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Endocrine Disruptors: a Real Concern for Humans?

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Abstract: The role of Endocrine Disruptors as real risk for ecosystems, wildlife and humans represents a concern and the debate on this issue is open owing the conflicting interests between the producers of these products and the scientific community. A concise overview of the nature, presence and adverse effects induced in wildlife and humans by Endocrine Disruptors is illustrated. Some indications to reduce the exposure risk to Endocrine Disruptors are suggested.

Keywords: Adverse effects, BPA, endocrine disruptors, environmental pollution, exposure risks.

1. INTRODUCTION

Since 1962 with the publication of the book "Silent Spring" by Rachel Carson [1] and, more, after the publication on 1996 of "Our stolen future" by Colburn *et al*. [2] there has been increasing awareness that some chemicals compounds in the environment exert harmful effects on wildlife and humans. Consequently the health of living organisms appears to be strictly related to the health of environment and the two systems reciprocally influence. These chemicals, having the potential to mimic or interfere with the hormones function in the body, have been called Endocrine Disruptors Chemicals (EDCs). Among the many definitions of Endocrine Disruptors we are particularly fond of that given by the World Health Organization and International Program on Chemical Safety: "An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations" [3] [WHO/IPCS, 2002]. All definitions, however, have in common the observation that the Endocrine Disruptors have the function of inducing biological effects mainly in the offspring of exposed subjects. Maybe this is one of the reasons by which the harmful effects of EDCs are often not considered and underestimated.

Chemicals with suspected disrupting activity encompass natural and synthetic hormones, pesticides, alkylphenols, bisphenol A, phthalates, dioxins, organotins, polyfluoroalkyl compounds, brominated flame retardants and heavy metals.

Pesticides include organochlorine pesticides (OCPs), organophosphates, carbamates, triazines and pyrethroids. The most famous OCP is the insecticide dichlorodiphenyl trichloroethane (DDT). Despite DDT has been banned in most developed countries its environmental contamination still persists.

Alkylphenols, such as Nonylphenol and Octylphenol, are surfactants widely used in detergents, emulsifiers and solubilizers. They are also used as additives to plastics, such as polyvinylchloride (PVC) and polystyrene, from which they can be released.

Bisphenol A (BPA) is the monomer constituting the polycarbonate plastic and it is used also in epoxy resins and as dental sealant. BPA, as the alkylphenols, is also used as additive to other plastics. BPA results to be one of the high-volume-production monomer ($>2.5 \times 10^6$) Kg/year and perhaps for this reason is the Endocrine Disruptor more

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studied. Halogenated derivatives of BPA are widely used as flame retardants.

Phthalates esters are used worldwide as softeners to impart flexibility and elasticity to otherwise rigid polymers such as PVC. These compounds are found mostly in industrial paints and solvents but also in toys, personal-care products, and medical devices such as intravenous tubing and blood transfusion bags.

Dioxins consist of a group of organochlorines including the polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs). Dioxins are fat-soluble and readily climb the food chain through bioaccumulation in fat tissues.

Organotins, including tributyltin chloride (TBT) and bis(triphenyltin) oxide (TPTO), are persistent organic pollutants that have been widely used as agricultural fungicides and in antifouling paints.

Polyfluoroalkyl compounds (PFCs) are synthetic fluorinated organic compounds used in a wide range of industrial applications and consumer products, including paper, leather, textile coatings, fire-fighting foam and in the polymer industry. Among them, the perfluorooctanesulfonic acid (PFOS) and the perfluorooctanoic acid (PFOA) are detected in the environment at high concentrations.

Brominated flame retardants (BFRs) are additives used in a great number of consumer products such as clothing, house electronic equipment and furniture.

Heavy metals, such as Fe, Cu, Cr, Zn, Pb, and Cd are persistent, ubiquitous and non-biodegradable elements with long biological half-live. They have been found to accumulate mainly in fish.

The majority of the EDCs is dispersed in the environment and, being persistent, can be transported at long distances. They have been found in all regions of the world, some unexpected, as the Arctic one. Others EDCs are rapidly degraded. This does not mean that their dangerousness disappears, since in some cases the degradation products are more dangerous and toxic than the parents.

Concerns regarding EDCs exposure are mainly due: i) to the adverse effects observed in some wildlife, fish, and in ecosystems; ii) to the increased incidence of some endocrine-related human diseases; and iii) to their biological effects observed also at low doses in studies on laboratory animals. As a consequence, in agreement with international political and scientific organizations, many national governments established specific research programs to address and evaluate the risks associated to EDCs exposure.

Despite the numerous scientific publications (9,800 documents surveyed in SCOPUS and 5,200 in PubMed at April 2015) no certainty on the real risk from exposure to EDCs has been acquired and the debate is still alive whether this argument is a legend or a fact [4]. This disagreement is due since: a) the exposure to the same level of an endocrine signal during different life stages may produce different effects; b) the exposure when the “planning” of endocrine system is in progress may result in a permanent change of function or sensitivity to stimulatory/inhibitory signals; c) the exposure during the adulthood can be compensated for by normal homeostatic mechanisms and may therefore not result in significant or detectable effects. Moreover several studies on EDCs have approached this kind of chemicals using toxicological methods. The problem is that EDCs exert their biological effects in non-toxic concentration.

Endocrine disruptors act through genomic and non-genomic pathways. They can interact *via* nuclear receptors, non nuclear steroid hormone receptors (membrane ERs), non steroid receptors (neurotransmitter receptors such as the serotonin receptor or the dopamine receptor), aryl hydrocarbon receptors (AhRs), enzymatic pathways involved in steroid biosynthesis and/or metabolism, and numerous other mechanisms affecting the endocrine and reproductive systems.

The most important aspects of endocrine disruption are related to xenoestrogens, antiestrogens, antiandrogens, disruption of thyroid function, disruption of corticoid and reproductive functions, and other metabolic disorders.

Several experimental observations and laboratory studies have shown that exposure to EDCs induces adverse effects in living species. These effects range from subtle changes in the physiology and sexual behavior of exposed species, permanently altered, to sexual differentiation. Aquatic species seem to be the most affected, but relevant effects have also been observed in terrestrial animals. Effects have also been observed in humans. The major route of exposure for humans is food.

A brief list of adverse effects, related to the exposure to EDCs and observed in wildlife and humans, is here in the following reported.

2. WILDLIFE

2.1. Vertebrates

A spill of pesticides in the Lake Apopka (Florida, USA) provides one of the first examples of potential EDCs effects on population decline in alligators [5, 6]. Gonad and developmental abnormalities were attributed to high levels of various organochlorine contaminants that disrupt endocrine homeostasis [7, 8]. Similarly marked population declines, related to dysfunction of reproductive system or to immune function, have been observed in Baltic seals owing the exposure to organochlorines (PCBs, DDT) pesticides [9] and heavy metals [10]. In addition egg shell thinning and altered gonad development have been observed in birds exposed to DDT [11]. Moreover in **G**reat **L**akes **e**mbryo **m**ortality, **e**dema and **d**eformities **s**yndrome (GLEMEDS) have been observed in several species of colonial fish-eating birds there resting [12].

2.2. Invertebrates

Exposure of marine gastropods to Tributyltin provided the clearest example of endocrine-mediated adverse effects in invertebrates caused by exposure to environmental contaminants. Masculinization of marine gastropods exposed to TBT has resulted in worldwide declines of gastropods [13]. The imposition of masculine characters on female species is known as IMPOSEX [14].

3. HUMANS AND ANIMAL MODELS

The impossibility of performing experiments on humans is the main drawback in establishing the relationship of cause and effect between adverse effects and exposure to EDCs for humans. To this aim only epidemiological studies on large numbers of persons are required and only indirect conclusions can be derived.

In vitro studies on human cell lines represent a useful tool to evaluate adverse outcome pathways and information on EDCs mechanism of action. In addition, animal models are used to confirm the cause-effect relationship of EDCs exposure and diseases.

A brief list of some EDCs-related diseases is reported in the following.

3.1. Reproductive Effects

EDCs are able to act on both male and female reproductive systems. A number of studies in several countries [15 - 17] reported a decline in male sperm quality and quantity. Even if the deterioration in semen quality has been observed, this not necessarily has been attributed to endocrine disruption by EDCs. Analysis of existing studies reached different conclusions and the issue remains controversial. In any case, available human and experimental animal studies demonstrated that high-level exposure to some environmental chemicals impairs fertility and increases the rate of spontaneous abortion [18, 19]. Declining sex ratios (fewer males) have been recorded in a number of regions and countries [20, 21] evidencing how external influences, such as exposure to EDCs, are associated with these changes. Unlikely the involved mechanisms are still unknown. Incidentally it is interesting to observe as sex ratio decreases have been observed also in bivalves grown in polluted waters [22]. Development abnormalities of the male reproductive tract, particularly cryptorchidism and hypospadias [17, 23, 24], have been reported, but also in this case the role of exposure to EDCs is still unclear. Experimental data, in any case, show that some chemicals can alter the development of the male reproductive tract *via* endocrine mechanisms, acting as xenoestrogens or antiandrogens.

It has been also suggested an association between EDCs exposure and age of menarche in girls living in industrialized countries [25] as well as there are strong evidences that the duration of menstrual cycle is influenced by EDCs [25 - 27]. Besides, strong link between exposure to Endocrine Disruptors and endometriosis has been reported. Recent experiments on animal models [28] and epidemiological studies in women with endometriosis have shown, beyond any doubt, the existence of this strong relationship [29, 30].

3.2. Hormone Related Cancer

Several epidemiological and *in vitro* studies suggest a link between EDCs and some types of cancer, such as testicular, prostate, breast, thyroid and endometrial cancer [31].

3.2.1. Breast and Endometrial Cancer

Epidemiological studies revealed that xenoestrogens are related to an elevated risk of breast cancer development [32]. BPA, for example, has been found to be able to up-regulate breast cancer marker genes on human cell lines [33]. It has been also reported a relationship between high serum level of 2,2-bis(p-chlorophenyl)-1,1-dichloroethylene (DDE) and endometrial hyperplasia, the first step for the onset of endometrial cancer [34].

3.2.2. Testicular and Prostate Cancer

Increases in the incidence of testicular cancer have been reported and associated to EDCs exposure [35]. The incidence of cryptorchidism and hypospadias has shown similar geographic variations. In some studies it has been suggested that exposure to some pesticides and organochlorines increases in the incidence of prostate cancer [31]. Other studies, however, have not found this association and the mechanism remains unknown.

3.2.3. Thyroid Cancer

A direct association between exposure to EDCs and thyroid cancer has not been soundly demonstrated, even if an increasing number of studies on this topic is well documented [31, 36]. A strong incidence of thyroid cancer and pesticide exposure has been observed in people working in agriculture [37 - 39].

3.3. Cardiovascular Diseases and Obesity

Recent studies reported the influence of some EDCs on cardiac diseases (arrhythmias, blood pressure, and so) and obesity. Moreover, a dramatic increase of metabolic disorders has been observed in the recent years. For example, BPA has been recognized to act as obesogen [40, 41] so inducing obesity in animal model and in children [42, 43]. Many results have evidenced the relationship between EDCs exposure and the onset of type 2 and type 1 diabetes [44, 45].

Before concluding this introduction it is important to underline that even if there are strong data supporting the relationship between EDCs and some disorders, very often they are not sufficient to give certainty. In the presence of this ambiguity may be important: 1) to apply bluntly the precautionary principle reducing their presence in consumer products; 2) to implement researches to find new substitutes without estrogenic activity; 3) to implement the studies on the molecular mechanisms and pathways underlying the direct action of EDCs exposure on functioning and regulation of cellular machine; 4) to develop more effective pollution removal systems, 5) to consider the real situation for establishing new safety thresholds considering that humans are exposed to mixtures of weakly active substances that can produce additive or even synergistic effects: the well known “cocktail effect”. Thus there is a strong difficulty of considering all possible pollutants to which humans are exposed simultaneously and the consequent risks for human health [46, 47].

If only these indications are seriously considered, environmental health would be better preserved, the biodiversity of the species would be better safeguarded, and the quality of health of humans would be better guaranteed.

To conclude it is important to notice that the debate on the risks for humans associated to EDCs exposure cannot be clarified until contradictory inputs are coming from the authoritative sources. It is very confusing to declare, for example, that BPA uptake through the food is not dangerous for humans and simultaneously to establish a reduction of the temporary Tolerable Daily Intake (t-TDI) from 50 μg/kg body weight per day to 4 μg/kg body weight per day (Scientific Opinion on the risks to public health related to the presence of Bisphenol A (BPA) in foodstuffs published on 21 January 2015 on EFSA Journal 2015; 13: 3978).

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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