Cloning & Transgenesis

Mandrich, Clon Transgen 2014, 3:1
DOI: 10.4172/2168-9849.1000e110

Editorial Open Access

Endocrine Disrupters: The Hazards for Human Health

Luigi Mandrich*

Institute of Protein Biochemistry, National Research Council, Italy

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, alkylphenoles, bisphenoles, 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 similarly 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

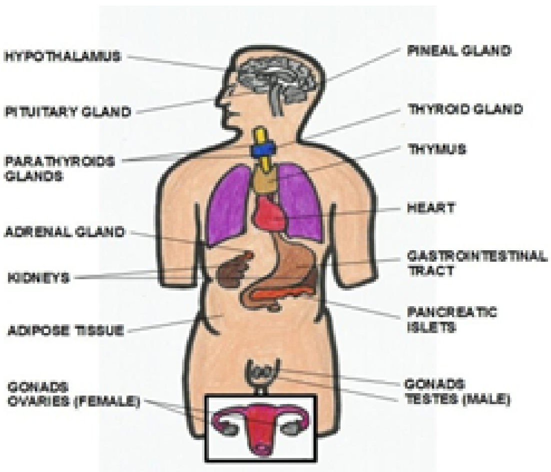

Figure 1: Schematic representation of endocrine system. Glands with primary endocrine function are pituitary gland, hypothalamus, pineal gland, thyroid and parathyroid glands, thymus, adrenal glands, pancreatic islets and gonads; organs showing secondary endocrine functions are heart, kidneys, adipose tissue and gastrointestinal tract (colored by Irene Mandrich).

***Corresponding author:** Luigi Mandrich, Institute of Protein Biochemistry, National Research Council. Via Pietro Castellino 111, 80131, Naples, Italy, Tel: +39 081 6132581; Fax: +39 081 6132248; E-mail: l.mandrich@ibp.cnr.it

Received January 16, 2014; **Accepted** January 17, 2014; **Published** January 19, 2014

Citation: Mandrich L (2014) Endocrine Disrupters: The Hazards for Human Health. Clon Transgen 3: e110. doi:10.4172/2168-9849.1000e110

Citation: Mandrich L (2014) Endocrine Disrupters: The Hazards for Human Health. Clon Transgen 3: e110. doi:10.4172/2168-9849.1000e110

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 done about 10 years ago, were measured levels of some contaminants in the tissues (cadmium, mercury, selenium, polychlorinated biphenylis (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, chlordanes 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, phosphinicor, phosphoramidic 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 homoeostasis 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

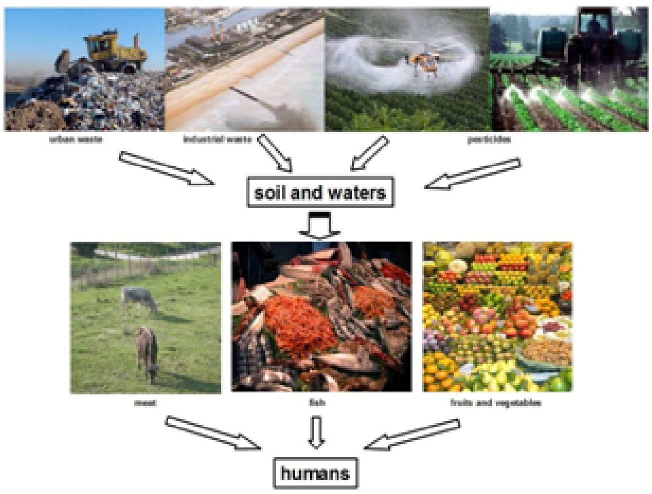

Figure 2: Schematic representation by pictures of sources and ways of contamination. The cycle of material released in the environment provides the absorption at various levels in animals and plants and therefore to humans.

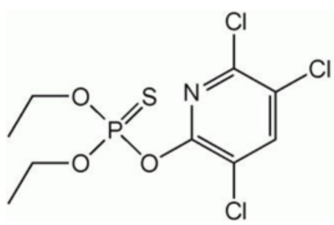

Figure 3: Structure of the organophosphate pesticide chlorpyrifos. The phosphorous is linked by a double bond to a sulphur atom, two alkoxy groups and a heterocyclic group.

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 [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.

References

1. Melmed S, Williams RH (2011) Williams textbook of endocrinology. Elsevier, Philadelphia.
2. Prüss-Üstün A, Corvalán C (2006) Analysis of estimates of the environmentally attributable fraction, by disease. Preventing disease through healthy environments: towards an estimate of the environmental burden of disease. World Health Organization. Geneva, Switzerland.
3. Johansen P, Muir D, Asmund G, Riget F (2004) Human exposure to contaminants in the traditional Greenland diet. Sci Total Environ 331: 189-206.
4. Johansen P, Asmund G, Riget F (2001) Lead contamination of seabirds harvested with lead shot--implications to human diet in Greenland. Environ Pollut 112: 501-504.
5. Hansen JC (1998) Pollution and Human Health. AMAP Assessment Report: Arctic Pollution Issues. Arctic Monitoring and Assessment Programme (AMAP), Oslo, Norway.
6. van Oostdam J, Trembley N (2003) Biological monitoring: human tissue levels of environmental contaminant. AMAP Assessment 2002: Human Health in the Arctic. Arctic Monitoring and Assessment Programme (AMAP), Oslo, Norway.
7. Dickerson EH, Sathyapalan T, Knight R, Maguiness SM, Killick SR, et al. (2011) Endocrine disruptor & nutritional effects of heavy metals in ovarian hyperstimulation. J Assist Reprod Genet 28: 1223-1228.
8. Bretveld RW, Thomas CM, Scheepers PT, Zielhuis GA, Roeleveld N (2006) Pesticide exposure: the hormonal function of the female reproductive system disrupted? Reprod Biol Endocrinol 4: 30.
9. McGovern V (2006) PCBs Are Endocrine Disruptors: Mixture Affects Reproductive Development in Female Mice. Environ Health Perspect 114: A368-A369.
10. Nicolopoulou-Stamati P, Pitsos MA (2001) The impact of endocrine disrupters on the female reproductive system. Hum Reprod Update 7: 323-330.
11. Fry DM (1995) Reproductive effects in birds exposed to pesticides and industrial chemicals. Environ Health Perspect 103 Suppl 7: 165-171.
12. Muir D, Braune B, DeMarch B, Norstrom R, Wagemann R, et al. (1999) Spatial and temporal trends and effects of contaminants in the Canadian Arctic marine ecosystem: a review. Sci Total Environ 230: 83-144.
13. Bromwich P, Cohen J, Stewart I, Walker A (1994) Decline in sperm counts: an artefact of changed reference range of "normal"? BMJ 309: 19-22.
14. Auger J, Kunstmann JM, Czyglik F, Jouannet P (1995) Decline in semen quality among fertile men in Paris during the past 20 years. N Engl J Med 332: 281-285.
15. Dich J, Zahm SH, Hanberg A, Adami HO (1997) Pesticides and cancer. Cancer Causes Control 8: 420-443.
16. Palanza P, Morellini F, Parmigiani S, vom Saal FS (1999) Prenatal exposure to endocrine disrupting chemicals: effects on behavioral development. Neurosci Biobehav Rev 23: 1011-1027.
17. Wright JP, Shaw MC, Keeler LC (2002) Refinements in acute dietary exposure assessments for chlorpyrifos. J Agric Food Chem 50: 235-241.
18. Schulz R (2004) Field studies on exposure, effects, and risk mitigation of aquatic nonpoint-source insecticide pollution: a review. J Environ Qual 33: 419-448.
19. Kang HG, Jeong SH, Cho JH, Kim DG, Park JM, et al. (2004) Chlropyrifos-methyl shows anti-androgenic activity without estrogenic activity in rats. Toxicology 199: 219-230.
20. Joshi SC, Mathur R, Gulati N (2007) Testicular toxicity of chlorpyrifos (an organophosphate pesticide) in albino rat. Toxicol Ind Health 23: 439-444.
21. McKinlay R, Plant JA, Bell JN, Voulvoulis N (2008) Endocrine disrupting pesticides: implications for risk assessment. Environ Int 34: 168-183.
22. Eaton DL, Daroff RB, Autrup H, Bridges J, Buffler P, et al. (2008) Review of the toxicology of chlorpyrifos with an emphasis on human exposure and neurodevelopment. Crit Rev Toxicol 38 Suppl 2: 1-125.
23. Slotkin TA, Seidler FJ (2009) Oxidative and excitatory mechanisms of developmental neurotoxicity: transcriptonal profiles for Chlorpyrifos, Diazinon, Dieldrine, and divalent Nikel in PC12 cells. Environ Health Perspect, 117: 587-596.
24. Sherman JD (1996) Chlorpyrifos (Dursban)-associated birth defects: report of four cases. Arch Environ Health 51: 5-8.
25. Andersen HR, Vinggaard AM, Rasmussen TH, Gjermandsen IM, Bonefeld-Jørgensen EC (2002) Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro. Toxicol Appl Pharmacol 179: 1-12.
26. Jacobsen H, Østergaard G, Lam HR, Poulsen ME, Frandsen H, et al. (2004) Repeated dose 28-day oral toxicity study in Wistar rats with a mixture of five pesticides often found as residues in food: alphacypermethrin, bromopropylate, carbendazim, chlorpyrifos and mancozeb. Food Chem Toxicol 42: 1269-1277.
27. Jeong SH, Kim BY, Kang HG, Ku HO, Cho JH (2006) Effect of chlorpyrifos-methyl on steroid and thyroid hormones in rat F0- and F1-generations. Toxicology 220: 189-202.
28. Scheil V, Zürn A, Köhler HR., Triebskorn R. (2010) Embryo development, stress protein (Hsp70) responses, and histopathology in zebrafish (Danio rerio) following exposure to nickel chloride, chlorpyrifos, and binary mixtures of them. Environ Toxicol 25: 83-93.
29. Canesi L, Negri A, Barmo C, Banni M, Gallo G, et al. (2011) The organophosphate Chlorpyrifos interferes with the responses to 17Î²-estradiol in the digestive gland of the marine mussel Mytilus galloprovincialis. PLoS One 6: e19803.
30. Taxvig C, Hadrup N, Boberg J, Axelstad M, Bossi R, et al. (2013) In vitro-in vivo correlations for endocrine activity of a mixture of currently used pesticides. Toxicol Appl Pharmacol 272: 757-766.
31. Bonilla E, Hernández F, Cortés L, Mendoza M, Mejía J, et al. (2008) Effects of the insecticides malathion and diazinon on the early oogenesis in mice in vitro. Environ Toxicol 23: 240-245.
32. Jayachandra S, D'Souza UJ (2013) Pre- and postnatal toxicity of diazinon induces disruption of spermatogenetic cell line evidenced by increased testicular marker enzymes activities in rat offspring. J Environ Pathol Toxicol Oncol 32: 73-90.

33. Cheng TC, DeFrank JJ, Rastogi VK (1999) Alteromonas prolidase for organophosphorus G-agent decontamination. Chem Biol Interact 119-120: 455-62.

34. Aubert SD, Li Y, Raushel FM (2004) Mechanism for the hydrolysis of organophosphates by the bacterial phosphotriesterase. Biochemistry 43: 5707-5715.

35. Merone L, Mandrich L, Porzio E, Rossi M, Müller S, et al. (2010) Improving the promiscuous nerve agent hydrolase activity of a thermostable archaeal lactonase. Bioresour Technol 101: 9204-9212.

36. Singh BK (2009) Organophosphorus-degrading bacteria: ecology and industrial applications. Nat Rev Microbiol 7: 156-164.