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Thuốc trừ sâu: mục tiêu, cơ chế hoạt động và đánh giá rủi ro

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TÓM TẮT

Thuốc trừ sâu (chủ yếu là thuốc diệt cỏ, diệt côn trùng, sâu và diệt nấm) được sử dụng để tiêu diệt một số loài thực vật, động vật hoặc vi sinh vật có hại cho nông nghiệp. Do những điểm tương đồng cơ bản trong tất cả các sinh vật sống, việc tấn công mục tiêu là các loài không mong muốn mà không ảnh hưởng đến những loài khác, kể cả con người là một thách thức. Theo quan điểm này, việc xác định chính xác các phân tử hoặc cơ chế tấn công mục tiêu của thuốc trừ sâu là vô cùng quan trọng để đánh giá rủi ro và phát triển các chế phẩm thuốc trừ sâu hiệu quả, ít gây nguy hiểm đến cây trồng, động vật hoang dã và con người. Bài báo này sẽ trình bày ngắn gọn về các nhóm thuốc trừ sâu phổ biến, cơ chế hoạt động cũng như độc tính của chúng đối với mục tiêu và tác dụng phụ có thể xảy ra đối với các thành phần của môi trường như quần thể côn trùng và thực vật, không khí, nước hoặc hệ sinh vật đất.

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Pesticides: targets, mechanisms of action, and risk assessment

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ABSTRACT

Pesticides (mainly herbicides, insecticides, and fungicides) are used to chemically combat certain plants, animals, or microorganisms perceived as harmful to agriculture. Due to the fundamental similarities in all living beings, it is challenging to target unwanted species without affecting others, including humans. In this perspective, precisely identify the molecules or mechanisms targeted by pesticides is of utmost importance for assessing risk and developing efficient pesticide preparations with limited damage to crops, wildlife and humans. This review will briefly present the group of common pesticides, their mechanisms of action as well as their toxic effects on the target and possible side effects on the components of the environment such as insects and plants populations, air, water, or soil biota.

1. INTRODUCTION

Originally, the term pest was limited to "*Insects or small animals which damage crops or food supplies*".[1] With this first definition, only insecticides (meaning insect killer) and rodenticides (rodent killer in general) would be called pesticides. The definition has now been extended to "*Something resembling the pest (plague) in destructiveness especially, a plant or animal detrimental to humans or human concerns, such as agriculture or livestock production*".[2] With this definition, herbicides are included among pesticides, representing about 80% of their total use. Moreover, in the scientific literature, fungicides (fungi killers) and bactericides (bacteria killers) are now taken into consideration under the general term of "pesticide" as well as many specialized products such as molluscicides (snails and slugs killers), nematicides (nematodes killer), etc.

The pesticides are intended to protect crops by acting against deleterious weeds, insects (and other invertebrates), fungi, or microorganisms. It is obvious that the mechanisms of action against such a variety of targets should be different to retain the highest possible specificity to destroy the undesired species without negatively affecting the crop to be protected as well as humans and wildlife.[3] About a thousand chemical pesticides

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employing more than a hundred unique mechanisms have been developed. One of the challenge is to have available strains resistant to the pesticides used against the organisms harmful to the crops.[3] Thus, it is of utmost importance to have good knowledge of the pesticides targets and mechanisms of action to protect crops without affecting wildlife and human health.

2. PESTICIDE FAMILIES (STRUCTURES AND TARGETS)

Numerous pesticides with various structures have been developed to combat different pests affecting crops (Table 1 and figure 1). In term of total quantity, around 55% are herbicides, 6% insecticides and 29% fungicides in order to control ~1800 weeds, ~10 000 insect pests, and ~80 000 fungi.

Table 1. Overview of the main classes of pesticides.

Chemical Class	Herbicides	Insecticides	Fungicides
Organochlorines	2,4-Dichlorophenoxyacetic acid (2,4-D) dichlorodiphenyltrichloroethane (DDT)	Endosulfan	Hexachlorobenzene
Organophosphates	Glyphosate	Diazinon, Omethoate, Dimethoate, Chlorpyrifos, Maldison, Methidathion	
Carbamates and thiocarbamides		Aldicarb, Carbofuran, Oxamyl, Carbaryl, Methomyl, Pirimicarb, Thiodicarb	
Metal-organic dithiocarbamates	Nabam (algicide)		Maneb, Mancozeb, Zineb
Urea derivatives	Diuron, Fenuron, Metoxuron, Miuron, Linuron, Monuron		
Heterocyclic compounds	Brassinazole	Triazines Atrazine	Strobilurins, Benzimidazole, Triazole derivatives
Phenol and nitrophenol derivatives	Dinocap	Dinoseb	Dinoseb
Fluorine-containing compounds	Phenylpyrazoles, Acetopyrazole	Fipronil	Dichlofluanid
Copper-containing compounds			Cuprous oxide, Copper sulfate, Copper octanoate. Copper hydroxide, Copper oxychloride sulfate

Synthetic pyrethroids	Allethrin, Alpha-cypermethrin, Beta-cyfluthrin, Bifenthrin Cypermethrin, Cyfluthrin, Deltamethrin, Esfenvalerate, Fluvalinate, Fenvalerate, Lambda-cyhalothrin, Pyrethrins
Neonicotinoids	Acetamiprid, Clothianidin, Imidacloprid, Thiamethoxam
Others	Spiroxamine

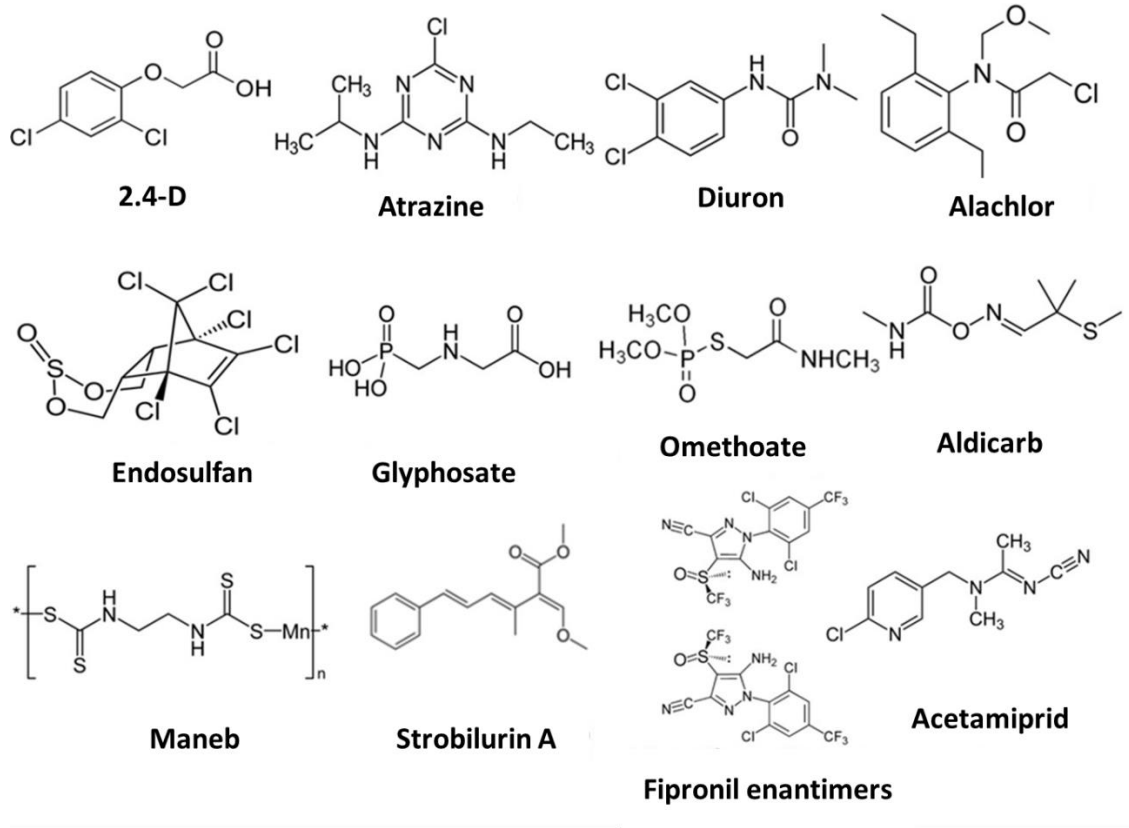

Figure 1. Chemical structure of a few pesticides.

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2.1. Herbicides

Prominent herbicides belong to seven main families:

1) Photosystem II (PSII) inhibitors showing various cross-resistances among sub-families a) triazines (e.g. atrazine), pyridazinone (e.g. pyrazon), phenylcarbamate, b) anilide (e.g. propanil), ureas (e.g. diuron), c) benzothiadiazinone (e.g. bentazone), hydroxybenzonitrile (e.g. bromoxynil).

2) Superoxide promoters in chloroplasts such as paraquat and diquat.

3) Shikimimate inhibitors such as glycine derivatives (e.g. glyphosate).

4) Tubulin polymerization inhibitors such as dinitroanilines (e.g. pendimethalin).

5) Gibberillin pathway inhibitors such as chloroacetamides (e.g. acetochlor, S-metolachlor).

6) Auxin pathway disruptors such as phenoxy and benzoic acids (e.g. 2,4-dichloro-phenoxyacetic acid 2,4-D).

7) 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitors (e.g. mesotrione).

2.2. Insecticides

Prominent chemical insecticides include organochlorines, organophosphates, carbamates, pyrethroids, and neonicotoicoids.

1) Organophosphates (e.g. chlorpyriphos, acephate, dimethoate) and carbamates largely replaced organochlorines such as DDT. All operate through the inhibition of the acetylcholinesterase enzyme (AChE), causing acetylcholine to transfer nerve impulses endlessly, and then inducing weakness or paralysis. The toxicity of Organophosphates to vertebrates led to their partial replacement by the less toxic carbamates (e.g. carbofuran).

2) Pyrethroid insecticides (e.g. λ-cyhalothrin) are the synthetic counterparts of the pyrethrin pesticide, naturally found in chrysanthemums.

3) Neonicotinoids (e.g. imidacloprid) are insecticides of the neuro-active class structurally similar to nicotine[5-6] and target the nicotinic ACh receptor (nAChR).

2.3. Fungicides

Contact fungicides work by preventing fungal spores from germinating or penetrating into the plant from the leaf surface. They require care in the application as complete coverage is essential for effectiveness.

Penetrant fungicides work inside the plant and can be locally systemic or translocated throughout the plant. They can be preventative and curative.

The most common fungicides are:

1) Respiration inhibitors like succinate dehydrogenase inhibitors (SDHIs) or quinone outside inhibitors (QoIs).

2) Sterol biosynthesis inhibitors such as demethylation inhibitors DMIs which disrupt the fungi cell membrane and organelles after spore germination.

3) Fungicides are also necessary to combat fungi affecting animals, particularly humans (*Candida albicans* and others). These products for humans are pharmaceutical drugs and not « pesticides » as they are not dispersed in the environment to protect crops. Nevertheless, themselves or their metabolites can be found in the environment and exert toxic effects.

3. PESTICIDE CHEMICAL STRUCTURES AND MECHANISMS OF ACTION

Depending on their structure (Figure 1), the most commonly used pesticides can be divided into different chemical groups[7] with various usages (Table 1). The different biological targets are, of course, determined by the chemical structure of their targets. It is expected that chemical specificity would lead to biological specificity. Nevertheless, many of them exert non-specific oxidative stress.[8] A number of pesticides now consist of microorganisms or toxins from them, instead of chemicals.[9-10]

3.1. Herbicides

The main molecular targets of herbicides are the following:

1) Auxin (IAA) receptor (2,4-D, 2,4,5-T, phenoxy, and benzoic acids): The strong downstream stimulation of the auxin signaling pathway leads to uncontrolled growth of meristem cells, disorganizing the development of their vascular structures.[11] These pesticides kill most broad-leaf weeds such as plantain, common chickweed, dandelion, ground ivy, yellow wood sorrel, prostrate knotweed, or white clover.

2) Acetolactate synthase (sulfonylurea derivatives): The inhibition of this enzyme controlling the branched-chain amino acid biosynthetic pathway[12] in targeted weeds leads to their death by starvation and also breakdown, accelerated at a high light intensity, in the electron transport process.

3) D-1 plastoquinone-binding (QB) protein in photosystem II electron transport (triazines): These herbicides inhibit photosystem II by disturbing the photosynthetic electron transport through competition with the native plastoquinone for the D1 protein QB-specific site.[13-15]

4) BZR1 (Brassinazole Resistant 1) transcription factor (brassinazole triazole): Brassinazole inhibits brassinosteroid effects through binding to the BZR1 (Brassinazole Resistant 1) transcription factor in the targeted weeds.[16-18]

5) 5-enolpyruvylshikimate-3-phosphate synthase (glyphosate): Through this inhibition of 5-enolpyruvylshikimate-3-phosphate synthase, glyphosate disrupts the shikimic acid pathway, which is indispensable for the synthesis of aromatic amino acids, and thus for protein (including enzymes) expression in the targeted weeds[19] but also in a number of prokaryotes and fungi.[20-22]

3.2. Insecticides

The main targets of insecticides are the following:

1) Acetylcholinesterase (organophosphoruses, carbamates, neonicotinoids): The inhibition, by covalent binding to an active site serine residue of cholinesterase (AChE), at the cholinergic junctions of the target insect nervous system, leads to a sustained, lethal influx.[23-25] Together, the different insecticides can exert additive effects if acting the same way, or synergic effects if not.[26-27]

2) GABA-gated chloride channel (fipronil, endosulfan, lindane,): These compounds act as antagonists by stabilizing non-conducting conformations of the chloride channel and so antagonize the GABA action on insect neurons in a noncompetitive manner.[28-31]

3) Ca^{2+}, Mg^{2+} ATPase inhibitor (endosulfan): Endosulfan uncouples oxidative phosphorylation and inhibits the electron transport chain. The *in vivo* cytotoxic/insecticidal effects of endosulfan and its metabolites could be damaged mitochondrial bioenergetics.[32]

4) Cytochrome P450 monooxygenase induction (atrazine): atrazine increases cytochrome P450 monooxygenase activity by enhancing their oxidative activation to sulfoxide analogs with increased anticholinesterase activity, leading to increased toxicities of demeton-S-methyl, disulfoton, and dimethoate.[33] In contrast, atrazine may reduce omethoate toxicity by enhancing oxidative metabolic detoxification because it does not need oxidative activation.[34]

5) Antioxidant enzymes (organophosphoruses, diazinon): The inhibition of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione S-transferase (GST), and Paraoxonases (PONs), which act as free radical scavengers, plays a complementary role in the effect of organophosphoruses, in particular for diazinon.

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6) Insect midgut enzymes and transporters (*Bacilus thuringiensis* toxins): The Cry or Cyt toxins produced during the sporulation phase of the entomopathogenic bacteria *Bacilus thuringiensis (Bt)* are proteins with specific and efficient insecticidal activities.[35-36]

Different *Bt* strains do not produce the same Cry toxins, which affect insect according to their order: dipteran, coleopteran, lepidopteran, etc. In contrast the Cyt toxins show mainly dipteran specificity, being able to kill mosquitoes and black flies, and can exhibit synergy with Cry toxins in some insects.[37] Cry toxin destroys insects by interacting with key toxin receptors like aminopeptidase (APN), alkaline phosphatase (ALP), cadherin (CAD), or ATP-binding cassette transporters.[38] The genes encoding these endotoxins can be expressed by transgenic plants to be protected from insects[39-40] at least in countries not banning GMOs.[41-42]

3.3. Fungicides

The number and variety of fungi are enormous, so it isn't easy to specifically control them. Many fungicides have multisite effects to reduce the selection of resistant strains. Nevertheless, there are a few fungicides with specific targets:

1) Multisite: Amine and thiol metabolism (hexachlorobenzene): By inhibiting these pathways, this product, first introduced in 1945 and discontinued after 1972, slows fungi's growth rates and sporulation. The primary molecular sites of action of hexachlorobenzene in fungi are not well defined.

2) Cytochrome b (strobilurin): Strobilurin binds to the quinol oxidation (Q_o) site of cytochrome b to inhibit mitochondrial respiration.[43] Numerous other fungicides have been recently developed, starting from the strobilurin scaffold structure.[44]

3) Lanosterol 14-demethylase CYP51 (triazoles): The inhibitory effect of triazoles affects CYP51, a key enzyme for sterol biosynthesis in fungi[31-32] and, unfortunately, in animals.[45] There is, therefore, active research to design fungicides that do not cross-react with the host CYP51.[46]

4) Succinate dehydrogenase (pyrazole carboxamide): The inhibition of this enzyme by various pyrazole-phenyl carboxamide derivatives is particularly efficient in combating plant fungi, such as *Sclerotinia sclerotiorum*, *Rhizoctonia solani*, and *Botrytis cinerea*.[47] This new class of inhibitors allows to overcome the resistance of fungi against previously launched succinate dehydrogenase inhibitors.

4. OFF-TARGET ACTIONS OF PESTICIDES (RISK ASSESSMENT)

Life has only emerged once during earth's history, so all living organisms share common hereditary support (DNA), some genetic material, and biochemical and physiological mechanisms whose similarities are proportional to their phylogenetic closeness. Consequently, it is problematic to target weeds without affecting cultivated plants or to target herbivore insects without affecting pollinator insects. Moreover, it has been observed that numerous pesticides interact at molecular sites unrelated to their assigned targets and thus exhibit unexpected effects in unrelated species. These off-target effects are responsible for environmental and human health concerns.[48] Risk assessment is crucial to deciding about new and existing pesticides.[49]

4.1. Environmental concerns (Biodiversity)

Phenoxy herbicides impact broad-leaf weeds much more than grasses. Even when they are not targeted at all, soil microorganisms can be greatly affected by herbicides in addition to the identified target.[50-51]

Insecticides often affect non-target insects such as pollinator insects[52-55] but also soil microorganisms,[54] invertebrates other than insects (earthworms in particular[56]), and even vertebrates.[57]

From an environmental point of view, it is good that a lot of organophosphates do not persist in nature, but they also need to not disappear too quickly to be efficient, and have been modified toward this objective. The balance between environmental respect and efficacy is, of course, primordial. Many chemicals are no longer used due to their adverse impact on human health or the environment (*e.g.,* DDT, chlordane, and toxaphene).

In the late 1990s, neonicotinoids became increasingly scrutinized for their negative impact on the environment. They are highly suspected to be directly detrimental to bee colonies, and indirectly to birds due to the greatly reduced number of insects they feed on. This is why they are partially restricted in many European countries since the 2010's.

In agricultural practices, the treatment of plant seeds with pesticides and/or fungicides can cause adverse effects on soil flora through single and combined effects of them. For example, the seed dressing of winter wheat (*Triticum aestivum* L. var. Capo) by insecticides (neonicotinoid) and/or fungicides (strobilurin and triazolinthione) significantly reduced the surface activity of earthworms.[56]

4.2. Human health concerns (Toxicology)

Research on toxicology aims at improving the knowledge of the field and developing new chemicals, assessing their efficiency and hazardousness, and regulating their usage.[4]

Hexachlorobenzene disrupts porphyrin metabolism by acting on catalytic sites through modification of sulfhydryl groups or substrate binding of the enzyme uroporphyrinogen decarboxylase. It inhibits the catalytic activity of uroporphyrinogen decarboxylase causing decarboxylation of uroporphyrinogen III to be deficient, leading to accumulation of uroporphyrin in the liver. Furthermore, cytochrome P-450 catalyzed metabolism of hexachlorobenzene produces electrochemically reactive metabolites that are covalently bound to proteins and DNA in the cells, causing irreversible damage. When the body is exposed to hexachlorobenzene, macrophages are attracted to organs such as the spleen, lungs, and skin, where they are activated by hexachlorobenzene through a chain of reactions involving innate immune cells. Evidence suggests that the importance of macrophages and granulocytes is due to gene expression profiles. Mediators secreted by these cells are directly involved in the adverse inflammatory response against hexachlorobenzene. In this way, T-cells can be activated through co-stimulatory or danger signals.

Diazinon, dieldrin, endosulfan, ivermectin, maneb, 1-methyl-4-phenyl-4-phenylpyridinium ion (MPP1), and rotenone affect Pg-P ATPase activity and modify its drug-expelling activity and, consequently, accentuate Parkinson's disease symptoms.[58] Diazinon is a prevalent compound and a food contaminant, absorbed by the gastrointestinal tract and quickly metabolized. High exposure to DZN induces the gene expression of antioxidant enzymes.

Atrazine may indirectly act as an estrogen activator and directly inhibit dopamine synthesis, and thereby reduce dopamine levels. Atrazine may also block feedback regulation, leading to increased prolactin levels and altered immune cell activation, including T-cell proliferation and antibody responses.

4.3. Risk assessment

The assessment process combines all the information from the toxicity tests (hazard) and the exposure information to evaluate the risk (risk = hazard x exposure).[59] It is a complex procedure with many actors. It is meant to ensure safety for operators, workers, bystanders, residents, consumers, non-target species as well as the environment, and to allow an efficient use of resources for risk assessment and risk management in the policy area of pesticides.[60]

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There are now numerous large-scale studies for evaluating the risk assessment of pesticides in humans,[61-72] wildlife,[73-82] and ecosystems.[83-86]

Cocktail toxic effects of pollutants are well known.[72-73,87-88] How are effects of pesticide cocktails related to their mechanism of action? Intuitively, molecules with identical targets and mechanisms of action should exhibit additive effects. In contrast, molecules with an identical target but different mechanisms of action may exhibit either antagonist or synergic effects.[89-97] If toxic molecules act on different molecular targets or organs, the situation is even more complex[98-99] and difficult to anticipate.[72] Moreover, the surfactants used to help pesticide cell penetration can exert toxic effects by themselves.[100-103]

It is also essential to evaluate pesticides from an epidemiological point of view.[104] People are exposed intermittently to chemicals at different concentrations. This is why toxicology alone is insufficient to evaluate accurately the effects of pesticides on human health and must be associated with epidemiology. For example, the very wide use of glyphosate in many countries allowed the gathering of valuable epidemiological data which pointed to its responsability in some cancers. However, the large scale of these data can make them either valuable or suspicious, depending on how they are observed: while the International Agency for Research on Cancer saw a link between glyphosate and cancer, other regulatory entities considered no causal link was established.[105]

The use of pesticides is not only based on scientific authorities but has an important political dimension.[106] Industrial companies, non-governmental organizations (NGO) and national and international public agencies as well as politicians are involved in decision makings. Thus, the European Food Safety Authority (EFSA) developed a methodology by grouping pesticides to take cumulative risk assessment into consideration. However, Pesticide Action Network Europe (PAN), representing more than 600 NGOs, deemed these studies "unfit for purpose," because they did not establish that pesticides had "no impact to human health and particularly to the most vulnerable groups in the population". Complementary studies are being conducted and EFSA is currently working with the European Commission on this matter.

5. CONCLUSION

Pesticides are amidst fierce societal, economic, and political debates, which often blur scientific data. Many of them have already been banned in Vietnam and in many other parts of the world, such as in European or American countries, for being directly or indirectly harmful to the environment or human health. It mostly concerns the endocrine disruption caused by the older kinds of pesticides, such as: organochlorines, organophosphates, carbamates and Thiocarbamides. These scientific data about pesticides are not always as objective as they should be, and many are more or less oriented (not always consciously) to support the authors' convictions, whatever they are. The problem of pesticide use is so complex that absolute objectivity is almost impossible. The number of viewpoints (scientific, societal, economic, political) is too huge to provide simple conclusions that would be acceptable to everyone. In the present work, we have concentrated on scientific issues, but we are aware that it is not the whole story.

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