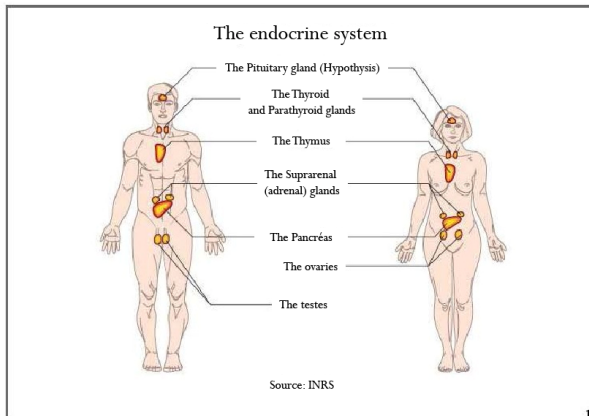


Endocrine Disruptors, *a time for precaution*

by Mr Gilbert Barbier, Senator of the Department of Jura

The **hormone or endocrine system** is made of a number of glands secreting hormones, which are chemical messengers carried through the blood. They control the **main functions of the organism such as growth and reproduction**, but also regulate metabolism.



Functions	Hormones	Response
REPRODUCTION	Androgens, estrogens, progesterone, pituitary hormones (LH, FSH, prolactin)	Came to genesis, growth factors, lactation, pregnancy, development of secondary sex characteristics and sexual behavior onset
GROWTH AND DEVELOPMENT	Growth hormone, thyroid hormones, insulin, glucocorticoids, androgens, estrogens, progesterone	Broad spectrum of action on growth
MAINTENANCE OF THE INNER ENVIRONMENT	Vasopressin, aldosterone, parathyroid hormone and prostaglandin	Control of blood volume and arterial blood pressure. Electrolyte balance control. Bone growth control. Control of bone, muscle and fat tissue metabolism
AVAILABILITY OF ENERGY	Insulin, glucagon, thyroid hormones	Regulation of metabolism

Over the past few decades, it has been revealed that there are some either **natural or artificial chemical substances foreign to the body**, that can disturb the proper functioning of the endocrine system and induce both short-term and long-term deleterious effects in an individual or his/her offspring. These substances are generally referred to

as **endocrine disruptors**. Endocrine disruption is an action mechanism that causes a disturbance in homeostasis. Both the targets and the effects are numerous.

I. A MULTIPLICATION OF ENVIRONMENTAL DISEASES

In Western countries, one has observed a **multiplication of environment-related diseases**, i.e., diseases associated with the way of life, including mainly certain types of cancers, fertility disorders and malformations of the urogenital tract in the offspring.

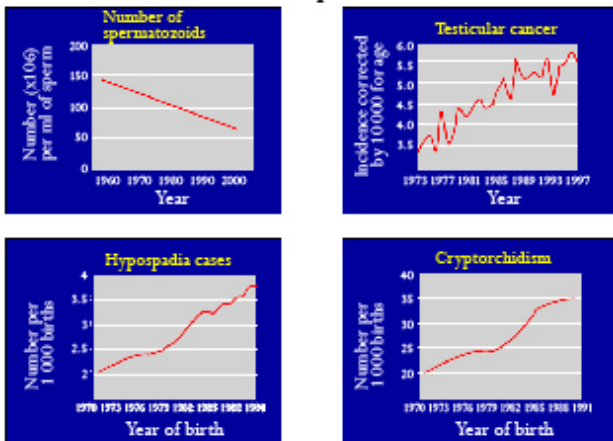
The increased incidence of **certain cancers** seems to be a cause for concern. In France, the incidence rate for all cancers has increased in men and women by 35 and 43 %, respectively, since 1980 (as per Inserm). **Endocrine disruptors may be implicated** in the occurrence of **hormone-dependent cancers**. In men, **prostate cancer** is primarily involved and has increased fourfold since 1975. **In women, the occurrence of breast cancer has doubled since 1980.**

Metabolic diseases like obesity are also rising very rapidly and may affect 25 to 30 % of the population in many countries.

Another subject for concern is the **possible degradation of human fertility**. Since 1992 and the publications by Danish authors Niels-Erik Skakkebaek and Elisabeth Carlsen, a consensus has progressively been reached in the scientific community to the effect that the number of spermatozooids has been divided by nearly two since 1950. Furthermore, Danish research scientists have **hypothesized a testicular dysgenesis syndrome** linking lesser sperm quality, increased cryptorchid and hypospadias cases and increased testicular cancer cases. Other data, like younger puberty age, tend to suggest that the female genital system might be disturbed, too.

These data are still being discussed. It is difficult to obtain any reliable elements regarding sperm quality or cryptorchidism which are subject to diagnostic bias. Concerning hypospadias cases (i.e., two genital malformations corresponding to failure of

Disorders of male reproductive function



Quoted by Gabriel Livera

one or both testes to descended and the fact that the urethral meatus is not placed at the tip of the penis, respectively), results are difficult to assess. However, in France, as in other countries, testicular cancer incidence has markedly increased by 2.5% yearly since 1980 (as per Invs).

II. THE ROLE OF THE ENDOCRINE DISRUPTORS

Such trends which are a matter for concern make one wonder about the role of the endocrine disruptors, as may be suggested by a whole array of available scientific findings.

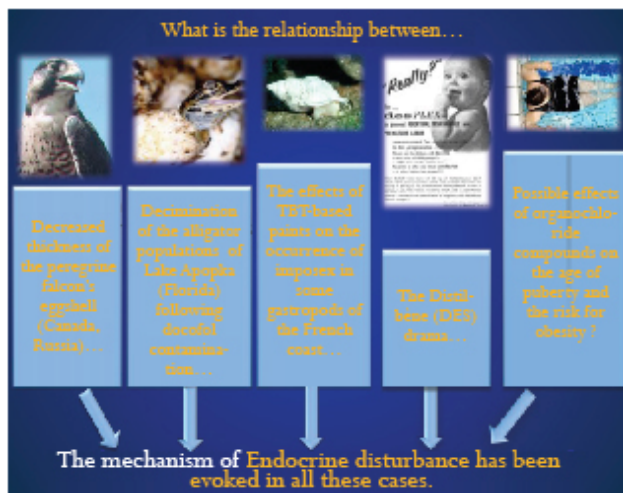
In fact, the impact of endocrine disruptors on Wildlife has been evidenced on several occasions. The use of DDT and DDE, two organochloride-based pesticides, of PCB compounds, artificial hormones, TBT-containing boat paints or medicines has been observed to have severe consequences. Several of these substances have already been banned, thereby allowing animal populations to be rebuilt, as well as confirming the cause and effect relationship. Their reproductive systems were often affected due to feminization (alligators, polar bears, panthers, fishes), or masculinization (gastropods). Those wild animals fell victim to pollutants either because those concentrated in their predator organisms, or because the animals were continuously in contact with the pollution (water environment).

The impact of pollution in water environments at the wastewater treatment plant outlet in certain rivers or estuaries is of real concern, in view of the important proportions of fish possibly exposed to intersexuality. This is mainly imputable to artificial hormones and estrogen-like acting disruptors; waters also contain other substances, like drug residues. While the impact of this pollution on man is poorly understood, it is mostly liable to remain circumscribed due to water dilution and the purification process. Nevertheless, wastewater treatment plants do not eliminate these products sufficiently and certain sources of pollution, such as hospitals, are inadequately treated. As a matter of fact, a recent report from the General Council for the Environment and Sustainable Development (CGEDD) emphasized the system's deficiencies inasmuch as drugs are the only substances not to be actually subjected to any environmental impact assessment tests.

Furthermore, several laboratory discoveries have evidenced the endocrine disruptive properties of substances – like Bisphenol A – in rodents, whereby cancer initiation might be promoted or reprotoxicity induced. These university publications raise the issue of a possible transposition to man. It is not perfect because there are true differences in the way organisms function, but rodents still remain an essential reference owing to the similarities and ease of utilization (breeding, number of generations, statistically significant numbers). In fact, such similarities are the mainstay of all approval studies. Although they would be welcome, such studies on larger mammals whose growth is slower, or on primates, are often very expensive and hard to organize. Thanks to the works that have been carried out on rodents, namely in the field of reproduction, a substantial documentation body is available, which was submitted for overall review by the Inserm on Government request. Bisphenol A and phtalates are the most studied substances. The most significant findings are obtained with Bisphenol A at doses potentially lower than the Acceptable Daily Intake (ADI), especially when ingested by pregnant females. Regarding phtalates, the effects thereof occur at higher exposure levels which, hence, draw attention on medically-originating overexposures, particularly in the new-born. On the other hand, it is Inserm's opinion is that there is still little evidence of the deleterious effects of polybrominated flame retardants, perfluorinated compounds and parabens on reproduction.

Two substances that have been used in the past can serve as examples in man. These are diethylstilbe-

strol (DES), marketed in France under the label Distilbène, and **chlordecone in the French Antilles**. Both products have now been banned. Chlordecone is the cause of ground and water pollution lasting over the long term with public health consequences, namely cancer of the prostate. As for Distilbène, in France it has been prescribed to pregnant women since 1977, leading to many cases of **severe malformations and rare diseases in the first and, henceforth, second generation of the offspring. 200 000 women and 160 000 first-generation children are concerned**. With its estrogen-like effect, Distilbène seems well fit to serve as a **reference by analogy to other endocrine disruptors** having the same type of action, like Bisphenol A for instance. While such similarity should not be overrated, it must be taken seriously.



Source : R. Slama

In 1991, during the Wingspread conference, a group of about twenty research scientists under the guidance of Théo Colborn, became conscious that these phenomena could be paralleled and regrouped under the term of endocrine disruptors. While the issue is still a matter for debate owing to its multiple aspects, the notion has become a reference today and mobilizes investigators worldwide. In fact, it **challenges the very foundations of modern toxicology, as was established by Paracelsius, according to which there is a relationship between the dose and the effect of a poison**. Actually, it is on this scientific fact that all the regulations concerning chemical products for the protection of workers and the general public are based, whereby they are the ones to define the effect-free lifetime dose of exposure and the Daily Acceptable Intake (DAI) values. However, endocrine disruptors do not seem to fit within this sole study format. **Low-dose effects have been noted** whereby the

endocrine disruptor acts as a key in a lock. **The response may also be non-linear**: strong at a low dose and weak at a higher one. **The combination of several substances** is likely to go beyond a simple additive effect, causing **synergy or potentiation**. Additionally, the organisms may be **much more sensitive during specific periods of their lives**, particularly in the intrauterine period. In this case, the poison effect is no longer related to the dose but to the timing. Lastly, some **transgenerational effects** were evidenced thereby substantiating the idea of **fetal exposure-induced diseases** manifesting later in the child's or adult's life.

III. TIME FOR ACTION

This **set of data** that bring forth evidence of the dangers and risks associated with the endocrine disruptors regarding the environment and human health is **sufficient and precise enough to incite one to action**. An **evolutive political approach of environment and population protection** should be developed based on scientific findings.

Your speaker proposes to rest on three basic principles : **knowing, preventing and banning**.

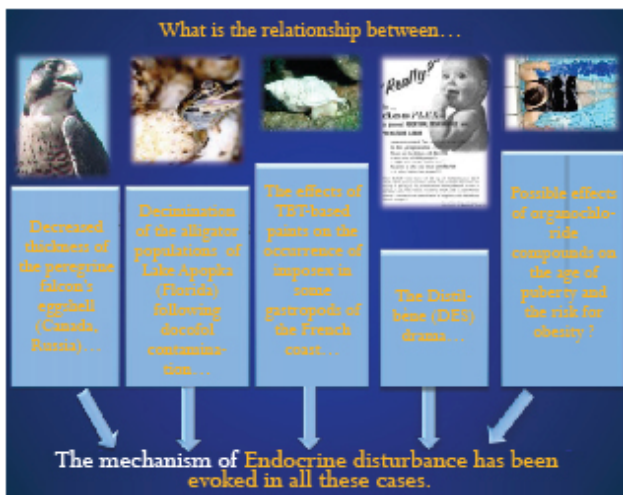
Increasing the information available is a priority. At European as at French levels, **substantial means have already been devoted** to this goal through the Ministry of Health's action plan, the national research program on endocrine disruptors, the National Research Agency and, more recently, through the ELFE cohort and future-oriented investments. **But this abundance of action programs is still not a strategy**. This is why, your speaker **calls for a more in-depth coordination** of the research endeavor based on a **specifically-defined joint ministerial strategy**. He also suggests associating the **enterprise world** into the effort because of the **economic stakes involved in any potential discoveries regarding the materials, the functioning of the hormone system, the diseases and future medicines**.

A broadening of the research scope is needed in terms of substances and target organs.

He also wishes that **true priority be granted for internationally-recognized tests identifying endocrine disruptors**, and that health and environment-related regulatory measures be based on more solid grounds at European level.

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pean regulation has made it possible to ban from the general public such products as were proven **carcinogenic, mutagenic and reprotoxic for man and animals alike**. More specifically, regarding pesticides, until 2013, pending the necessary tests, prohibition is prevailing if human exposure is negligible. **In order to define more specifically the endocrine disruptors in the Community legislation, the Commission has asked for a scientific report from Prof. Kortenkamp**, which should be provided by autumn of 2011.

On the French side, the Government has contacted several authorities, including the ANSES, that should turn in their conclusions within the coming months or years. **A political and parliamentary monitoring of the issue will therefore be needed to take into account the new evolutions and developing knowledge regarding the matter.**

Meanwhile, before such data are provided, your speaker **suggests setting up a preventive approach.**

Foremost, this policy must be intended towards **limiting the use of the incriminated substances**, taking into account their potentially endocrine disruptive nature, as well as reducing the release thereof to the environment. To this end, **adequate implementation of the PCB and echophyto 2018 plans** is paramount. Your speaker wishes also that the **problem raised by water-carried drug residues be addressed with the greatest of care, following the recommendations made by the National Pharmacy Academy and the CGEDD.**

Reducing perinatal exposure, meaning that of the young child and its mother, from conception to the first years of life, must become a goal. This is indeed the most sensitive period of life, during which the aftermath of any exposure, as mild as it may be, may be severe.

To this end, he recommends that **everyday consumption products containing substances presenting a high risk of endocrine disruption be submitted to special labelling to inform the mothers and incite them to use different ones.** He wishes that this information be apparent and explicit, as for instance retaining the type of pictogram already used for alcohol.



Source : INPES

Finally, as a third mainstay, **prohibition measures may be required in the framework of the European regulation in force.** These are to be considered depending on the products, their uses, the substitution possibilities, and the risk-benefit ratio. Hence, your speaker requests the **accelerated withdrawal of short-chain phthalates in medical applications intended for pregnant women and young children.**

Likewise, he wishes that **a principle be adopted to the effect that all products specifically intended for these populations be free from any endocrine disruptors.**

Lastly, your speaker wishes that the **French Parliament not multiply partially regulating laws in a strictly national setting, but invites the Government to act, via a resolution, at European level on the entire Community market.**

July 2011

