulture in France alone) use or have used pesticides, meaning that they are frequently exposed to contamination. The products can contaminate handlers, vehicles and storage facilities. The opening of containers for diluting substances and the filling of spreading/spraying equipment are phases that can generate high contamination levels through splashes, vapours or spills. For instance, a study conducted in agricultural areas showed that a large proportion of contamination occurred while preparing the mixtures before actually spreading/spraying them. In viticulture and orchards or in greenhouses, the spreading/spraying phase poses the greatest risk, as workers can be exposed for several hours during a single day.

Agricultural workers carry a “double burden”, being exposed both at work and, like the public at large, through food and air pollution. A study conducted in Europe analysed pesticide residues found in the hair of agricultural workers, identifying 33 different substances, including herbicides and fungicides. Some of them were substances which have since been banned, such as HCH (hexachlorohexane) or DDE (a DDT metabolite). The same products were found irrespective of the agricultural work currently being done, indicating long-term exposure to persistent organochlorine compounds and their widespread use. The families of agricultural workers are often confronted with very high levels of exposures, especially during periods when pesticides are being sprayed/spread on fields. Spraying involves the airborne suspension of the products and stretches to areas beyond the targeted surfaces. Workers’ clothing and shoes can also contaminate homes.

While the availability and use of pesticides are governed by regulations, this does not prevent the risk of them being present, even when protective clothing – gloves, overalls, masks, boots – is used. Such personal protective equipment (PPE) is meant to create

a barrier between the pesticide and the human body. However, several studies have shown that they do not always meet expectations.

For instance, a report issued in 2013 by the French health agency, Inserm (*Institut national de la santé et de la recherche médicale*) confirmed that protection of agricultural workers was in many cases ineffective. Workers in greenhouses are subject to high levels of skin exposure, even when wearing gloves. As regards wine-growing, practically identical exposure levels were measured, irrespective of whether or not workers wore an overall. Such observations have encouraged research into designing more effective protective equipment. In agriculture for instance, there are now tractors with cabins specifically designed to protect the driver during spraying. Nevertheless, in practice the cabins are rarely airtight and windscreens get blurred by the products sprayed, forcing the driver to open the cabin to keep the tractor on the right track. Filters are not always effective and do not get renewed very often.

Certain working conditions – high temperatures or humidity rates – are not conducive to wearing personal protective equipment. The contamination risks associated with entering treated facilities or coming into contact with soiled parts are often ignored by users.

The consequences for the health of agricultural workers and their families are serious, as all pesticides are per definition to a certain degree toxic because they are expressly designed to kill living organisms considered to be pests. They act chemically on the organs involved, affecting their vital functions or their reproduction. They disrupt nerve or hormone signalling, cellular respiration, cell division or protein synthesis, allowing “effective pest control”.

For human beings, several pesticides have turned out to be reprotoxic, to the detriment for instance of workers exposed to DBCP or chlordecone (see Chapter 1). However, the extent of their effects goes much further. The carcinogenic effects of certain pesticides have been proved in animal experiments, prompting the International Agency for Cancer Research (IARC) to assess and classify the carcinogenicity of several of them. The discovery of the hormonal properties of several pesticides has also prompted research into so-called hormone-dependent cancers.

3.5.2. Adult diseases

Since the 1980s, epidemiological studies based on observations of occupationally exposed cohorts have pointed to the involvement of pesticides in several diseases, especially cancer and neurological diseases. Research has drawn attention to the effects of even low levels of exposure during periods of increased sensitivity (*in utero* and early childhood).

Epidemiological data are being gathered via cohort studies and case-control studies which compare the number and causes of deaths in an exposed population relative to an unexposed one. However, it is very difficult to establish a retrospective link between a specific pesticide and a certain form of cancer, given the variety of products and uses with which a worker is confronted during his working life.

Though so-called “prospective cohort” studies are better suited to identifying the responsible agents, their results are only significant in the long term, i.e. requiring considerable investment over a long period of time. In such studies, a group of people recruited at a given point in time is tracked, taking into account various risk factors and targeting the related diseases. The Agricultural Health Study (AHS) represents the largest cohort of farm workers and pesticide users (more than 50,000) and their spouses (30,000). Set up in the US states of Iowa and North Carolina in 1993, the AHS is documenting the impact

of 50 pesticides (mainly insecticides and herbicides) used widely in these two agricultural states.

In France, a cohort study (the “Agrican cohort”) commenced in 2005. It involves 180,000 people belonging to the agricultural workers’ health fund MSA (*Mutualité sociale agricole*) in twelve French *départements* in mainland France.

Evaluations of the AHS cohort are published at regular intervals. In 2010, a study observed a 19% higher incidence of prostate cancer in farmers and a 28% higher one in occupational users of pesticides. This higher risk of prostate cancer was confirmed by a study which monitored 139,000 agricultural workers in California between 1988 and 2010, with a focus on those exposed to organochlorine and organophosphate pesticides and especially those with a history of prostate cancer in their families.

An interim report of the Agrican study published in 2014 showed an increased incidence of certain rare forms of cancer (lymphomas and myelomas) in the population studied. An increased incidence of lymphomas and myelomas has also been observed in other studies in Europe and the United States, especially among the AHS cohort, though without these diseases being related to pesticides in particular. By contrast, a link has been established between two organochlorine pesticides (chlordane and heptachlor) and leukaemia in the AHS cohort and in other studies.

Thyroid disorders have been observed in the AHS cohort and in several other studies. For instance, high levels of thyroid hormones have been measured in horticultural workers exposed to organophosphate pesticides.

3.5.3. Risks for the unborn children of greenhouse workers

In Denmark, some 9,000 women of child-bearing age were employed in Danish greenhouses in 2012. Many pesticides used in the production of vegetables, flowers and plants are neurotoxic and/or endocrine disruptors. Denmark applies measures for preventing health risks, and pregnant women are entitled to paid leave when it is not possible to offer them other, risk-free work.

Beginning in 1996, a prospective study was launched to measure the impact on children’s health of their mothers’ exposure right at the start of pregnancy, before being taken away from high-risk workplaces²⁷. The study revealed that the risk of exposure is mainly present when, after a pesticide has been sprayed, workers go back into the greenhouse to do potting or pruning. Around 20% of the women questioned stated having been in direct contact with pesticides, and more specifically with fungicides and growth retardants. More than one hundred different pesticides were involved (the majority non-persistent) and the women were susceptible to having been exposed in the first eight weeks of pregnancy, before being given a different function. The recommended prevention measures had been applied.

On examining the children at the age of three months, a higher incidence of cryptorchidism (non-descended testicles) was observed among the sons of exposed women compared to the overall population of Copenhagen. The study also came up with a higher proportion of small testicles and short penises, as well as a reduced rate of testosterone among the exposed small boys compared to their non-exposed counterparts. A number of

27. Andersen H.R. *et al.* (2008) Impaired reproductive development in sons of women occupationally exposed to pesticides during pregnancy, *Environmental Health Perspectives*, 116 (4), 566-572; Andersen H.R. *et al.* (2015) Occupational pesticide exposure in early pregnancy associated with sex-specific neurobehavioral deficits in the children at school age, *Neurotoxicology and Teratology*, 47, 1-9.

the children were re-examined between 6 and 11 years of age. Among exposed girls, early puberty and breast development were observed more frequently. An evaluation of neurological performance revealed lower performance levels with regard to language and execution speed among exposed children. The problem was more marked among girls than boys.

The authors of the 2015 study came to the conclusion that exposure to non-persistent pesticides before pregnancy was diagnosed, and thus before the prevention measures were taken, could affect the neurological development of unborn children. The effects observed in both girls and boys were in line with a neurotoxic effect on brain development right at the start of embryo formation. The authors are calling for tougher prevention measures, especially for young women.

A further Danish study conducted in the early 2000s and involving 1740 unionised women working in greenhouses showed an increase in the time taken to become pregnant among women exposed to sprayed pesticides.

Read more

Agrican (2014) Agriculture & cancer. <http://cancerspreventions.fr/wp-content/uploads/2014/12/AGRICAN.pdf>

Agricultural Health Study. <https://aghealth.nih.gov>

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Chapter 4

European legislation and endocrine disruptors

Endocrine disruptors are not regulated by just one piece of legislation in the European Union, but by a series of texts containing specific measures for this category of substances. For instance, we find provisions covering endocrine disruptors in the REACH Regulation, the Regulation on Plant Protection Products, the Biocidal Product Regulation, the Cosmetics Regulation and the Water Framework Directive. A proposal for amending the Medical Device Directive to cover endocrine disruptors is also being studied.

By contrast, there are no specific provisions for endocrine disruptors in the Regulation on the classification, labelling and packaging of substances and mixtures (CLP Regulation). Similarly, nothing is mentioned about endocrine disruptors in European legislation on medicines, food contact materials or toy safety.

Despite the extent of occupational exposure and its negative impact on exposed workers or their offspring, there are no specific provisions regarding endocrine disruptors in European legislation on safety and health at work. Insofar as these have been identified as Category 1A or 1B carcinogens or mutagens, the rules for preventing occupational cancers are to be applied. However, in all other cases (i.e. the large majority of endocrine disruptors), the relevant legislation is much less stringent and its application is greatly dependent on identifying other specific toxic effects causing endocrine disruption. There is thus a major legislative gap in the area of workplace prevention contributing to social health inequality.

In this chapter, we will look at each piece of European legislation covering endocrine disruptors, briefly explaining each one's scope, functioning and specific provisions for endocrine disruptors.

4.1. The REACH regulation

In force since June 2007, the REACH (Registration, Evaluation and Authorisation of Chemicals) Regulation²⁸ lays down provisions on the placing on the market and use of chemical substances in the European Economic Area. REACH makes it mandatory for manufacturers and importers of chemical products to prove, via a registration dossier, that the risks associated with the use of their substances can be properly controlled before they are marketed. Chemical substances produced in or imported to EU territory in quantities exceeding one tonne a year (some 30,000 substances) must be registered in the course of a period running up to 2018 with the European Chemicals Agency (ECHA) in Helsinki.

REACH also provides for “substances of very high concern” (SVHC) to be subjected to an authorisation procedure. Substances belonging to this category include: those with carcinogenic, mutagenic or reprotoxic (CMR) properties; persistent, bioaccumulative and toxic (PBT) substances; very persistent and very bioaccumulative (vPvB) substances; and substances which give rise to an equivalent level of concern (EQC), such as those with endocrine disrupting effects.

When substances are identified as being “of very high concern” and consequently listed in REACH Annex XIV, their manufacturers must apply for and obtain authorisation to continue using them. The aim of this long and costly authorisation procedure is to discourage the use of such dangerous substances and to encourage their substitution through safer alternatives.

SVHCs are identified by Member States in one of the ECHA committees and authorisations are granted on a case by case basis by the European Commission for a set period. The large majority of the 169 SVHCs listed up to now in the candidate list for authorisation (the step before being listed in Annex XIV) are CMR substances. A mere five substances are listed on account of their endocrine disruption effects²⁹ (Table 1). Just one of these five substances has as yet been included in Annex XIV, the Authorisation List containing 31 substances: DEHP³⁰, a substance belonging to the phthalates family, for which authorisation was requested for it to be used as a plasticiser in articles made from recycled PVC. The Commission recently granted authorisation following a long controversy due mainly to the fact that it is an endocrine disruptor.

Table 1 Endocrine disruptors identified by the REACH Regulation

Substance name	CAS No.	Date of inclusion in the Candidate List	Reasons
Bis (2-ethylhexyl)phthalate (DEHP)	117-81-7	28/10/2008	Repr 1B
		12/12/2014	PE
4-(1,1,3,3-tetramethylbutyl)phenol	140-66-9	19/12/2011	PE
4-Nonylphenol, branched and linear	-	19/12/2012	PE
4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated	-	19/12/2012	PE degradation
4-Nonylphenol, branched and linear, ethoxylated	-	20/06/2013	PE degradation

28. Regulation (EC) No 1907/2006.
29. <http://echa.europa.eu/en/candidate-list-table>
30. Diethylhexyl phthalate.

4.2. The Plant Protection Products Regulation

The placing on the market of plant protection products (commonly known as pesticides) is governed by a regulation which came into force in December 2009³¹. Pesticide products generally contain different components: one or more active substances protecting plants against pests (for instance fungi, insects or rodents) or diseases, and others aimed at facilitating or boosting the action of the active substances (co-formulants).

Pesticides may not be used or placed on the market without prior authorisation. A two-step system is applied. The first step takes place at European level, with the active substances being evaluated by Member State authorities under the coordination of the European Food Safety Authority (EFSA) and approved by the European Commission. They have to meet quality and safety criteria, proving that they are not a source of harm for humans (toxic for users and for food product consumers) and the environment. Approval of an active substance is granted for a specific timeframe (not exceeding 10 years) and is renewable.

More than 500 active substances currently have approval³², allowing them to be incorporated into a pesticide product. Links between a number of EFSA experts and pesticide manufacturers are a regular cause for concern³³.

The second step takes place at national level. Each Member State evaluates and authorises pesticide products (or preparations) containing the active substance(s) for its territory. A pesticide authorised in one Member State is not automatically authorised in all other EU Member States, though a system of mutual recognition is foreseen in Regulation 1107/2009 to facilitate this. Several tens of thousands of different pesticides are available on the European market.

One of the new principles introduced by the Regulation is the possibility to reject active substances on the basis of their intrinsic properties. This concept is referred to as “hazard-based cut-off criteria”. Annex 2 of the Regulation stipulates that certain substances (see Table 2) cannot be approved as active substances.

Table 2 Exclusion criteria for the approval of active substances (pesticides)

Human health	The environment*
1A & 1B carcinogens	PBT (persistent, bioaccumulable and toxic) substances
1A & 1B mutagens	POPs (persistent organic pollutants)
1A & 1B toxic for reproduction	vPvB (very persistent and very bioaccumulative) substances
Substances with potentially harmful endocrine disruption effects	Substances with potentially harmful endocrine disruption effects

* Organisms not targeted by the active substance

31. Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC.

32. <http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN>

33. European Corporate Observatory (2012) Conflicts on the menu: a decade of industry influence at the European Food Safety Agency (EFSA), Brussels, CEO.

These exclusion criteria are to be applied solely for the first approval of an active substance or during the renewal of active substances already subjected to approval (between 2016 and 2019 for most of them). As can be seen in Table 2, one of the exclusion criteria regards substances with potentially harmful endocrine disruption effects for humans. While the Regulation does not specifically define this type of substance, it compels the European Commission to come up with scientific criteria for their determination. The Commission should have done this by 14 December 2013, but we had to wait until June 2016 before, under pressure from certain Member States, a list of criteria was finally drafted. Pending the European Union's final adoption of the criteria for determining endocrine disruptors, temporary criteria continue to be applied to determine such substances. These criteria apply to substances classed as Category 2 carcinogenic and Category 2 toxic for reproduction.

Two derogations to the exclusion criteria continue to be applied:

- in the case of negligible exposure for human beings;
- where an active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods. In this case, approval is granted for a maximum of five years.

4.3. The Biocidal Product Regulation

The placing on the market and use of biocidal products in the EU are governed by a regulation which came into force in September 2013³⁴. A distinction needs to be made between biocides and pesticides: the latter are used mainly in agriculture. This regulation thus covers biocidal products designed to protect human beings, animals, materials or other articles against pests (fungi, bacteria, viruses, rodents). Wood preservation products, disinfectants, rodenticides and insecticides for instance belong to this large family of chemical substances. The regulation is constructed along the same lines as the regulation governing pesticides. All biocidal products must gain authorisation before being marketed and the active substances they contain require prior approval. The active substances are evaluated at European level by Member State authorities under the coordination of the ECHA (not the EFSA as is the case with pesticides) and approved by the European Commission. Approval of an active substance is granted for a specific timeframe (not exceeding 10 years) and is renewable. 181 substances are currently contained in the list of approved active substances.

The subsequent authorisation of biocidal products takes place at the level of Member States. An authorisation granted by one Member State may be extended to other Member States by way of mutual recognition. The Biocidal Product Regulation (BPR) also offers applicant companies the possibility of obtaining a new form of authorisation at EU level (EU authorisation). Some 5,600 biocidal products are currently authorised for sale on the European market.

The BPR similarly defines exclusion criteria based on the dangers emanating from a substance, and thus its intrinsic properties (see Table 3). When a substance meets one of these criteria, it may not be approved as an active substance.

³⁴. This regulation repeals Directive 98/8/EC on biocidal products.

Table 3 Exclusion criteria for the approval of active substances (biocides)

Human health	The environment
1A & 1B carcinogens	PBT (persistent, bioaccumulable and toxic) substances
1A & 1B mutagens	-
1A & 1B toxic for reproduction	vPvB (very persistent and very bioaccumulative) substances
Substances with potentially harmful endocrine disruption effects	Substances with potentially harmful endocrine disruption effects

Among the exclusion criteria, we again find substances with potentially harmful endocrine disrupting effects, both for human beings and the environment. In line with the Pesticides Regulation, the BPR text also contains the requirement for the European Commission to come up with a list of scientific criteria for determining this type of substance, as well as the same temporary criteria, by 14 December 2013 at the latest.

The derogations to the exclusion criteria however differ greatly in the Biocidal Product Regulation. There are three conditions, at least one of which must be met:

- the risk to humans, animals or the environment from exposure to the active substance in a biocidal product, under realistic worst case conditions of use, is negligible, in particular where the product is used in closed systems or under other conditions which aim at excluding contact with humans and prevent its release into the environment;
- it is shown by evidence that the active substance is essential to prevent or control a serious danger to human health, animal health or the environment; or
- not approving the active substance would have a disproportionate negative impact on society when compared with the risk to human health, animal health or the environment arising from the use of the substance.

In addition, Article 19(4) stipulates that a “biocidal product shall not be authorised for making available on the market for use by the general public where ... (d) it has endocrine-disrupting properties”. The same applies when it shows acute oral/dermal/inhalation toxicity (categories 1, 2 or 3), when it is a CMR (1A or 1B) substance, a PBT or vPvB substance or when it has developmental neurotoxic or immunotoxic effects.

4.4. The Cosmetics Regulation

The Regulation establishes rules to be complied with for any cosmetic product made available on the market, in order to ensure the functioning of the internal market and a high level of protection of human health.³⁵

The Regulation’s Article 10 requires manufacturers, prior to placing a cosmetic product on the market, to compile a cosmetic product safety report in accordance with Annex I. They are not allowed to market any product before designating a responsible person

35. This regulation (EC No 1223/2009) repeals and replaces (as of 11 July 2013) the Cosmetics Directive (76/768/EEC) amended seven times since 1976.

(a legal or natural person), whose role it is to ensure compliance with all the safety requirements set out in the regulation.

Annex II lists all prohibited substances, while Annex III lists restricted substances. The regulation normally prohibits the use of substances classified as CMRs (categories 1A, 1B or 2). Category 2 CMR substances may however be used when they have been considered as safe by the Scientific Committee for Consumer Safety (SCCS). Similarly, category 1A or 1B substances can be exceptionally used when they comply with food safety legislation, when there is no safer alternative, and when their use is considered to be safe by the SCCS.

The Regulation also contains a list of colourants (Annex IV), preservatives (Annex V) and UV filters (Annex VI) allowed in cosmetic products.

It also provides for a “cosmetics watchdog” system, allowing any information relating to possible serious side effects associated with the use of cosmetics to be quickly identified. Responsible persons and distributors are required to report such effects to their national authorities which must in turn share the information with their counterparts in other EU countries.

Packaging must list certain information, including the name and address of the responsible person, the contents, usage instructions and the list of ingredients.

Specific provisions are foreseen when the product contains nanomaterials. The responsible person must inform the European Commission of such contents, which will then, after obtaining the opinion of the SCCS and when there is a potential risk to human health, include such substances in Annex II or III.

By contrast, the Cosmetics Regulation is extremely low-key as regards endocrine disruptors, solely stipulating that the Commission should review the Regulation by 11 January 2015 when the criteria for determining substances with endocrine disrupting properties are available. The Commission has not complied with this requirement. Numerous studies point to the fact that cosmetic products on the market contain endocrine disruptors. Those using such products in the course of their work (for instance hairdressers or nail stylists) may be subject to a whole cocktail of exposure, the health impact of which is generally neglected.

4.5. The Water Framework Directive

The Water Framework Directive³⁶, in force since October 2000, constitutes a core piece of legislation covering the main water management requirements in the EU. Its aim is to prevent and reduce water pollution, promote its long-term use, protect the environment, improve the status of aquatic ecosystems and mitigate the effects of floods and droughts. It establishes rules to halt deterioration in the status of EU water bodies and achieve “good status” for Europe’s rivers, lakes and groundwater by 2015. This legislation assigns clear responsibilities to national authorities.

They have to:

- identify the individual river basins on their territory;
- designate authorities to manage these basins in line with the EU rules;
- analyse the features of each river basin, including the impact of human activity and an economic assessment of water use;

36. Directive 2000/60 summarises and simplifies all previous EU directives on inland and maritime waters (some 30 texts since the 1970s).

- monitor the status of the water in each basin;
- register protected areas, such as those used for drinking water, which require special attention;
- produce and implement ‘river-basin management plans’ to prevent deterioration of surface water, protect and enhance groundwater and preserve protected areas;
- ensure the cost of water services is recovered so that the resources are used efficiently and polluters pay;
- provide public information and consultation on their river-basin management plans.

Annex VIII of the Water Framework Directive provides an indicative list of the main pollutants (see p. 54) for which Member States must establish pollution and environmental quality standards. Substances for which there is proof that they have potential endocrine disrupting effects are included in the water pollutants recognised by the Framework Directive.

Article 16 of the Directive lists strategies for fighting water pollution. The first step involved establishing an initial list of “priority substances” for specific monitoring as they present a significant risk to or via the aquatic environment. These substances are listed in Annex X of the Framework Directive.

Annex X has since been replaced by Annex II of the Directive³⁷ which sets environmental quality standards for substances in surface waters. This lists 22 substances or groups of substances³⁸ including pesticides, biocides, metals, brominated flame retardants and well-known endocrine disruptors such as DEHP or nonylphenol.

4.6. Legislation on medical devices

The aim of the Medical Device Directive³⁹ is to ensure universally high safety standards for patients, giving the public confidence in the system. It enables the products to be used in any European Union country.

National authorities must ensure that all medical devices available in the EU are safe for patients, users and any other third party when they are properly installed, maintained and used as they should be. Medical devices must comply with strict health and safety requirements set out in the legislation. Two committees – one on standards and technical regulations, the other on medical devices – provide advice to the Commission on implementation of the legislation.

The Directive stipulates that medical devices containing certain phthalates (DEHP, DBP, DIBP and BBP) classified as carcinogenic, mutagenic or reprotoxic (CMR) must be identified. It also specifies that if such devices are used in the treatment of children or pregnant or breastfeeding women, the manufacturer must justify the use of such substances. A new proposal, currently in the course of evaluation at European level⁴⁰, requires that substances with endocrine disrupting properties and suspected health effects be reduced in medical devices. The proposal does not however include any mechanism for progressively eliminating them or for encouraging the development of safer alternatives.

37. Directive 2008/105/EC on environmental quality standards in the field of water policy.

38. http://ec.europa.eu/environment/water/water-framework/priority_substances.htm

39. Directive 93/42/EEC has been amended several times. A consolidated text is available at <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:01993L0042-20071011>

40. Proposal for a regulation on medical devices – 2012/0266 (COD) and Proposal for a regulation on in vitro diagnostic medical devices – 2012/0267 (COD). www.consilium.europa.eu/en/policies/new-rules-medical-in-vitro-diagnostic-devices

Indicative list of the main pollutants
(Annex VIII of the Water Framework Directive)

1. Organohalogen compounds and substances which may form such compounds in the aquatic environment.
2. Organophosphorous compounds.
3. Organotin compounds.
4. Substances and preparations, or the breakdown products of such, which have been proved to possess carcinogenic or mutagenic properties or properties which may affect steroidogenic, thyroid, reproduction or other endocrine-related functions in or via the aquatic environment.
5. Persistent hydrocarbons and persistent and bioaccumulable organic toxic substances.
6. Cyanides.
7. Metals and their compounds.
8. Arsenic and its compounds.
9. Biocides and plant protection products.
10. Materials in suspension.
11. Substances which contribute to eutrophication (in particular, nitrates and phosphates).
12. Substances which have an unfavourable influence on the oxygen balance (and can be measured using parameters such as BOD, COD, etc.).

Chapter 5

20 years of European policy on endocrine disruptors

The history of EU policy on endocrine disruptors goes back some two decades and can be characterised in two particular ways. Describing it in chart form, we would see a bell-shaped Gauss curve, showing a rapid rise in the 1990s and early 2000s, plateauing in the late 2000s, and then falling dramatically in the 2012-2016 period, corresponding to the increasingly direct influence of the chemical industry on policy choices.

The other aspect of this history is difficult to portray in chart form, with a more psychiatric metaphor necessary to describe its schizophrenic character. At the same time as funding independent high-level research into endocrine disruptors, the European Union has backed away from adopting or implementing legislation which would allow the risks to be effectively confronted. This has resulted in a growing dissociation between scientific work initiated and directly funded by various EU programmes, and the regulatory use of the results thereof. The chemical industry has managed to permanently increase its influence, even though scientific data contradicting its proposals is piling up.

There are three factors explaining this:

1. Legislation has come to be based on what European institutions call “the principles of better regulation”, which give precedence to calculations of the hypothetical economic consequences of any legislation. At the same time, the role of scientific expertise has been minimised. This finding may seem strange as it contradicts the language used in new regulations which would seem to have become more scientific and less political and can be seen as the immediate and direct consequence of scientific data. The appointment of Anne Glover as “Chief Scientific Adviser” to José Manuel Barroso, the President of the European

Commission, can be seen as a good illustration of this paradox. This new function (which, however, only existed as a position between 2012 and 2014) could be seen as recognition of the importance of scientific expertise aimed at guiding policy choices and legislative content. Yet the person designated – who made no secret of her scepticism towards the precautionary principle – was destined to create a sort of filter between “economically correct” expertise (from a company perspective) and the “irresponsible” expertise put forward by researchers independent of the industry and not sufficiently aware of the economic consequences of applying the precautionary principle.

2. The chemical industry has cleverly managed to promote a policy of doubt with the aim of delaying the adoption of any legislation which would put shackles on the marketing of dangerous products, using a model perfected over the last hundred years in debates over such issues as lead, asbestos, tobacco, etc. With the EU’s regulatory system increasingly entrusting the production of expertise to industrial companies, the relative weight of independent research has declined, with regard to both toxicology and the epidemiology of industrial risks. We are now seeing what can be called “regulatory science”, widely entrusted to those companies producing the risk products, to the detriment of fundamental science.⁴¹.
3. The progressive reduction of the targets of EU policy on endocrine disruptors is no isolated phenomenon, but can be seen as part of a transformation of power relations within EU institutions. Its most visible element is the dramatic loss of influence of the DG Environment vis-à-vis other sectors of the European Commission (DG Enterprise has now become DG Grow, DG Health and Consumer Affairs is now DG Health and Food Safety). There has been an ongoing offensive in this field under Commission Presidents José Manuel Barroso (2004-2014) and Jean-Claude Juncker (2014-) to whittle down environmental protection targets, whether with regard to climate change, GMOs or air quality. While obviously not isolated from the international context, this shift in EU policy has followed its own momentum and schedule.

5.1. 1999: an innovative and ambitious strategy for the time

The political context at the end of the 1990s provides an explanation of why the European strategy on endocrine disruptors was ambitious at that time, taking priority account of human health and environmental concerns. This was the time of the first phase of REACH negotiations, the project for regulating chemical substances. In 1995, three countries whose regulation on chemical risks was generally more advanced than EU legislation (Austria, Finland and Sweden) joined the EU. During the accession negotiations, these three countries managed to secure an agreement from the EU that it would tighten up its various pieces of legislation on chemical risks. In this context, DG Environment exerted a growing influence on EU policies. From 1999 to 2004, it was headed by Margot Wallström, a Swedish politician who wanted to give the DG a dynamic role in regulating chemical risks. This domain had previously been mainly in the hands of DG Enterprise, which had always been much more open to industry lobbying.

At an international level, we were going through a dynamic phase triggered by the 1992 Rio Summit. That same year, the precautionary principle was included in the Treaty

41. Borraz O. and Demortain D. (2015) *Science réglementaire*, in Henry E., Gilbert Cl., Jouzel J.-N. and Marichalar P. (eds.) *Dictionnaire critique de l'expertise: santé, travail, environnement*, Paris, Presses de Sciences Po.

on European Union (the Maastricht Treaty). During this period, conventions were being negotiated in various fields concerning chemical risks: the Kyoto Protocol on climate change (1997), the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade (1998), the Aarhus Convention on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters (adopted in 1998), and the Stockholm Convention on Persistent Organic Pollutants (adopted in 2001). The European Union participated in the negotiation of these international instruments, generally upholding positions that were more progressive than in certain industrialised countries. This upsurge of international negotiations on the environment is partly explained by the optimism of the ruling classes during a short transition period following the end of the Cold War, when it seemed that capitalism no longer had any enemy and that the “dividends of peace” would allow the many unresolved problems of that time to be tackled, whether with regard to the environment or poverty. While formulating often ambitious targets, the dominant discourse on the environment became increasingly liberal⁴². At the end of the day, the market would come up with solutions, and any approaches getting in the way of business activities were to be rejected in favour of models combining economic incentives and self-regulation.

The 1999 strategy on endocrine disruptors was preceded by a workshop held in Weybridge (England) in December 1996, during the course of which policymakers and scientists discussed the necessity of regulating such substances on account of their proven extremely serious health consequences⁴³ (in particular an increase in testicular cancer).

On 4 March 1999, the EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) published a report stating that links existed between the chemical substances disrupting the endocrine system and various human health problems such as testicular cancer, breast cancer and prostate cancer, the drop in sperm counts, deformities of the reproductive organs, thyroid dysfunctions, as well as intellectual and neurological disorders⁴⁴. Moreover, the issue of causality mechanisms ought to be the subject of further research.

Based on the precautionary principle, the Commission’s strategy, adopted in December 1999, recommended immediate intervention, simultaneously developing research activities and legislative initiatives.

With regard to research, the immediate priority was to establish a list of substances considered to be potential endocrine disruptors, for which it was crucial to go ahead with assessments in greater depth. As regards legislative action, a series of EU texts requiring modification were identified. A work programme distinguished between short-, medium- and long-term amendments. The strategy considered that, to start with, one could use the existing classification of hazardous chemical substances, characterising them by their specific (carcinogenic, reprotoxic, dangerous for the environment) effects. In the longer term, it could be useful to create a new category identifying endocrine disruption as an intrinsic risk of certain chemical substances.

All of these activities were intended to lead to increased international cooperation, both within specialist institutions (in particular the OECD) and in the negotiation of international legal instruments.

42. Morin J.-F. and Orsini A. (2015) *Politique internationale de l’environnement*, Paris, Presses de Sciences Po.

43. No breast cancer specialist was invited to Weybridge. Greatly criticised, this led to a recommendation to include breast cancer research in future debates on endocrine disruptors.

44. “Human and Wildlife Health Effects of Endocrine disrupting chemicals, with emphasis on Wildlife and on Ecotoxicology test methods”, Report of the Working Group on Endocrine Disruptors of the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE), adopted on 4 March 1999.

This was thus an evolutionary strategy where research was supposed to support policy decisions, allowing more restrictive laws to be progressively adopted, based on the principle of substitution. The strategy similarly acknowledged the importance of informing populations. In a context marked by the Aarhus Convention, this was an implicit acknowledgement that mobilising people in defence of health and the environment was essential in order to create a counterweight to the chemical industry. Though pursued with great effectiveness over the following decade⁴⁵, its evolutionary character has however waned. The necessity to review this strategy has not led to anything more than mere exchanges of opinions between Commission departments, Member State authorities and experts.

5.2. Identification of endocrine disruptors

Belonging to different families of chemical substances, endocrine disrupting substances are used for a wide range of products, ranging from cosmetics to plastic materials. In certain cases, they result from the degradation of materials which do not themselves have endocrine disrupting properties. Their health and environmental effects also vary greatly. It was thus logical to start by compiling a list of substances whose effects on hormone production had been identified at varying degrees of certainty.

A Dutch company, BKH Consulting Engineers, was commissioned to draw up the list, the aim of which was twofold: to inform users and to allow priorities to be established for public authorities' assessments of these substances. Different criteria were used to set the priorities: production volumes, persistence in the environment, endocrine disrupting effects attested by scientific works, and exposure-related considerations. On this basis, 533 substances were identified. They were then grouped into three categories reflecting these priorities. For a certain number of substances, it was decided to initiate a risk assessment taking account of endocrine disrupting effects. For 435 substances, the recommendation was to gather more comprehensive data.

Major funding was assigned to assessing the priority substances and, on the basis of this research, information was regularly updated to inform the public. The overall identification balance is quite positive despite the fact that efforts slowed down from 2012 onwards, the initial list not being regularly updated.

Regulation of endocrine disruptors proved to be principal problem, as it required the definition of legal identification criteria. Without these, a considerable amount of time was going to be lost. Moreover, the approach would become fragmented, with each substance being investigated separately. The scientific work on defining the criteria was carried out very efficiently, ending in the publication of a report summarising available knowledge on endocrine disruptors at the end of 2011. Commissioned by the European Commission, the report was compiled by toxicologist Andreas Kortenkamp (and is hereinafter referred to as the "Kortenkamp Report"⁴⁶).

45. The strategy was the subject of four assessment reports by the Commission in 2001, 2004, 2007 and 2011. After this date, the Commission ceased to be accountable to the European Parliament on the implementation of the strategy. The last assessment indicated that the Commission was going to review the EU strategy, taking account of the growing concerns for human fertility. At the time of writing this guide (August 2016), this review has still not taken place.

46. Kortenkamp A. *et al.* (2011) State of the art assessment of endocrine disruptors: final report. http://ec.europa.eu/environment/chemicals/endocrine/pdf/sota_edc_final_report.pdf

5.3. Regulation of endocrine disruptors

Legislative work took place in various fields (see Chapter 4), with the concept of endocrine disruption being included in several pieces of legislation. As regards pesticides, biocides and cosmetics, the general rule is to ban such substances, though derogations are possible on the basis of criteria which are not harmonised throughout all legislation. As regards the general regulation of the use and placing on the market of chemical products (REACH), the principle used is that an endocrine disrupting substance should be subject to authorisation. Without authorisation, the substance can no longer be placed on the market. The process is however very slow, as all authorisation procedures involve many steps and the identification of possible endocrine disrupting effects is very much dependent on information provided by the producers. On the other hand, the tests stipulated by REACH do not allow the identification of all endocrine disruptors.

With regard to the specific regulations (biocides, pesticides, cosmetics), the effective application of a ban is obviously dependent on the adoption of legal criteria defining what an endocrine disruptor is.

However, the strategy had one major deficiency. There was no concrete proposal regarding the protection of workers against exposure to endocrine disruptors at work. The sole text dealing with this issue is marked by imprecision and non-specificity. The strategy states the following: “Once an EDC priority list has been established, it will be possible to identify those substances, which already feature on priority lists or which may be included in subsequent priority lists using the methodology agreed under existing legislation. For those substances on the EDC priority list, which are not covered by the current legislation, the Commission intends to consult stakeholders on the establishment of monitoring programmes. This would give an estimation of exposure, both direct and indirect, by determining the quantity of these chemicals likely to be released into the environment. Such programmes would also need to estimate the proportion of this release to air, water and soil as well as their use and fate in food, consumer products and in the workplace.”

In an annex, the strategy mentions the various directives related to health at work which could serve as a basis for regulating workplace prevention. However, this list has not been backed up by any concrete proposal. The only clear position provided by the Commission is to be found in its 2011 evaluation of the strategy, where it mentions the possibility of extending the scope of the directive on the protection of workers from the risks related to exposure to carcinogens or mutagens at work to reprotoxic substances. It explains that, in many cases, reprotoxicity is linked to endocrine disrupting effects. This proposal was subsequently abandoned by the Commission.

In May 2016, Marianne Thyssen, the commissioner in charge of employment and social affairs, justified this by citing the uncertain economic benefits of such a measure. In her view, the impact assessment of this proposal “did not sufficiently clarify the potential costs and benefits”⁴⁷. The consequences of such a deficiency are made worse by the fact that the specific regulations on pesticides, biocides and cosmetics authorise derogations that are essentially based on data concerning consumers’ health. The health of workers subject to exposure at work (generally in higher concentrations) is for all intents and purposes never taken into account. Generally speaking, implementation of the strategy defined in

47. Roberts G. (2016) Thyssen rules out adding reprotoxins to workplace law: Employment Commissioner reiterates position on carcinogens and mutagens Directive, Chemical Watch. <https://chemicalwatch.com/47684/thyssen-rules-out-adding-reprotoxins-to-workplace-law>

1999 has taken place without the involvement of DG Employment and Social Affairs, the directorate responsible for work-related health questions within the European Commission.

5.4. The Commission chooses to violate EU law

The 2009–2012 period was marked by a decisive turnaround. In 2009, two new pieces of legislation were adopted (see Chapter 4) concerning cosmetics and pesticides. After many debates, the issue of endocrine disruptors was treated on the basis of the principle of substitution, i.e. that the industry should replace products containing endocrine disruptors with other less harmful ones; derogations could however be granted. A comparable approach was pursued in 2012 with regard to biocides.

For these various regulations to become applicable, a legal definition of what constitutes an endocrine disruptor was required. The European Commission was given the task of coming up with definition criteria by the end of 2013. Such criteria could not be determined on the basis of economic opportunity considerations. Instead they needed to be formulated on the basis of a scientific analysis of the interaction between synthetic chemical substances and the hormone system. The principle established by the new pieces of legislation was in line with that adopted three decades ago for carcinogens, with a regulation needing to take account of the intrinsic dangers associated with a substance's chemical and physical properties. It could not be based solely on a risk assessment related to concrete exposure conditions. Indeed, experience in the field of cancer showed that controlling exposure in real-life situations (whether exposure at work or in the environment) is very uneven and that risks considered low or negligible may be much more significant than expected depending on many specific circumstances.

To define the criteria for identifying endocrine disruptors, it was necessary to establish a link between the research findings, which had greatly increased since the late 1990s, and the policy defining the targets and legislative instruments needed to achieve them.

In 2010, the Commission established an ad hoc committee on endocrine disruptors made up of some forty experts: Commission officials, experts from the national institutions of several Member States, many industry representatives (especially the two multinational companies, Bayer and Syngenta) and NGOs active in the field of the environment, public health and consumer protection. Trade union organisations were not included, once again confirming the very low attention paid to work-related exposure to endocrine disruptors. Professor Andreas Kortenkamp was tasked with drafting a report on the status of scientific knowledge.

Without waiting for this report, the chemical industry started its offensive aimed at defining criteria as restrictive as possible. They only wanted a minimum number of substances to be considered as endocrine disruptors, most of which were already subject to regulatory measures and which, sooner or later, would have to be removed from the market.

Two Member States acted as spokespersons of the chemical industry: the United Kingdom and Germany. On 16 May 2011, they produced a joint document drafted by the German Risk Management Institute (BfR). Relatively short, the document showed which way the wind was blowing, expressing concern for the economic impact of the regulatory decisions. It was therefore necessary to “tune” the scientific data to make it “economically correct” from the perspective of the multinational companies potentially concerned. The report dogmatically reaffirmed the belief that “only the dose makes a thing not a poison”, stating that “in general terms, toxic effects are only of regulatory relevance when they occur at relevant dose levels”. The BfR report was to a great extent based on the proposals put

forward in 2009 by a chemical industry lobby group, ECETOC (the European Centre for Ecotoxicology and Toxicology of Chemicals). The criteria proposed meant a tacit revision of the regulations previously adopted by the European Parliament and the Council of Ministers, taking less account of the intrinsic dangers (endocrine disruption) than the severity of the reported effects. This took the form of a proposal for a criterion measuring the “potency” of endocrine disruptors. Bans and other restrictions would only affect substances for which particularly serious effects had already been established. To limit as much as possible the aims of the regulation, this proposal considered that environmental effects did not need to be taken into account.

The Kortenkamp Report was published at the end of December 2011. One of the most active lobbying organisations in the European Union since the period spent negotiating the REACH Regulation (1998-2006) was set up by the chemical industry, or more specifically by those sectors considered the most affected (producers of pesticides, cosmetics and plastics).

The data needed to define the criteria was available by the beginning of 2012. The European Commission chose not to fulfil its obligation, not coming up with criteria by the set deadline (December 2013). Instead, it initiated an impact assessment study based less on the consistency of the criteria as such and more on the hypothetical consequences of their adoption in economic terms.

Other Member States had however put forward proposals in line with EU legislation and consistent with the policy guidelines behind the European strategy on substances of very high concern. The most comprehensive proposals are to be found in a report of the Danish environmental protection agency published in May 2011, setting forth criteria comparable to those in force for carcinogens. Based on the intrinsic dangers, these criteria, in line with the uncertainties expressed in the scientific literature, use a classification in three categories: proven endocrine disruptors (category 1), suspected ones (category 2A) and potential ones (category 2B). This approach was generally supported by various Member States (other Nordic countries, Belgium, the Netherlands and France), by environmental, public health and consumer protection NGOs and by union organisations, even though there were differing opinions relating to specific aspects of the Danish report.

While the battle over the definition of the criteria seems complex and difficult for non-specialists to understand, what is at stake is simple. The adoption of the Anglo-German criteria would end up with regulations only applying in exceptional cases, whereas the adoption of the Danish ones would have allowed the majority of substances with already-existing data on their endocrine disrupting effects to be regulated. A French study covered 24 currently used substances.⁴⁸ On the basis of the Anglo-German criteria, just three of these would have met the criteria to be classified as endocrine disruptors, while 19 would have been excluded and with a question mark over the classification of the remaining two. On the basis of the Danish criteria, 15 substances would have been classified in categories 1 or 2A, six substances in category 2B and three would not have been classified as endocrine disruptors. A Danish study covering 22 substances came up with comparable results. Application of the Anglo-German criteria would have classified just four of them as endocrine disruptors, whereas application of the Danish ones would have led to 21 of them being classified as endocrine disruptors (15 in category 1 and 6 in category 2A). All of these

48. Avis de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) relatif à une demande d'appui scientifique et technique concernant la révision de la stratégie européenne relative aux perturbateurs endocriniens (*Opinion of Anses on the request for scientific support with regard to the review of European strategy on endocrine disruptors*), 27 March 2012.

substances have been identified as endocrine disruptors by the NGO ChemSec on the basis of the REACH criteria⁴⁹.

The Commission's refusal to respect the deadlines set by EU legislation sparked a strong reaction from several States. At the head of the movement, Sweden took unprecedented action, initiating proceedings against the European Commission in the European Court of Justice (CJEU) for non-respect of EU legislation in the context of an "Action for failure to act". Other Member States – France, Denmark, Finland and the Netherlands – backed the Swedish action, as did the European Council and the European Parliament. In its judgment of 16 December 2015, the CJEU ruled in favour of Sweden, considering that the Commission had indeed violated the European regulation on the placing on the market and use of biocidal products.

5.5. The criteria proposed by the European Commission

Finally, more than two years late, the European Commission came up with criteria for identifying endocrine disruptors on 15 June 2016.

The criteria are worded in line with policy targets, i.e. revising downwards the initial targets of the European strategy on endocrine disruptors. They pose a compliance problem with respect to the European treaties, as it is not within the Commission's remit to amend legislation adopted by the European Parliament and the Council of Ministers. The very wording of the criteria implies that the approach followed by the European regulations on pesticides (2009) and biocides (2012) could not be applied consistently. Hidden behind a text which should have been limited to defining the technical conditions of applying the adopted rules, one discovers the political will to again lower the level of health and environmental protection in order to protect the market shares of European companies.

The one positive aspect of the Commission's proposal is the abandonment of the concept of "potency" as a criterion for identifying endocrine disruptors. Demanded and defended by companies, the aim of this criterion was to minimise the number of substances identified as endocrine disruptors. Indeed, only the most "potent" pesticides or biocides would have been banned, even though many substances causing low levels of endocrine disruption would have continued to have been marketed.

The Commission followed the advice of the scientists who considered that "potency" could not be used as a criterion for identifying endocrine disruptors, as these substances could have harmful effects even at low doses.

Nevertheless, the Commission found another way of satisfying the business world, proposing very restrictive identification criteria. An active substance will only be considered an endocrine disruptor when the following three conditions are met:

- it is known to cause an adverse effect for human health or the environment;⁵⁰
- it has an endocrine mode of action;
- the adverse effect for human health or the environment is a consequence of the endocrine mode of action.

49. Danish Centre on Endocrine Disruptors (2012) Evaluation of 22 SIN List 2.0 substances according to the Danish proposal on criteria for endocrine disruptors, Copenhagen, DTU Food.

50. The term "environment" is meant to cover non-target organisms.

Organisations defending the environment and public health, European trade unions, Green parties and several European governments criticise the fact that, before any substance is banned, it has to be proved that it has a harmful effect on human beings. This excludes all disruptors suspected of having adverse effects on humans due to proof of harmful effects on animals, as well as potential disruptors for which there is (as yet) insufficient proof in humans or animals. For the Green MEP Michèle Rivasi, “this proposal turns human beings into guinea pigs”.

The Commission has refused to classify endocrine disruptors into different categories (proven, suspected or potential) as is the case with CMR substances. This option would have allowed a harmonised approach to regulating the chemical substances of highest concern.

The Commission’s refusal has also been criticised by the Danish Minister of the Environment, Lunde Larsen. In his view, excluding the identification of suspected endocrine disruptors and limiting regulation to proven ones contradicts the general approach to regulating chemical substances of highest concern.

Moreover, the defenders of public health and the environment are up in arms against the possibilities to derogate from the exclusion criteria in the case of “negligible exposure” for human beings. These possibilities are linked to the logic of “risk assessment”, while the European regulation of 2009 on pesticides requires (via its exclusion criteria) an approach based solely on “danger”.

The proposals presented by the Commission must now be approved by the Member States. The European Parliament will have no say in the matter, as the Commission has intervened in the context of an “adaptation to technical progress”. This choice has been strongly criticised by environmental NGOs and trade unions because the Commission has not just limited itself to proposing missing criteria, but is also modifying the very substance of the Pesticide Regulation. It plans to strengthen and make more explicit the “risk” approach though extending the system of derogations. An active substance identified as an endocrine disruptor could thus be authorised in a pesticide preparation, no longer in the case of “negligible exposure” (as was previously the case), but now in the case of a “negligible risk” for human beings.

Read more

Communication from the Commission to the Council and the European Parliament, Community Strategy for Endocrine Disruptors – a range of substances suspected of interfering with the hormone systems of humans and wildlife, COM(1999) 706 final, 17 December 1999.

Corporate Europe, A Toxic Affair: How the chemical lobby blocked action on hormone disrupting chemicals, 2015. <http://corporateeurope.org/food-and-agriculture/2015/05/toxic-affair-how-chemical-lobby-blocked-action-hormone-disrupting>

Horel S. (2015) Intoxication: perturbateurs endocriniens, lobbyistes et eurocrates, une bataille d’influence contre la santé, Paris, La Découverte.

Roumegas J.L. (2014) Rapport d’information déposé par la commission des affaires européennes sur la stratégie européenne en matière de perturbateurs endocriniens, Document No 1828, Paris, Assemblée nationale.

Conclusions

The health dangers caused by endocrine disruptors are sufficiently severe to warrant specific workplace prevention measures. Answers need to be found to four major challenges.

There is a reduced visibility of these health dangers. The majority of effects differ over time, sometimes even affecting the next generation. There is a crucial need to document and analyse workplace exposure. This implies that health surveillance must be organised in a way comparable to that foreseen for carcinogens and covering the whole lifespan of those exposed. On the other hand, it is important to establish a better connection between work-related health data (on exposure) and public health data (covering for instance fertility problems, congenital deformities and other transgenerational afflictions).

Prevention policies must also be promoted and developed within a legislative context sufficiently precise to monitor prevention practices in companies. In our view, the most rational approach is to extend the scope of application of the rules on carcinogens to all substances of highest concern. As an urgent first step, European legislation on workplace prevention against carcinogens must be extended to reprotoxic substances. This would cover a number of endocrine disruptors. Once the criteria for identifying endocrine disruptors have been adopted, the scope of the directive on workers' protection against cancer-causing chemicals can be extended to all such substances.

The absence of a threshold below which exposure can be considered safe should prompt policymakers to promote substitution as a priority element of prevention. Substitution is also the only way of avoiding discriminatory consequences in terms of employment. Scientific data indicates that the risks caused by endocrine disruptors can be particularly high in certain phases of life, especially for women of childbearing age.

Implementation of such measures in workplaces must go hand in hand with stricter regulation of the market. It is essential to identify endocrine disruptors using harmonised criteria applied via all legislative acts involved in this issue. To this end, we need to envisage the introduction of specific endocrine disruptor categories in the CLP Regulation. We also need to speed up the authorisation procedure foreseen by REACH as a way of stimulating innovation and promoting the substitution of endocrine disruptors. As regards the specific regulations on pesticides, biocides, cosmetics and medical devices, we need to greatly modify the current approach used in their application. Equal priority must be given to protecting both workers' health and consumers' health.

Any revitalisation of EU occupational health policies is largely dependent on mobilisations in companies and the ability of the union movement to create alliances with organisations defending the environment and public health.

