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Endocrine disruptors

Endocrine Disruptor Compounds (EDCs) and agriculture: The case of pesticides

Yves Combarnous [a,b,*]

[a] INRA, CNRS, université de Tours, UMR « Physiologie de la reproduction & des comportements », 37380 Nouzilly, France
[b] Académie d'agriculture de France, 75015 Paris, France

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ABSTRACT

A number of pesticides are suspected or proved to act as endocrine disruptor compounds (EDCs). In the present survey of the literature, we try to define the main issues to be considered to classify individual pesticides as EDC or not.

1. Introduction

Pesticides are synthetic molecules aimed at being toxic towards fungi, plants or animals that are detrimental to cultures. Fungicides, herbicides, and insecticides have been developed in order to control as specifically as possible these pests in order to protect cultures. Nevertheless, these pesticides can be toxic to Human and wild fauna. These molecules are intended to be toxic since they are aimed to destroy living organisms, but they are selected to affect precise steps in target organism(s) that are not present in non-target organisms. Also, their intended use is to acutely eradicate unwanted species, and most toxicity tests are also done in acute situations rather than in long-term experiments. And it is generally in long-term situations that xenogeneic molecules can potentially act as endocrine disruptors.

Our aim in the present paper is to define the functional characteristics of endocrine disruptors in order to evaluate if their toxicity toward non-target species is primarily due to endocrine disruption or not.

2. Endocrine disruptors definition(s)

Endocrine disruptor compounds (EDCs) have been defined in 2002 by the WHO: "An endocrine disruptor 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".

The endocrine system is constituted by a large network of hormones allowing the coordinate functions of dozens of different cell types in multicellular organisms. This network possesses numerous loops of stimulation and retroaction in cascade so that the different physiological parameters (such as glycaemia, lipedema, hydro-mineral balances, etc.) and physiological functions (such as development, growth, reproduction, etc.) are set in the proper range for the good health of the whole organism and for the survival of the species.

* INRA, CNRS, université de Tours, UMR « Physiologie de la reproduction & des comportements », 37380 Nouzilly, France.
E-mail address: Yves.Combarnous@inra.fr.

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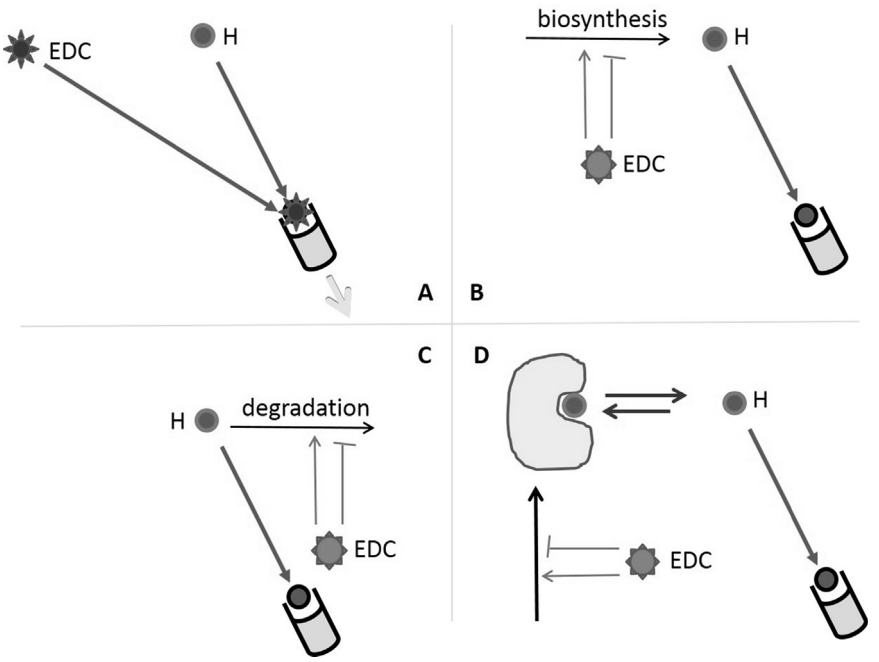

Fig. 1. Mechanisms of action of Endocrine Disruptor Compounds (EDCs). **A**. Direct interaction of EDC with a hormone nuclear receptor leading to stimulation (agonism) or inhibition (antagonism) of its transcriptional activity. **B**. Stimulation or inhibition of endogeneous hormone biosynthesis. **C**. Stimulation or inhibition of endogeneous hormone degradation. **D**. Stimulation or inhibition of endogeneous hormone binding protein leading to decreased or enhanced circulating hormone availability.

In this paper, our aim is to introduce a number of central questions concerning EDCs with particular interest in pesticides.

3. Endocrine disruption mechanisms

EDCs are molecules, natural or synthetic, that happen to interfere with the endocrine network of vertebrates, provoking adverse dysregulation of the hormonally controlled physiological parameters or functions [1]. This interference can occur through different mechanisms (Fig. 1) either directly by binding to the hormone receptor, or indirectly by increasing or decreasing the concentration of endogenous hormone(s):

- the most direct one is an interaction of the EDCs with an hormone receptor leading either to stimulation (Fig. 1A) [2] or inhibition (Fig. 1A) of downstream cellular pathway in target cells;
- or endogenous active hormone concentrations can be affected by the stimulation or inhibition of either their synthesis (Fig. 1B), or degradation (Fig. 1C) [2,3], or availability (Fig. 1D).

A number of *in vitro* and *in vivo* tests have been set up by diverse national and international agencies to identify EDCs [4–7].

4. Structures and intended toxic activity of pesticides

A large majority of pesticides are small organic molecules with molecular weights around 300 to 2000 Da.

The insecticides control insects by interfering with their nervous system or by inhibiting their molt. For example, acetylcholinesterase inhibitors (organophosphates, carbamates) and sodium channel agonists (pyrethroids) act on the insect's nervous system [8,9] as well as neonicotinoid insecticides (imidacloprid, acetamiprid, thiacloprid, clothianidin, thiamethoxam, and dinotefuran) that act through their preferential affinity for nicotinic receptor (nAChR) subtypes [10–15]. The latter have favourable safety profiles, due to their poor penetration of the mammalian blood–brain barrier and low application rates, and they effectively control pest species that have evolved resistance to other insecticide classes. However, due to their high intrinsic toxicity to honey bees [16,17], nitro-substituted neonicotinoid insecticides have been intensively examined worldwide by regulatory agencies and temporarily suspended in the European Union for seed treatment, soil application, and foliar treatment in crops attractive to bees. This illustrates the difficulty to develop and use insecticides without affecting non-target insects [18,19].

The herbicides control development of unwanted plants by inhibiting synthesis of some of their amino-acids or their photosynthesis or by specifically antagonizing the action of natural regulators of their development [20–22]. For example, triketone herbicides alter the formation of carotenoids and therefore disrupt the photosynthetic electron transport in plants. Since the aim is to have physiological impact on specific weeds and not on crops, the rapid metabolism of triketones by maize, in particular by cytochrome P450 enzymes, makes this plant insensitive to the herbicide treatment [23]. A precise knowledge of the weed species is important to obtain maximum efficiency by

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