Endocrine Disrupters: The Hazards for Human Health

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Abstract
In last decades an increasing number of cases have been described in humans and wildlife ascribed to the effects of xenobiotics compounds which interfere with hormonal system. Generically, these compounds are described as endocrine disrupters; due to their potential hazard they have received great attention by the scientific community and the media. In this brief editorial will be considered some general aspect, and in particular related to a class of endocrine disrupters: the organophosphate pesticides.

Introduction
Related to the industrial and agricultural activities thousands of compounds have been released into the environment, being not of natural origin they undergo a slow degradation. Some of these compounds are able to bind receptors of various hormones as agonists or antagonists, because they are spread in soils and waters they are found in the food chain reaching high levels of dangerousness. These compounds are known as Endocrine Disrupters compounds (ED), in particular they interfere with the synthesis, secretion, transport, binding, action or elimination of natural hormones in the body, responsible for the development, behavior, fertility, and maintenance of cellular homeostasis. These substances can be natural constituents of some foods, such as phytoestrogens contained in Medicago sativa (used as forage) and Soya beans, or xenobiotic compounds.

In 1999 European Commission lunched a strategy, reported in document COM (1999)706, to list a number of substances to be evaluated as possible endocrine disrupters. At beginning were considered 564 substances: 118 with evidence of ED or evidence of potential ED; 11 substances considered not to be ED based on available data and 435 substances with insufficient data to assess the hazards. Among these there were alkylbenzenes, alklyphenoles, bisphenoles, chlorophenols, benzenes, furanes, dioxins, phthalates, triazines, triazoles and pesticides (DDT derivatives and metabolites, carbamates, chlorophenols, benzenes, furanes, dioxins, phthalates, triazines, triazoles and pesticides (DDT derivatives and metabolites, carbamates, dithiocarbamates, organophosphates).

In the last 10 years, several in vitro and in vivo assays and theoretical predictions for ED have been developed to study mechanisms of action and to screen large numbers of chemicals for hormone activity, in order to ensure their safety. Actually about 800 chemicals are suspected to be ED, but only a small fraction is well known to affect the endocrine system. The lack of data leads to underestimate the risks from chemicals that potentially could disrupt the endocrine system. The results of many studies have highlighted that endocrine disrupters can have latent effects due to the exposure during early life or even in past generation (epigenetic effects), generating some questions, such as: When the exposure occurred? What is the magnitude of the exposure? What is the length of exposure? How the exposure is measured? What are the critical windows in development when ED would most likely occur? It’s difficult to answer at these questions because it must consider critical time windows for exposure, the long latency between exposure and effect, and the realization that every similar acting ED in a combination contributes to the overall mixture effect; this is a problem related to the pesticides (organophosphates or not), because they are used in different combinations and at different stages of growth and fruits ripening.

The Endocrine System
To understand why the ED are very dangerous to human health, it is necessary to introduce -briefly-what is the endocrine system and how it is regulated. The endocrine system is constituted by a series of ductless glands that secrete hormones into the blood, hormones are essential to regulate the majority of physiological functions. Hormones can be defined as molecules produced by endocrine glands circulating into the blood to reach their target [1]. Typically, the endocrine glands are the pituitary gland, hypothalamus and pineal gland in the brain, the thyroid and parathyroid glands, the adrenal glands, thymus, the gonads and pancreatic islets; moreover there are other organs that have secondary endocrine functions, such as heart, adipose tissue, kidneys and gastrointestinal tract (Figure 1). Circulating hormones act on cells and tissues recognized by specific receptors. Hormones are fundamental for to control many processes in the body, and differently...
during the embryogenesis, cell differentiation, organogenesis and function regulation in adults; this is valid for both vertebrates and invertebrates [1].

Environmental Factors and Diseases

Some studies have shown that about 25% of human diseases take as possible origin from environmental factors [2], because many diseases take origin from disorders of the endocrine system, the attention has been focused on some chemicals that potentially could be considered endocrine disruptors; up today more than 500 scientific publications report negative effects by chemicals on the endocrine system. Many evidences has been obtained by studying restricted area in which animals and peoples consuming the same food or being included in the same food chain shown similar diseases. An example is Greenland, in this huge island population has a traditional diet based mainly on fish, shellfish and shrimp caught in the area, native birds and whales, these animals have the characteristic to accumulate some contaminants in muscle tissues, liver and in fats; so the regular consumption of these foods leads to the transfer and accumulation of contaminants in humans [3]. In particular, in a study about done 10 years ago, were measured levels of some contaminants in the tissues (cadmium, mercury, selenium, polychlorinated biphenyls (PCB), dichlorophenyltrichloroethane (DDT), Chlordane, hexachlorocyclohexanes (HCH), chlorobenzenes, dieldrin and toxaphene) and it was measured the average amount of each food consumed: the results showed that for some of these compounds, such as cadmium, chlordane and toxaphene levels were taken up to 6-7 times greater than the tolerable intakes; whereas mercury, PCB and dieldrin exceed approximately 50% [4-6]. Mercury [7], selenium [7], cadmium [7], DDT [8], PCB [9] are endocrine disrupters; the pesticides HCH are toxic but only suspected to be endocrine disrupters (http://www.mst.dk/English/Chemicals/endocrine_disruptors/the_EU_list_of_potential_endocrine_disruptors/). The presence of these chemicals in food chain lead to an accumulation of dangerous substances in human and wildlife populations because they have not mechanisms to detoxify and/or degrading these chemicals. For these reasons similar effect on endocrine system have been observed in human and animal [10], in particular have been observed deceased hatching in birds, turtles and fish [11,12], lower sperm quality in humans [13,14]; disordered behavior in birds and mammals, increase of malformations and cancers [15,16].

Pesticides as Endocrine Disrupters

Pesticides are considered very dangerous for their potential effects on human health and also because their extensive worldwide utilization leading to potentially widespread exposure through residues in food and environment. Many aspects about the toxicity of pesticides are well know, in particular about their neurotoxic effects, in fact pesticides organophosphates and carbamates act as covalent and irreversible inhibitors of acetylcholinesterase, the key enzyme of the central nervous system. It has been reported that many organochlorine pesticides, such as DTT, methoxychlor and dieldrine [8] are identified as endocrine disrupters, even if organophosphorous and carbamate pesticides are less persistent in the environment with respect to the organochlorines, they are also present in food and in animals and humans [17,18], many evidences are collecting regard their effect as endocrine disrupters [17,19-21].

Organophosphate pesticides are phosphoric, phosphonic, phosphinicon, phosphoramic acid derivatives, the phosphorous is linked by a double bond to an oxygen or sulphur atom, two alkoxy or amine group and an aromatic or heterocyclic group, among these chlorpyrifos (called also Dursban, Figure 3) has been the first introduced in commerce in 1965 [22], and for this reasons is one of most studied in terms of toxic effect on humans and wildlife. Up today has been reported several effects due to the exposure of chlorpyrifos at dose levels not inducing brain acetyl cholinesterase inhibition, in particular it has been shown in mammals and cell lines oxidative stress in the developing brain [21,23], brain defects [22], genital defects [24], estrogenic activity [25], moreover there are indication that chlorpyrifos may have effect on thyroid and adrenal gland homeostasis both in human and animal models [26,27]. In zebrafish can cause histopathological damage and induce the Hsp70 mediated response [28]. In bivalve chlorpyrifos induce defects in digestive gland in Mytilus galloprovincialis [29]. For other two organophosphate pesticides has been collected several data on their toxic effect: malathion and diazinon. In the case of malathion has been investigated its effect mixed with others pesticides, demonstrating an altered steroidogenesis in vitro [30] and early oogenesis in mice, when is in combination with diazinon [31]. Moreover there are evidences on diazinon that acts on cell adrenal gland and disruption of spermatogenic cell line in rat [32].

What Message

For authorities

It’s clear that when the toxicity of pesticides is investigated we get evidences on their effect as endocrine disruptors, and the effect seem...
to increase when there is a mixing of different compounds and/or pesticides.

In the case of pesticides quantifying the risks due to the different mechanisms of exposure will play an important rule to obtain an attenuation of risk due to their exposure.

The main difficulties to develop a model to predict the human risk by pesticide exposure are the uncertainties on the poor quality or paucity of the data available for some of them. There are at least five main ways of human exposure (agricultural spray drift, dietary exposure, municipal, medicinal and home pesticide use, Figure 2), which must be quantified and accurately monitored to allow the protection of human health and wildlife. Therefore, local and regional authorities constantly should monitor, regulate or reduce, if necessary, the use of certain pesticides.

For next generations

The message for the next generations should be that whatever is released into the environment early or later it will be in contact with humans and could have critical consequences for current and future generations.

From research

Currently there are many studies ongoing to design effective methods to remove pesticides from the environment, in particular a rapid increase in the field of bioremediation has been observed, principally based on the use of free enzymes and microorganisms [33-35] and microorganisms [36]. Encouraging results has been obtained but they are not applicable on a large scale, therefore the development of these new technologies is important but the rational use of pesticides and the control of industrial and urban waste is essential to preserve wildlife and human health.

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