Chapter 8

Impact of Pesticides on Environmental and Human Health

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1. Introduction

Pesticides constitute any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest. They can also serve as plant regulators, defoliants, or dessicants [1].

Chemicals have long been used to control pests. Sumerians already employed sulfur compounds to control insects and mites 4500 years ago. Pyrethrum, a compound derived from the dried flowers of *Chrysanthemum cinerariaefolium*, has been applied as an insecticide for over 2000 years. Salt or sea water has been used to control weeds. Inorganic substances, such as sodium chlorate and sulfuric acid, or organic chemicals derived from natural sources were widely employed in pest control until the 1940s [2].

During World War II (1939-1945), the development of pesticides increased, because it was urgent to enhance food production and to find potential chemical warfare agents [3]. Consequently, the1940s witnessed a marked growth in synthetic pesticides like DDT, aldrin, dieldrin, endrin, parathion, and 2,4-D. In the 1950s, the application of pesticides in agriculture was considered advantageous, and no concern about the potential risks of these chemicals to the environment and the human health existed [2].

In 1962, Rachel Carson published the book "Silent Spring", in which she mentioned problems that could arise from the indiscriminate use of pesticides. This book inspired widespread concern about the impact of pesticides on the human health and the environment. In 1967, Ratcliffe [4] noted increased incidence of raptor nests with broken eggs in the United Kingdom. This author showed that the sharp decline in eggshell thickness coincided with the beginning of the widespread use of DDT in agriculture (1945–1946). In the 1970s, pest resistance emerged

which, combined with influence of the book "Silent Spring", and accumulated evidence on the effects of pesticides, culminated in banning of the use of DDT in the United States in 1972. Thereafter, other countries discontinued the use of DDT, as well [5].

The 1970s and 1980s saw the introduction of more selective pesticides. In the 1990s, research activities concentrated on finding new members of existing pesticides that were even more selective. Besides, pesticides with new chemical groups emerged. During this period, safer chemicals arose. In addition, Integrated Pest Management (IPM) systems, came into play – these systems used crop production methods that attracted predators or parasites that attacked pests and timed pesticide applications to coincide with the most susceptible period of the pest's life cycle, thereby reducing the amount of applied pesticides [2].

However, IPM or related methods did not eliminate the need for pesticides. These chemicals ensure the production of adequate quantities of high quality pest-free crops, which is important for food supply, prevents human diseases transmitted by insect or rodent vectors, and positively impacts public health [6].

The best pesticide policies need to reconcile environmental concerns with economic realities – pest management is mandatory, and farmers must survive economically. A number of studies have described the problems that not using pesticides would cause. Without pesticides, food production would be lower, and larger cultivated farm areas would be necessary to produce the same amount of food, which would impact the wildlife habitat. More frequent cultivation of the fields would be increase soil loss due to erosion, too. Knutson et al. [7] have pictured the U.S. society without pesticides: agricultural production would decrease, food prices would rise, farmers would be less competitive in global markets, and U.S. exports would drop, leading to many job losses [8].

Despite their benefits, pesticides can be hazardous to both humans and the environment. Countless chemicals are environmentally stable, prone to bioaccumulation, and toxic [6]. Because some pesticides can persist in the environment, they can remain there for years. Environmental contamination or occupational use can expose the general population to pesticides residues, including physical and biological degradation products present in the air, water, and food [9].

Less than 1% of the total amount of pesticides applied for weed and pest control reach the target pests. A large quantity of pesticides is lost via spray drift, off-target deposition, run-off, and photodegradation, for instance, which can have undesirable effects on some species, communities, or ecosystems as a whole, as well as on the humans [10]. Another relevant factor is that low concentrations of many chemicals may not elicit acute detectable effects in organisms, but they may induce other damage, like genetic disorders and physiological alterations, which reduce life span in the long run [11].

There are various ways to group pesticides, including classification based on the pests they control. Some example, insecticides combat insect growth or survival, herbicides act against plants, weeds, and grasses, rodenticides tight against rats and other rodents, avicides act against bird populations, fungicides attack fungi, and nematicides combat nematodes [12]. The

global pesticide market divided according to the type of pesticide is as follows: 42.48% herbicides, 25.57% insecticides, 24.19% fungicides, and 7.76% other types of pesticides [13].

Pesticides grouping can also rely on their chemical structure. Organophosphorus (chlorpyrifos and diazinon), carbamates (carbaryl and aldicarb), organochlorine (DDT and aldrin), pyrethrins and pyrethroids (cyfluthrin and cypermethrin), benzoic acids (dicamba), triazines (atrazine and simazine), phenoxyacetic derivatives (2,4-D), dipyridyl derivatives (diquat and paraquat), glycine derivatives (glyphosate), and dithiocarbamates (maneb and ziram) [12].

Pesticides that bear similar chemical structures exhibit similar mechanism of toxicity and physicochemical properties, as well as comparable fate and transport properties. This chapter will deal with pesticides according to their chemical group. Pesticides belonging to different chemical classes but which have similar toxic effects, such as the ability to induce oxidative stress and act as endocrine disrupters will be treated as well.

2. Physical and chemical properties and stages of intoxication

2.1. Organophosphorus

Organic compounds containing phosphorus, the so called organophosphorus compounds (OP), have found application as pesticides and war gases since their synthesis, in 1937 [14]. OP contain carbon and derive from phosphorous acid. Their primary structure may vary depending on whether they bear sulfur (S) or oxygen (O) double binds. X is a group of the general structure that separates when the compound binds to acetylcholinesterase (AChE). On the basis of the variations in their general structure, it is possible to subdivide these compounds into phosphates, phosphorothioates, phosphoramidates, and phosphonate, for example. The structural difference between these compounds results in peculiar characteristics regarding OP metabolism and toxicity. Some representatives of this class of pesticides are Diazinon, Malathion, and Paration [15].

The skin, conjunctiva, gastrointestinal tract, and lungs rapidly absorb most OP compounds. Cytochrome P_{450} isozymes metabolize these chemicals in the liver, which sometimes generates metabolites that are more toxic than the parent compounds [16]. One example is the oxon form, which may bind to cholinesterase or undergo hydrolysis to a dialkyl phosphate and a hydrolyzed organic moiety specific to the pesticide [14]. Most OP are polar and hence water soluble. Their metabolites arise 12 to 48 h after exposure. However, a few compounds, such as dichlofenthion, possess high partition coefficients, which culminates in long-lasting symptoms [17].

These pesticides can reversibly or irreversibly stablish covalent bonds with the serine residue in the active site of acetyl cholinesterase, to prevent the natural function of this enzyme in the catabolism of neurotransmitters [14]. The formation of complexes between acetylcholinesterase enzymes and organophosphates leads to phosphorylation and deactivation, and the neurotransmitter acetylcholine consequently accumulates in the synaptic cleft. The accumulation of large amounts of acetylcholine stimulates and exhausts cholinergic synapses due to

the excessive cholinergic activity produced by these agents [18]. The cholinesterase-bound phosphate group can lose the o,o-dialkyl groups or undergo hydrolysis, to regenerate the active enzyme. This process occurs not only in insects, but also in humans and the wildlife [14].

The main symptoms of pesticides intoxication can be differentiated into syndromes like the muscarinic syndrome, in which the action of acetylcholine on the smooth muscle, heart, and exocrine glands increases bronchial secretion, tearing, and sweating; disrupts the gastrointestinal tone to cause nausea, vomiting, and diarrhea; and elicits urinary incontinence, bronchospasm, miosis, and bradycardia. Another example is the nicotine syndrome, in which acetylcholine accumulates at the motor nerve endings in the autonomic ganglia and causes tremors, spasms, hypertonicity, hyperreflexia, paralysis, or muscle weakness and stimulates the sympathetic autonomic ganglia, to promote tachycardia, pallor, hyperglycemia, and hypertension. Additional effects on the central nervous system (CNS) include anxiety, headache, dizziness, ataxia, sleep and memory disorders seizures, tremors, respiratory depression, and coma. Some OP still have teratogenic potential and mutagenic effects. Laboratory diagnosis of this syndrome involves determination of cholinesterase activity [19].

To treat poisoning with OP, it is necessary to maintain vital functions and assess cholinesterase levels in the red cells and pseudocholinesterase levels in the plasma, before therapy. It is important to avoid the use of parasympathomimetic agents, which may increase the anticholinesterase activity. Treatment should start with atropine, which acts as a competitive muscarinic anticholinergic agent, together with pralidoxime, until complete control of the symptoms. After atropinization, administration of furosemide prevents pulmonary congestion, whereas administration of benzodiazepines controls seizures [20].

2.2. Carbamates

Carbamates insecticides produce clinical signs and symptoms of cholinergic excess that resemble the signs elicited by organophosphate toxicity, except that the effects are more reversible and less severe [14]. The mechanisms underlying carbamates poisoning involve carbamylation of the active site of acetylcholinesterase, which inactivate this essential enzyme in the nervous system of humans and other animal species [21]. The reaction of carbamates with acetylcholinesterase is similar to the reaction of OP with the same enzyme. However, reactivation of the carbamylated enzyme by hydrolysis is faster as compared with reactivation of the phosphorylated enzyme, with reversal of inhibition typically occurring half an hour or less after exposure [22]. Nevertheless, reports on cases of neuropathy after poisoning exist [23].

Organisms readily absorb carbamates through the lungs, gastrointestinal tract, and skin. Fortunately, carbamates poorly penetrate the blood-brain barrier. Therefore, they affect brain cholinesterases activity minimally and promote fewer CNS symptoms as compared with organophosphates. In addition, the spontaneous in vivo hydrolysis of the carbamate-cholinesterase complex contributes to less severe and less enduring symptoms.

The main symptoms of carbamates intoxication are miosis, salivation, sweating, tearing, rhinorrhea, behavioral change, abdominal pain, vomiting, diarrhea, urinary incontinence, bronchospasm, dyspnea, hypoxemia, bradycardia, bronchial secretions, pulmonary edema,

respiratory failure, drop in body temperature, incoordination, lip tingling, tremors, and seizures. Less common symptoms include muscle spasms, twitching, muscle weakness (including respiratory muscles), paralysis, tachycardia, and hypertension [24].

The treatment of carbamates intoxication includes maintenance of vital functions. It is crucial to avoid the use of parasympathomimetic agents, because they may increase the anticholinesterase activity. Treatment should start with atropine, followed by administration of furosemide, only if necessary. If poisoning is due to pure carbamates only, it is not necessary to administrate pralidoxime, except in cases that these carbamates are associated with OPs [15].

2.3. Organochlorines

Organochlorine is used mainly as insecticides. Human body burden due to organochlorine pesticides results from the universal presence of these contaminants in the environment. This constitutes a major public health concern; indeed, organochlorines have been linked with cancer, asthma, diabetes, and growth disorders in children [25]. Organochlorine pesticides include cyclodienes, hexachlorocyclohexane isomers, and DDT and its analogues (e.g., DDE, methoxyclor, and dicofol) [14].

Exposure to organochlorines occurs via ingestion of contaminated food or water, inhalation of vapor, and absorption through the skin. Occupational and other domiciliary exposures are also possible. Dietary exposure results in bioaccumulation of these chemicals in the human body [26].

Organochlorines have similar structure – they all contain a cyclodiene ring. The lungs, gastrointestinal tract, and skin can absorb all these compounds. In addition, although the organism absorbs approximately 10% of the applied dose, lipid solvents increase dermal penetration [15], thereby raising the risk of intoxication in the case of workers who apply these products in crops without proper protective equipment.

The accumulation of organochlorine compounds is a result of their chemical structure and their physical properties such as polarity and solubility. These fat-soluble compounds persist in both the body and the environment. Consequently, researchers and regulatory agencies have banned several organochlorines [14].

The main symptoms of organichlorines intoxication are dizziness, headache, anorexia, nausea, vomiting, malaise, dermatitis, diarrhea, apprehension, excitement, irritability, gait disorders, excessive sweating, altered reflexes, muscle weakness, tremors, spasms, mental confusion, anxiety, seizures, coma, and death. The carcinogenicity of this class of compound is assigned to polychlorocyclodiene compounds that form epoxides during their biotransformation. Because organochlorines have long half-life, these levels in the serum constitute a marker of exposure to these pesticides [15].

To treat organochlorines intoxication, it is necessary to maintain the vital functions, administer diazepam and phenobarbital by slow injection, to control seizures, and to monitor the airways closely. Lorazepam constitutes an alternative to diazepam. Ion exchange resins can also be administered orally. Arrhythmias that damage the myocardium rarely occur. Lidocaine is the treatment of choice [27].

2.4. Pyrethrins and pyrethroids

Pyrethrins and pyrethroids function mainly as iseticides. Pyrethrins are natural compounds originating from the plant *Chrysanthemum cinerariaefolium*. They comprise active agents (pyrethrins I-VI), but pyrethrins I and II are the most active. These compounds decompose rapidly in the presence of light, but synthetic production of pyrethroids around 1950 overcame some disadvantages of natural pyrethrins [15].

Crude pyrethrum is a dermal and respiratory allergen, probably due it is to non-insecticidal ingredients. Contact dermatitis and allergic respiratory reactions (rhinitis and asthma) have occurred after exposure to this compound [28].

Both pyrethrins and pyrethroids bear an acid moiety, a central ester bond, and an alcohol moiety in their structure. This class of compounds typically exists as stereoisomers (*trans* and *cis*) for a total of eight different stereoenantiomers. In adittion, they comprise two main groups, Type I and Type II, which bear a cyano group in the alpha position or not, respectively [29].

After absorption, rapid pyrethroids distribution occurs in the organism. Therein, these compounds undergo biotransformation via two mechanisms: hydrolysis of the ester linkage by carboxylesterases and oxidation of the alcohol moiety by cytochromes P_{450} [30]. Pyrethroids exert the same mechanism of action in insects and mammals. Both pyrethrins and pyrethroids have insecticide potential because they can disrupt the muscular system and alter the normal functioning of voltage-dependent sodium channels. Sodium channels play an important role in the cell-to-cell communication, which is vital for the function of more excitable cells involved in the action potential that the excitable cells can propagate in the CNS. Pyrethroids bind to the α-subunit of the sodium channel that is left open for a longer time, to increase membrane permeability to sodium. Consequently, these compounds cause paralysis, especially in flying insects, known as knockdown. The specific interaction of pyrethroids with the sodium channel shows both the activation and inactivation properties of the sodium channel, making the hyperexcited cells [31]. After interaction of moderate levels of pyrethroids with the sodium channel, the cell can continue to operate in an abnormal state of hyperexcitability. The amplitude of the sodium current remains unchanged until the level of hyperexcitability overwhelms the maintenance of the activity of the sodium channel. This culminates in depolarization and blocks conduction of the action potential until the situation in the cell becomes unsustainable [31].

The toxicodynamics of pyrethroids may also include other mechanisms such as antagonism of gamma-aminobutyric acid (GABA), stimulation of chloride channels modulated by protein kinase, modulation of nicotinic cholinergic transmission, increased release of noradrenaline, and deregulation of calcium homeostasis. Authors have also proposed that pyrethroids act on the voltage-sensitive chloride channels as well as on the voltage-dependent calcium channels [31].

Diagnosis can be difficult because acute pyrethroid poisoning can be mistaken for OP intoxication. Pyrethroid poisoning symptoms are: tremors, spasms, incoordination, prostration, drooling, irregular movements of the limbs, tonic and clonic convulsions, and hypersensitivity

to stimuli. It can also cause skin irritation and tingling due to hyperactivity of cutaneous sensory nerve fibers. Eye miosis also occurs due to exposure [32].

Because exposure to pyrethroids does not usually prompt systemic effects, most patients only require decontamination of the skin and eyes, besides basic maintenance of the vital functions. Paresthesia usually subsides within 12-24 h, which dismisses direct treatment. If severe skin irritation occurs, application of DL-α-tocopherol acetate (Vitamin E) should alternate this problem. Gastric lavage is discarded in case of ingestion, because solvents present in many formulations may increase the risk of aspiration pneumonia. Ingestion of a potentially toxic amount requires administration of activated charcoal within one hour of the event [32].

2.5. Triazines

Triazines are effective and inexpensive compounds that have found application as herbicides. They combat a wide spectrum of weeds by inhibiting photosynthesis and the electron transport chain in plants. Physiological and molecular changes due to accumulation of these compounds in organisms remain unclear. Human exposure to triazines has been associated with carcinogenicity and endocrine disruption, but these effects are still debatable [33]. The chemical structures of triazine herbicides correspond to permutations of the alkyl substituted 2,4-diamines of chlorotriazine [14].

After absorption, these compounds undergo conjugation with glutathione or simply dealkylation. The chlorine group of the triazine structure is replaced with the free-SH group of glutathione, the terminal peptide is cleaved, and the cysteine moiety is N-acetylated. The mercapturate residues and the dealkylation metabolites are subsequently excreted in the urine [14]. Triazines have low acute oral and dermal toxicity. Chronic toxicity studies have primarily indicated reduced body weight gain [16].

Atrazine is the often most studied triazine herbicide. Authors have investigated their carcinogenic potential in mice and rats. Tumor incidence did not augment in mice, whereas atrazine appeared to increase the incidence of mammary carcinoma in Sprague-Dawley rats [34, 35].

Reports of human poisoning by this class of compounds are rare. When they happen, irritation at the site of contamination such as the skin, eyes, nose, and TGI occurs. Triazines may be carcinogenic and teratogenic, but there is still no evidence that this is really the case. Contamination with atrazine may also cause sensory motor polyneuropathy [15, 33].

Because exposure to triazines usually causes local irritation, in most cases it is only necessary to decontaminate the site exposed to the substance, besides offering basic life support [15].

2.6. Phenoxy derivatives

The structures of phenoxy derivatives bear an aliphatic carboxylic acid moiety attached to a chloride or methyl-substituted aromatic ring. The commonest phenoxy herbicides are 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). A combination of these two herbicides in equal proportions affords Agent Orange, a product applied in the jungles of Vietnam, Laos, and Cambodia during the Vietnam War. Manufacture of

phenoxy herbicides often requires co-formulation with ioxynil and/or bromoxynil, which are generally more toxic than the herbicides. Moreover, other more toxic substances can emerge during the fabrication of some of these herbicides at excessively high temperatures, such as at chlorinated dibenzo dioxin and chlorinated dibenzo furan [36]. Because 2,4,5-T contains the highly toxic and persistent 2,3,7,8-tetrachlorodibenzeno-*p*-dioxin along with other chlorinated dioxins and furans, regulatory agencies have banned it for most applications [14].

Phenoxy salts and esters rapidly dissociate or hydrolyze in vivo, so the toxicity of the derivative will depend mainly on the acid form of the pesticide. Individuals and species vary substantially in terms of phenoxy herbicides elimination. The biological half-life of herbicides in humans reportedly varies from 12 to 72 h [36], but long half-lives occur at large doses and after prolonged exposure [28].

The gastrointestinal tract absorbs phenoxy derivatives. The lungs absorb them less, their cutaneous absorption is minimal, and fat does not store them. Phenoxy derivatives exhibit a variety of mechanisms of toxicity including dose-dependent cell membrane damage, uncoupling of oxidative phosphorylation, and disruption of acetylcoenzyme A metabolism [36]. Phenoxy acids and esters are moderately irritating to the skin, eyes, and the respiratory, gastrointestinal, and mucous membranes. Their toxicity on the CNS is dose-dependent. These derivatives disrupt the blood-brain barrier and the neuronal membrane transport mechanisms, and damage to the intracellular membrane results in uncoupling of oxidative phosphorylation [36]. In addition, prolonged inhalation of these herbicides may cause burning sensation in the nasopharynx and dizziness. Some recent studies have examined female exposure to herbicides and assessed effects such as spontaneous abortion, birth defects, and infertility, among others [28].

Intoxication by this class of compounds is uncommon, but when they occur they can cause serious sequelae. The main symptoms are nausea, dizziness, vomiting, burning in the mouth, constipation, abdominal pain, numbness, diarrhea, gastrointestinal bleeding, gastrointestinal fluid loss, vasodilation and/or direct toxicity due to grafting hypotension, ECG alterations like ventricular or supraventricular tachycardia and, on rare occasions, sinus bradycardia. In more severe cases, agitation, confusion, weakness, paralysis, coma, and death by ventricular fibrillation can occur, and chances of survival are small. Other disrupted functions comprise changes in the NCS [36]. Some compounds of this class (e.g., 2,4,5-T) can also produce carcinogenic and teratogenic effects as well as hepatotoxicity. As for metabolic acidosis, clinical signs such as hyperthermia (due to uncoupling of oxidative phosphorylation), renal failure, increased aspartate aminotransferase and alanine and lactate dehydrogenase, thrombocytopenia, hemolytic anemia, and hypocalcemia activities can arise [36].

In general, treatment of phenoxy derivatives poisoning includes maintenance of the vital functions. If the poisoning is due to ingestion, administration of activated charcoal is necessary for adsorption of the compounds, provided that intoxication occurred within an hour. Systemic poisoning calls for hemodialysis, but other effective purification methods exist, like alkalinization of the urine flow and increase of urine volume to facilitate excretion. To control seizures, administration of benzodiazepines is mandatory [36].

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2.7. Dipyridyl derivatives

The dipyridyl compounds paraquat and diquat are non-selective contact herbicides that have found wide application in agriculture and industries. They help to control weeds. However, these compounds are highly toxic and managing poisoning with these substances requires a great skill and knowledge of proper management procedures [28].

Paraquat (1,1′-dimethyl-4,4′-dipyridylium) is a dipyridylium quaternary ammonium compound related to diquat and morfamquat. The latter product is the least toxic but also the least effective herbicide [15]. Their biotransformation produces free radicals, with consequent lipid peroxidation and cell injury [37].

Paraquat causes aggressive tissue damage in the lungs, kidney, and liver. The major target organ of paraquat poisoning is the lung, which consists of the most lethal and the least treatable manifestation of toxicity. Reactive oxygen species (ROS) play a crucial role in paraquat induced pulmonary injury, characterized by edema hemorrhage and hypoxemia, as well as infiltration of inflammatory cells [28, 38].

The other representative of this class is diquat (1,1′-ethylene-2,2′-bipyridilium), which causes fewer poisoning events than paraquat, the reason why reports on human toxicity and animal experimental data are less extensive for diquat than paraquat. The mechanisms of paraquat and diquat toxicity are similar: radicals destroy lipid membranes. After absorption, diquat does not selectively concentrate in the lung tissue, but it exerts severe toxic effects on the CNS, an event that is not typical in the case of paraquat [28]. The kidney is the main excretory pathway for absorbed diquat. Renal damage is therefore an important feature of diquat poisoning [15, 28].

A very interesting action against poisoning by diquat and paraquat is the addition of an emetic agent in their formulations, wherein the additive acts rapidly in the body and causes the individual to regurgitate the pesticide before it performs its toxic action [38 - 40]. The main poisoning symptoms are dehydration resulting from vomiting. The high oxidative stress elicited by these herbicides causes necrosis in the gastrointestinal tract, kidney tubules, liver, and lung; in the latter case, respiratory failure and pulmonary fibrosis may occur. Ingestion of large amounts of these compounds leads to death within two to three weeks, a result of acute renal failure, hepatitis, and especially respiratory failure caused by pulmonary inflammation and fibrosis. In addition to the systemic effects, these compounds are very harmful to the skin and may cause severe burns [38, 41].

The treatment of poisoning with dipyridyl derivatives includes maintenance of the vital functions, minimization of the absorption of the compound more cathartic (activated charcoal), acceleration of excretion (forced diuresis, hemodialysis, or hemoperfusion), abatement of the effects on the affected tissue, and fluid replacement. Topical lesions should be treated with topical silver sulfadiazine, combined with systemic antibiotics [41]. An addition method to recognize paraquat poisoning is to test the urine with sodium dithionite [42].

2.8. Glycine derivatives

Two representatives of this class are glyphosate (N-phosphonomethyl glycine) and glufosinate (N-phosphonomethyl homoalanine), marketed primarily as the isopropylamine salt (glyphosate) or ammonium salt (glufosinate). Both substances are broad-spectrum nonselective systemic herbicides with application in for post-emergent control of annual and perennial plants. Although both compounds contain a P=O moiety, they are not organophosphates, but organophosphonates, and they do not inhibit AChE [36].

Glyphosate, which contains phosphorus, is a herbicide used in 75% of all the genetically modified crops (GMCs), which tolerate high concentrations of this compound [36, 43]. Glyphosate inhibits an enzyme in the biosynthesis of tryptophan, phenylalanine, and tyrosine, present in plants, fungi, and bacteria, but not in animals or humans. [44]. However, according to literature reports, glyphosate can enter living organisms, including humans, where it exerts various toxic effects [45].

One pathway of glyphosate metabolism involves formation of aminomethylphosphonic acid (AMPA) by action of glyphosate oxidoreductase; AMPA is also the metabolite that emerges in humans [36]. Knowledge of the toxicokinetics of glyphosate derives mainly from animal studies and the similar patterns of absorption, metabolism, and eliminations in humans [46]. Rats absorb only 30% glyphosate after oral administration [36]. Glyphosate plasma concentrations peak at 1-2 h, and declined thereafter, with distributions to the intestine, colon, kidney, and bones [47].

The mechanisms of toxicity of glyphosate formulations are complicated [36]. The most widely used glyphosate product is Roundup®, formulated as a concentrate containing 41% glyphosate [16]. Some in vitro studies have suggested that, at high concentrations of glyphosate, its metabolites and impurities may reduce acetylcholinesterase (AChE) activity [48], although no evidence for significant AChE inhibition in mammals in vivo exists [36]. A study published in the *Archives of Toxicology* by Koller and colleagues showed increased in nuclear aberrations after exposure to glyphosate concentrations between 10 and 20 mg/L, which indicated DNA damage [49]. In adition, in vitro tests using isolated rat liver mitochondria showed that glyphosate uncoupled the electron transport chain [50].

Glufosinate inhibits the synthesis of glutamine in plants, and plant death occurs as a consequence of the increased ammonia levels [16]. Glufosinate supress the activity of glutamine synthetase and glutamate decarboxylase, reducing glutamic acid levels and elicits various types of moderate-to-severe CNS toxicities [51]. Given the differences in the biochemical and metabolic pathways of plants and mammals, glufosinate ammonium formulations are minimally toxic to humans [52]. However, ingestion of the undiluted form can cause grave outcomes such as seizures, respiratory arrest, coma, and disturbance of consciousness, which appear after a latent period of 4 – 60 h [53]. No work has reported that this compound induces genotoxic or carcinogenic effects or that impacts reproduction and fertilization [16].

The effects of this class of compounds range from irritation upon local contact (skin, GI), to hypotension, development of acute renal failure with oliguria, and severe hypoxia and death [54].

The treatment of glycine derivatives poisoning includes maintenance of the vital functions. Hemodialysis is crucial to reduce the amount of toxins normally excreted by the kidney, thereby preventing the impacts on this organ [54].

2.9. Dithiocarbamates

Dithiocarbamates comprise two groups: [1] dimethyldithiocarbamate and [2] ethylenebisdithiocarbamate, depending on which metal cation is present in the chemical structure. The nomenclature of various compounds of this class is related to the association of the metal cations; e. g., maneb (manganese), and zineb and ziram (zinc) [16, 50].

The slow absorption of these compounds means that they have low acute oral and dermal toxicity. On the other hand, chronic exposure to dithiocarbamates leads to adverse effects due to contact with dithiocarbamate acid or metal ligand [16].

The metabolite that arises from dithiocarbamates biotransformation is ethylenethiourea (ETU), which induces thyroid cancer and modifies thyroid hormones. Moreover, dithiocarbamates and disulfiram have similar structures, and both can inhibit acetaldehyde dehydrogenase, the enzyme that converts acetaldehyde into acetic acid [55].

Although these products are little toxicity to humans, they are potential precursors of ethylenethiourea, which has carcinogenic and teratogenic action.

There is no specific treatment for poisoning with this class of compounds, so only maintenance of vital functions and minimization of their absorption (activated charcoal) are necessary.

2.10. Others

Others classes of pesticides exist, including the chloroacetanilide commonly used in agriculture. A number of chloroacetanilides, like alachlor, acetochlor, metolachlor, and propachlor are carcinogenic [56]. The metabolism of chloroacetanilides most likely proceeds via conjugation with glutathione, as judged from the amount of glutathione-related metabolites in the urine of rats treated with these herbicides. [57]. However, the predicted differences between humans and rats in terms of disposition together with the lower rates of alachlor metabolism in human nasal microsomes have led scientists to question the human relevance of chloroacetanilide olfactory carcinogenicity [58].

Benzimidazoles are another important class of pesticides. They are commonly used as veterinary medicines (anthelmintics) and pesticides. They inhibit microtubule formation when they bind to free β-tubulin monomers at the colchicine-binding site [59].

Regarding new technologies, nanopesticides or nanoplant protection products represent an emerging technological development. In relation to pesticide use, these technologies could offer a range of benefits including increased efficacy and durability, and they use of smaller amounts of active ingredients [60]. Nanopesticides "involve either very small particles of a pesticide active ingredient (ai) or other small engineered structures with useful pesticidal properties" [61]. Nanoformulations combine several surfactants, polymers (organic), and metal nanoparticles (inorganic) in the nanometer size range [62].

	Physical and Chemical Properties	Exposition	Toxicokinetics	Toxicodynamics	Signs and Symptoms	Treatment
Organophosphorus	Organic compounds containing phosphorus[15]. The properties vary with the size and structure. In general are more soluble in organic solvents [65].	Skin, conjunctiva, gastrointestinal tract, and lungs[16].	Rapidly absorbed and metabolized by P450 isozymes in oxom form, more toxic than the parent compounds[16].	Covalent bonds with the serine residue in the active site of acetyl cholinesterase (reversibly or irreversibly)[14].	Muscarinic syndrome and nicotine syndrome, resulting of excess acetylcholine in the synaptic cleft[19].	Maintenance of vital functions and cholinesterase levels. It is important to avoid the use of parasympathomimetic agents[20].
Carbamates	The carbamate is an ester derivative[14]. A wide range of melting points (50 to 150ºC) is found for these compounds and the majority have low vapor pressures and poor volatiliry at usual temperatures [21].	Lungs, gastrointestinal tract, and skin[22].	Readily absorbed by organisms with exception the blood-brain barrier[22].	Carbamylation of the active site of acetylcholinesterase[22].	Miosis, salivation, sweating, tearing, rhinorrhea, behavioral change, abdominal pain, vomiting, diarrhea[24].	Maintenance of vital functions and cholinesterase levels. It is important to avoid the use of parasympathomimetic agents[24].
Organochlorines	They all contain a cyclodiene ring. Fat-soluble compounds persist in both the body and the environment[15]. The majority of organochlorines are sparingly soluble and semivolatile [66].	Lungs, gastrointestinal tract, and skin[26].	The organism absorbs approximately 10% of the applied dose, but the lipid solvents increase the accumulation[15].	Endocrine disrupters and growth disorders in children[25].	Dizziness, headache, anorexia, nausea, vomiting, malaise, dermatitis, diarrhea, muscle weakness, tremors, spasms, mental confusion, anxiety[15].	Maintenance of vital functions and administer diazepam and phenobarbital to control seizures, and to monitor the airways closely[27].
Pyrethrins and Pyrethroids	Both bear an acid moiety, a central ester bond, and an alcohol moiety in their structure[29]. Generally, have been low vapor pressures, low Henry's law constants, and large octanol/	Skin, lungs and gastrointestinal[28].	After absorption, are rapidly distributed in the organism and undergo biotransformation by	They can disrupt the muscular system and alter the normal functioning of voltage-dependent sodium channels. This interaction	Tremors, spasms, incoordination, prostration, drooling, irregular movements of the limbs, tonic and clonic convulsions, and	Decontamination of the skin and eyes, besides basic maintenance of the vital functions[32].

	Physical and Chemical Properties	Exposition	Toxicokinetics	Toxicodynamics	Signs and Symptoms	Treatment
	water coefficients (Kow), and are not very soluble in water [67,68].		hydrolysis or oxidation by P450 isozymes[30].	shows the hyperexcited cells[31].	hypersensitivity to stimuli[32].	
Triazines	Permutations of the alkyl substituted 2,4-diamines of chlorotriazine[14]. The retention in soils can varies as a function of the alkyl chain-length, such as the melting point varies between (133 – 177 °C) [69].	Skin, eyes, nose, and gastrointestinal[16].	Undergo conjugation with glutathione or dealkylation[14].	Mechanism not defined[34, 35].	Irritation at the site of contamination. Carcinogenic and teratogenic evidences[15, 33].	It is necessary to decontaminate the site exposed to the substance[15].
Phenoxy Derivatives	An aliphatic carboxylic acid moiety attached to a chloride or methyl-substituted aromatic ring[36]. It's adsorption coefficient (Koc) varied by four-fold, from 76 to 315 L kg(-1) [70] and the main compound has melting point is around 140 °C [71].	Gastrointestinal and Lungs[36].	They rapidly dissociate or hydrolyze in vivo, and fat does not store them[36].	Cell membrane damage, uncoupling of oxidative phosphorylation and and esters are irritating to the skin, eyes, and the respiratory, gastrointestinal, and mucous membranes[36, 28].	Nausea, dizziness, vomiting. As for metabolic acidosis, clinical signs such as hyperthermia (due to uncoupling of oxidative phosphorylation), renal failure, increased aspartate aminotransferase and alanine and lactate dehydrogenase[36].	Maintenance of the vital functions, decrease the adsorption of the compounds[36].
Dipyridyl Derivatives	Are a dipyridylium quaternary ammonium[28]. Diquat for example it is practically nonvolatile with a vapour pressure of <0,013 mPa and very soluble in water [21].	Skin, eyes, lungs, and gastrointestinal[28, 38].	Their biotransformation produces free radicals, with consequent lipid	Tissue damage in the lungs, kidney, and liver as consequence to lipid peroxidation[37, 38].	Dehydration resulting from vomiting. The high oxidative stress causes necrosis in the gastrointestinal tract,	Minimization of the absorption of the compound more cathartic, acceleration of excretion, abatement of the effects on the affected tissue, and fluid

	Physical and Chemical Properties	Exposition	Toxicokinetics	Toxicodynamics	Signs and Symptoms	Treatment
			peroxidation and cell injury[37].		kidney tubules, liver, and lung[38, 41].	replacement [41, 42].
Glycine Derivatives	Marketed primarily as the isopropylamine salt (glyphosate) or ammonium salt (glufosinate). Although compounds contain a P=O moiety they do not inhibit AChE such as organophosphates[36]. Glyphosate is a relatively strong acid with a pH of 2 in 1% aqueous solution [21].	Skin, gastrointestinal[36].	Formation of aminomethylphosphonic acid (AMPA) by action of glyphosate oxidoreductase[36].	DNA damage and uncoupling the electron transport chain [49,50].	Seizures, respiratory arrest, coma, and disturbance of consciousness and irritation upon local contact[33].	Maintenance of the vital functions[54].
Dithiocarbamates	Maneb and Zineb, for example, are identical in structure with exception the cátion. Maneb is moderately water soluble and stable under normal conditions, while Zineb are slightly soluble in water and unstable in light[21].	They show slow absorption by oral and dermal contact [16].	Biotransformation of dithiocarbamates form ethylenethiourea (ETU) [55].	Your metabolic induces thyroid cancer, modifies thyroid hormones and can inhibit acetaldehyde dehydrogenase [55].	Carcinogenic and teratogenic action and thyroid problems [55].	There is no specific treatment for poisoning [55].

Table 1. Summary of the physicochemical properties and phase of the intoxication of different classes of pesticides

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Recently, some studies have reported on the nanomaterial-induced perturbation of different cell death pathways. In the majority of the cases, the key to understanding the toxicity of nanomaterials is that their smaller size as compared with cells and cellular organelles allows them to penetrate these basic biological structures and disrupt their normal function [63]. Thus, advances in research into the mechanism of action of nanopesticides will allow better prediction of the consequences of human exposure to these materials.

All these compounds are among more than 1000 active ingredients that are marketed as insecticide, herbicide, and fungicide. However, with the news pest resistance and need to hygienic controls the quantities of the formulations have been increased constantly [64].

Ass seen above, pesticides currently used over the world are numerous and have various chemical and physico-chemical properties [21]. Nevertheless, is already known that long-term contact to pesticides can harm human life and can disturb the function of different organs in the body, including nervous, endocrine, immune, reproductive, renal, cardiovascular, respiratory systems, and chronic diseases, including cancer, Parkinson, Alzheimer, multiple sclerosis, diabetes [64].

3. Pesticides and oxidative stress

Interest in the toxicological aspects of oxidative stress has grown in recent years. Many researchers have focused on the mechanistic aspect of oxidative damage and cellular responses in biological systems, mainly in the case of pesticides, because oxidative stress is a condition that stems from exposure to various classes of these compounds.

Oxidative stress occurs when the rate of reactive species production exceeds the rate of reactive species decomposition in antioxidant systems, which culminates in increased oxidative damage in different cellular targets [72]. Reactive species comprise substances that do not necessarily have unpaired electrons but are very reactive due to their instability [73]. Free radicals are atoms, molecules, or ions with unpaired electrons on an otherwise open shell configuration are examples of reactive species. Their electrons are usually highly reactive [74].

Oxygen and nitrogen free radicals play an essential role in the physiological control of cell function in biological systems. Living cells continuously produce these radicals [73]. In aerobic organisms, several basic cellular metabolic processes induce production of reactive oxygen species (ROS) within cells. Cellular respiration involves reduction of molecular oxygen (O_2) to water during oxidative phosphorylation in the electron transport chain, to generate reactive, partially reduced intermediates such as the superoxide anion radical ($^{\cdot}O2^{-}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($HO^{\cdot}$) [75]. Around 5% of these ROS originate from electron transport chain processes and can damage cellular components [76]. Moreover, several enzymes produce ROS, thereby constituting a second source of ROS synthesis in cells [77].

Regulated ROS production is higher in organisms, and maintenance of redox homeostasis is essential for the physiological health [78]. Living organisms have developed adequate

enzymatic and nonenzymatic antioxidant mechanisms to protect cellular components from oxidative damage [79].

Exposure to some xenobiotics, especially toxic chemical pollutants, such as pesticides, may produce an imbalance between endogenous antioxidants and ROS, with subsequent decrease in antioxidant defenses to trigger oxidative stress in biological systems, damage to tissues, inflammation, degenerative diseases, and aging [79]. As mentioned previously, many classes of pesticides induce oxidative stress, through several different mechanisms. They may affect the redox cycle by donating electrons to or withdrawing electrons from cell components. During metabolism, they may deplete glutathione (endogenous antioxidant) or even inactivate other endogenous antioxidants [74]. In short, oxidative stress can take place either through overproduction of free radicals or alteration in antioxidant mechanisms [80]. Increased concentration of plasma and red blood cell thiobarbituric acid reactive substances (TBARs), changes in the antioxidant status, and altered activities of cellular enzymes such as superoxide dismutase (SOD) and catalase (CAT) indicated higher oxidative stress in pesticides sprayers. Hence, many researchers have associated exposure to pesticides with oxidative stress [81].

Several works have described oxidative stress induction after exposure to organophosphorus insecticides. The stress is a result of intracellular Ca^{+2} influx, which leads to cholinergic hyperactivity and activates proteolytic enzymes and nitric oxide synthase, which in turn generates free radicals [74]. Fenitrothion, a phosphorothioate, has been linked to histopathological effects on the liver and kidneys and cytotoxic effects on the lungs. These effects originate from ROS generation via pesticide metabolism by P450 or via high-energy consumption coupled with inhibition of oxidative phosphorylation [82]. Moreover, hydrocarbon insecticides chlorinated like DDT can induce oxidative stress after metabolic activation by CYP_{450} [80].

Synthetic pyrethroids are less persistent and less toxic to mammals and birds. Deltamethrin is one of the pyrethroids that has found wide acceptability. Nevertheless, this pyrethroid has effects on the nervous, respiratory, and hematological systems in fish, and it displays tumorigenicity in rodents [80]. All these effects are due to oxidative stress; they impact various antioxidants [83].

A classic example of oxidative stress induction among pesticides is the action of dipyridyls such as paraquat. This compound enters the redox cycle and constantly generates ROS such as the superoxide anion and the hydroxyl and peroxyl radicals [74]. ROS play a crucial role in the development of paraquat-induced pulmonary injury [38]. The basic mechanism of oxidative stress in this class is simple: the dipyridyl initiates a cyclic oxidation/reduction process. First, they undergo one-electron reduction by NADPH to form free radicals. The latter donate their electron to O_2, to give a superoxide radical. Upon NADPH exhaustion, to superoxides react to produce hydroxyl free radicals and other reactive species that lead to oxidative stress and consequent cell death [80]. The free radicals react with lipids in cell membranes, to start a destructive process known as lipid peroxidation. The lung is the organ that is mostly involved in this case [38]. Other compounds, like dithiocarbamates mainly inhibit antioxidant enzymes, such as SOD and catalase [84].

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Pesticides can induce free radical formation by altering the way that cell organelles, like mitochondria operate. Rotenone, an insecticide of the class of rotenoids, strengthens the case for complex I inhibition – rotenone specifically binds to complex I, to inhibit the electron flow through the respiratory chain. Deficiencies in the mitochondrial respiratory chain diminish ATP synthesis and produce ROS, which culminates in oxidative stress, mitochondrial depolarization, and initiation of cell death processes [16, 75].

In this context, many studies in human or animals have evidenced that pesticides exert their toxic action in the body via oxidative stress induction both upon acute and chronic exposure.

4. Pesticides and endocrine disruption

The endocrine system refers to glands located in several areas of the body. Glands release some hormones that enter the circulation and act on specific "target" organs. If an event disrupts the endocrine system, some organs will not receive the correct amount of hormones and might not function properly or even function wrongly. In this context, low levels of some pesticides in the environment can impair the endocrine system [85].

Besides their primary action as pesticides, organophosphorus, carbamates, and organochlorines can act as endocrine disruptors and affect the function of hormones by blocking, mimicking, displacing, or acting to subvert their natural roles in living species. DDT and its metabolites are among the most famous endocrine disruptors. DDT was widely used in the 1950s and 1960s, and it is still allowed in some countries. Its proven estrogenic action can affect the reproductive system of mammals and birds [86].

In vitro and in vivo studies have shown that pyretroids also act as endocrine disruptors, but their effects only arise at relatively high levels [87]. Atrazine, a triazine herbicide, may also exert endocrine-disrupting effects on amphibians [5].

5. Pesticides and human health

Many workers and residents, especially in the rural sector, are in contact with pesticides on a daily basis, so they are at high risk of poisoning by these compounds. This exposure can cause neuropsychiatric sequelae (mood disorders, depression, and anxiety), because many pesticides underlie changes in the function (e.g., cholinergic crisis) of the central, peripheral, and autonomic nervous system, which are often followed by suicide attempts. In addition to being causative agents of neuropsychiatric disorders that might culminate in suicide, these effects may lead to the use of pesticides as a weapon [88].

According to data released by the World Health Organization (WHO) [89], suicide by pesticides is common in many Asian and Latin American countries. Pesticides are often poorly controlled and widely available, particularly in countries of low and middle income [42]. The first epidemiological reports of suicides involving pesticides appeared in the beginning of the

1990s. Currently, homicides and suicides involving pesticides have raised the concern of many organizations and governments as, depression and suicide clearly correlate with high exposure to pesticides. This concern has motivated and still motivates many studies into how and why exposure to pesticide occurs; researchers have also caught methods to solve this serious social problem [88].

Detoxification measures after poisoning are crucial, no matter whether exposure was intentional, accidental, or occupational. Recognition of poisoning is easy when the patient knows which pesticide he/she was exposed to or when symptoms are typical. However, poisoning may be unclear if the patient has generalized symptoms. Therefore, along with the procedures to terminate contamination, an investigation with family members and the people present at the time of contamination, and information on patient care should exist. These individual will be questioned, about the way in which the patient was exposed to the contaminant and about the possibility of simultaneous intoxication with other poisons [27]. Along with these recognition steps the analytical detection of pesticides is mandatory.

Decontamination methods must be combined with care and maintenance of vital signs and administration of antidotes. It is important to bear in mind that new cases of contamination may appear. Furthermore, professionals as well as other patients staying in the same ward as the contaminated individuals must wear protective equipment until decontamination and treatment are complete [27].

Methods exist to decontaminate patients poisoned via gastrointestinal tract. Gastric lavage is extremely invasive and aggressive to the body, so it is indicated only in potentially fatal cases. The cathartic method, which elicits bowel movement to force excretion of the pesticide, is not suitable when poisoning induces diarrhea. Administration of adsorbents is an alternative – adsorbents can bind to the toxic agent, to form a stable compound. This compound is not absorbed by the gastrointestinal tract and is subsequently excreted with the feces. This method is commonly performed in conjunction with the cathartic method. The most usual adsorbent is activated charcoal, but it does not adsorb all pesticides. Finally, the syrup ipeac, a medicinal plant, can help to induce vomit. However, this procedure is contraindicated in the case of ingestion of hydrocarbons or corrosive substances [27, 28].

In the case of dermal exposure, it is necessary to start the decontamination process by placing the patient under a shower and using soap and water to remove the chemicals from the skin, hair, nails, ear canals, and other possibly contaminated body parts. If contact occurs by the ocular route, it is essential to rinse the eyes with plenty of clean water. All the materials and clothes used by the patient at the time of intoxication, like clothes and shoes, should be removed. In cases of large contamination, it is crucial to consider the need to decontaminate all the people who work in the emergency system [27, 28].

Because hundreds of pesticides compositions exist, we will focus on the clinical profile and treatment of pesticides that cause major poisoning, in terms of quantity and severity of cases. In general, treatment aims to override the mechanism of action of the toxic pesticides, and many possibilities exist (Table 2).

Pharmacological antagonism - competes with pesticides for the target site
Physiological antagonism - reversal of a physiological effect of the pesticide
Changing distribution to tissues – e.g., competition with membrane pumps
Modification of biochemical pathways - interferes with the biochemical response of the pesticide
Chelation of a pesticide to disable it
Treatment of pathological response to tissue injury caused by pesticides

Table 2. Methods used to override the mechanism of toxic action of pesticides [39].

An example of suicide attempt has been the case of a man aged 22 who tried to kill himself by drinking a solution of paraquat (50 mL). He underwent gastric lavage and received activated charcoal. Later, he was discharged. However, the treatment did not suffice – four days later, the man returned to the hospital with sore throat, dysphagia, retrosternal pain, hemoptysis, and blistering and ulceration of the mouth and tongue. Biochemical tests revealed elevated creatinine levels, leukocytosis, hyponatremia, and metabolic acidosis. Because the effect had become systemic, the patient had to undergo hemodialysis and immunosuppressive therapy (cyclophosphamide, methylprednisolone, and dexamethasone). The patient did not improve and presented hemoptysis. Examination of the thoracic region detected localized alveolar infiltrate, pulmonary opacities, pneumomediastinum, pneumothorax, and subcutaneous emphysema. The patient's condition worsened, and he -underwent the same immunosuppressive therapy again. The patient recovered gradually; he was discharged after four weeks. After four months, he was working again. His lungs did not return to perfect condition – the man still this place crackles in the lower lung fields, universally distributed wheezing and pleural friction in the right hemithorax, and dyspnea after physical exertion [40].

An example of homicide involving pesticides is the case of a 52-year-old entrepreneur that was killed by injections of poison in his abdomen, conducted by their business rivals. Soon after he was attacked, the man was taken to a private clinic to receive primary treatment, and later he was taken to a hospital, where hours later he was pronounced dead. The body was sent to the morgue for post-mortem examination. Necropsy revealed distended abdomen and two punctures by needles in this region; necrotic changes appeared in the tissue around these two holes. Analysis of the organs revealed congested and edematous brain and lungs, as well as congested stomach with hemorrhagic spots. The toxicological analysis report described the presence of organochlorine pesticides in the region of the piercings and all viscera. This suggested that the man died due to cerebral and pulmonary edema after organochlorine poisoning [90].

Apart from intentional exposure to pesticides, cases of accidental poisoning occur frequently. A Latin American man (66 years old), who had a history of diabetes mellitus (type 2), hypertension, and alcohol abuse, was admitted to the emergency department unconscious, reaching a score of 5 in the Glasgow Coma Scale; he also presented hypotension (blood pressure 87/45 mmHg), sweating, and hypoxia. On the basis of reports by his wife, she had accidentally mixed

Roundap in his alcohol, and he had ingested between 350 and 500 mL of rum Roundup. About two hours after ingestion, she found him with altered mental status, non-bilious vomiting, and difficulty to wake, but he did not present bleeding. Biochemical analysis revealed high hypoxia and lactic acidosis as well as AG and high osmolar gap. First care included intubation, ventilation, and fluid bolus with 2 L of normal saline and 1 L of sodium bicarbonate. His condition worsened, and he rapidly went into shock (blood pressure 66/43 mmHg), with acute renal failure, hyperkalemia, leukocytosis, and worsening lactic acidosis. On the basis of these results, health professionals administered high dose of Levophed (Hospira, Lake Forest, Illinois) and vasopressin to provide pressure support and continuous veno-venous hemofiltration. After 24 h, the patient's conditions improved. Treatment was discontinued, and renal and cerebral functions were fully recovered [91].

Finally, cases of poisoning due to occupational exposure exist. Some pesticides can cause topical damage when they come in contact with the skin, as in the case of two farm workers admitted to the hospital in great pain due to extensive chemical burns in the perineal and scrotal regions, caused by Ducatalon (a dipyridyl herbicide containing a mixture of diquat and paraquat). The men suffered burns due to a leak in the equipment they used to spray the herbicide. Lesions reduced upon topical treatment with silver sulfadiazine associated with systemic administration of antibiotics. Fortunately, in a few days, the damaged skin recovered without scars. After replacement of the faulty equipment, no more injuries occurred [41].

6. Pesticides and environmental health

Pesticides reach the environment primarily during preparation and application. Application can take place via different techniques, depending on factors such as the formulation type, the controlled pest and, the application timing. In agriculture, it is possible to apply pesticides to the crop or to the soil. Liquids sprays are commonly used in crops; for example, boom sprayers, tunnel sprayers, or aerial application. Systemic pesticides can also be employed. As for soils, pesticides can be applied as granules, injected as a fumigant, or sprayed onto the soil surface, which is possibly followed by pesticide incorporation into the soil top layer. Seeds are sometimes treated with pesticides prior to planting. [92].

After application, pesticides can be taken up by target organisms, degraded, or transported to the groundwater; they can also enter the surface water bodies, volatilize to atmosphere, or reach non-target organisms by ingestion, for example. The physical and chemical properties of the pesticide, soil, site conditions, and management practices influence the behavior and fate of pesticides [93].

Concerning the physical and chemical properties of pesticides, their solubility determines their transport in surface runoff and their leaching to groundwater. The higher the solubility, the greater the carrying and leaching. The partition coefficient also affects the behavior of pesticides, and many chemicals do not leach because soil particles adsorb them.

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Adsorption depends on the chemical and also on the soil type. The volatility of pesticides indicates their tendency to become a gas; the higher the volatility (high vapor pressure), the larger their loss to the atmosphere. Environmental conditions such as temperature and humidity impact volatility, which can occur from soil, plants, or surface water, and may continue for several days or weeks after pesticide application. In the atmosphere, the chemicals can be transported over long distances. Subsequent atmospheric deposition can contribute to surface water pollution. Finally, the degradation of pesticides that also determines the behavior and fate of these compounds in the environment. Degradation (their brake down into other chemical forms) can occur by photodecomposition, microorganisms, and a variety of chemical and physical reactions. Pesticides with low biodegradation are called persistent, they can remain in the environment for a long time [94, 95].

Soil properties can also affect the movement of pesticides. In relation to the soil texture, coarse-textured sands and gravels have high infiltration capacities, and water tends to percolate through the soil and reach groundwater. Fine-textured soils such as clays generally have low infiltration capacities, so water tends to run off, reaching streams and lakes. Moreover, soil containing more clay in its composition bears larger surface area to adsorb pesticides. Regarding permeability, highly permeable soils allow water to more easily. This water may contain dissolved pesticides, which will reach groundwater. Texture influences soil permeability. Ultimately, soils with high organic matter content can adsorb pesticides and retain water with dissolved chemicals. Moreover, these soils possess a larger population of microorganisms that can degrade the pesticides [93, 94].

The site conditions that can determine pesticide behavior in the environment are depth until the groundwater, geological conditions, topography, and climate. In the case of shallow groundwater, the soil filters smaller amount of water with chemicals and adsorbs and degrades lower quantities of pesticides, so contamination is a major concern. Regarding the geological conditions, the presence of wells, sinkholes, and highly permeable materials, such as gravel deposits, facilitates groundwater contamination. On the other hand, the existence of drainage ditches, streams, ponds, and lakes increases the probability that rainfall or irrigation runoff will contaminate surface water. In relation to topography, flat landscapes, areas with closed drainage systems where water drains toward the center of a basin, and especially sinkhole areas, are more susceptible to groundwater contamination. As for climate, large rainfall or irrigation may culminate in large amounts of water percolating through the soil, to reach groundwater. Rainfall can also carry pesticides to surface waters, contaminating rivers, lakes, and seas, and taking these chemicals to distant places [94].

Finally, management practices can affect the movement of pesticides. With respect to the application methods, pesticides injected or incorporated into the soil are more available for leaching and reaching groundwater, whereas pesticides sprayed onto crops are more susceptible to volatilization and surface runoff, reaching surface waters and the atmosphere. Concerning the application rates and timing, the use of larger amounts of a pesticide during are rainfall or irrigation facilitates the assess of the chemical to groundwater. With respect to handling practices, correct storage and disposal of the pesticides containers impact environmental contamination [94].

The fact that a contaminant is present in the environment does not necessarily mean that it will reach an organism. The contaminant and the organism must overlap in time and space for exposure to occur. Contact can be dermal or oral or even via inhalation, gills, and, more rarely, injection [5].

Once pesticides reach non-target organisms, they may undergo biotransformation via reactions like hydrolysis, oxidation, reduction, or conjugation catalyzed by liver enzymes. Biotransformation is an effort of the organism to detoxify and eliminate xenobiotics, but this process can also produce metabolites that are more toxic than their parent compound, a phenomenon called bioactivation. An example of bioactivation is the biotransformation of DDT, which is not highly toxic to birds, into DDE, which causes thinning of eggshells because it disrupts calcium metabolism [5].

In organisms, the absorption of a pesticide with high lipid solubility and low elimination rate can lead to bioaccumulation of this chemical in the fatty tissue, and the final concentration of the chemical in the organism will be higher than its concentration in the environment [96]. When the bioaccumulated chemical passes from lower to higher trophic levels through the food chain, successively greater pesticide concentrations emerge in animals of higher trophic level. This phenomena is called biomagnification. The offspring of top predators can also become contaminated, mainly in the case of marine mammals, because they can consume milk with extremely high fat and pesticides content [5].

Application of pesticide involves not only the active ingredient but also the whole formulation. Therefore, the environment and the human are exposed to both the active and inert ingredients. Although inert ingredients have no pesticidal activity, facilitate application of the pesticides – they enhance the active compound penetration into the target organism as well as the toxic action. Hence, the inert ingredients raise the formulation toxicity even in non-target organisms [35]. One example is the formulation of glyphosate, which is an active ingredient. It contributes a little to the total toxicity of the formulated product, particularly in the case of aquatic organisms, which are more sensitive to surface-active substances [97].

The categorization of pesticides commonly relies on their persistence in the environment. Organochlorine pesticides are persistent, whereas organophosphates, carbamates, phenoxyacid derivatives, chloroacetanilides, pyrethroids, and others are non-persistent. Compared with persistent pesticides, non-persistent chemicals have much shorter environmental half-lives and do not tend to bioaccumulate. Nevertheless, because of the heavy agricultural use of these chemicals, exists concern about their presence in the environment [14].

The non-persistent pesticides organophosphorus and carbamates act on acetylcholinesterase. The presence of this enzyme in insects, birds, fish, and all mammals allows these pesticides to reach both target and non-target organisms. [98]. Pesticides such as organophosphorus and carbamates can affect numerous teleost behaviors [99]. The pesticides that inhibit acetylcholinesterase are polar and water soluble. Moreover, their metabolism in the body is fast, and their degradation in the environment is relatively rapid. Therefore, organophosphorus and

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carbamates do not tend to bioaccumulate in aquatic species. However, the accumulation of these compounds in fish and invertebrates was reported long ago [100].

Organophosphorus compounds do not persist in the environment. However, their large-scale use and their decomposition rates in the environment cause these compounds to accumulate in soils, from where they subsequently enter groundwater and rivers [101]. A recent study detected the organothiophosphate insecticide chlorpyrifos in air and seawater in the Arctic, which demonstrated the long-range transport of this chemical [102]. Diazinon, another organophosphorus compound, frequently occurs in point sources (wastewater treatment plant effuent) and non-point sources (storm water runoff) in urban and agricultural areas. This pesticide is extremely toxic to birds and the aquatic life [103].

Organophosphorus compounds are acutely toxic, broad-spectrum pesticides. In the environment, secondary poisoning can occur when predators consume animals poisoned by these chemicals. Examples of contamination by organophosphorus are numerous. In Argentina in 1995–1996, approximately 6000 wintering Swainson's hawks (*Buteo swainsoni*) became poisoned after they fed on grasshoppers sprayed with the organophosphorus insecticide monocrotophos [5].

An example of carbamate contamination occurred with the pesticide, aldicarb, which polluted groundwater in the United States. Other carbamates such as carbaryl and its degradation product 1-naphthol have emerged in surface waters. The metabolite 1-naphtol is more toxic than its parent compound, and it has arisen in India [104].Methomyl, carbaryl and carbofuran, commonly used carbamates, have appeared in the aquatic environment [105].Carbofuran has commonly been associated with wildlife pesticide poisoning events when applied in the granular form. Apparently, birds mistake them for seeds [5].

Organochlorines have long environmental half-lives and tend to bioaccumulate and biomagnify in organisms. A series of evaporation and deposition steps as well as migration of animals containing bioaccumulated organochlorines can transport these compounds through the environment, carrying it to animals in higher levels of the food chain. These persistent chemicals thus occur thousands of miles away from their origin [14]. The properties of organochlorines like aldrin and dieldrin result in direct mortality of predatory birds, such as sparrow hawks and kestrels [5]. These chemicals have intensive use in agricultural and industrial activities, so they emerge across the world, including the deserted plateau and the polar zone [106]. The organochlorine chlorothalonil is a fungicide that has arisen in seawater and air in the Arctic as well as in snow cores in Arctic Canada. Endolsulfan, an organochlorine insecticide, has appeared in animals from Greenland like marine fish and mammals [102].

Despite the ban on many organochlorine compounds in the 1970s, some countries still fabricate and use chemicals such as DDT to control vector disease [98]. Other countries have replaced organochlorines with the less persistent and more effective organophosphorus compounds [107].

Pyrethrins and Pyrethroids are non-persistent pesticides used worldwide as insecticides in agriculture, forestry, households, public health and stored products [108]. Therefore, urban and peri-urban populations are potentially chronically exposed to these compounds [87].

Pyrethrins and Pyrethroids act on sodium channels in the nervous system of numerous phyla, such as arthropods and chordates [87]. Pyrethrins and Pyrethroids present low acute toxicity to mammals and birds and constitute one of the safest insecticides to man. However, at low concentrations these chemicals are acutely toxic to a wide range of aquatic organisms and insects [108].

Pyrethrins are natural compounds extracted from chrysanthemum flowers; pyrethroids are synthetic compounds whose structure resembles the structure of pyrethrins [87]. Light degrades these chemicals. Modification of pyrethroids over the years has enhanced their insecticidal activity and persistence in the environment [109]. Compared with pyrethrins, pyrethroids are more stable under light [108], which incurs increased environmental risks associated with their use [5]. Pyrethrins and Pyrethroids display high selectivity and easy degradability in the environment as compared with other pesticides, been a favored replacement for organophosphorus compounds [110].

Pyrethroids strongly adsorb to soil particles, but they can move in runoff with soil particles and reach sediments, consequently entering aquatic ecosystems and affecting aquatic organisms like invertebrates and fish [108]. Fish are highly sensitive to pyrethrin and pyrethroid products, and contamination of lakes, streams, ponds, or any aquatic habitat is a concern [109]. Moreover, some formulations contain additional insecticides, insect repellents, and solvents such as alcohol and petroleum, which increase pesticide toxicity [109].

Triazines basically consist of herbicide compounds, are relatively persistent and migrate easily through the soil into surface and ground waters [111]. In soil, they undergo degradation mainly in a microbial action, but the role of photodegradation is still significant [112]. Residues of triazines have emerged in soil, surface waters, and groundwater in areas where the application of agrochemicals has taken place [111].

Herbicides are often benign with regard to impacts on animals; however, these compounds can have toxic effects at concentrations found in the environment [5]. Furthermore, indiscriminate use of this herbicide, careless handling, accidental spillage, or discharge of untreated effluents into natural water ways can harm the fish population and other aquatic organisms and may contribute to long-term effects in the environment. Atrazine, a triazine herbicide, is one of the most often detected pesticides in streams, rivers, ponds, reservoirs, and groundwater [113].

Phenoxy derivatives basically consist of compounds with herbicide action. They are soluble in water and can pollute surface and ground waters. Phenoxy derivatives display moderate toxicity, but some chlorinated metabolites can be toxic to human and aquatic organisms [114]. In addition, the metabolites may have mutagenic and carcinogenic properties. 2,4-D and MCPA, which are also phenoxy herbicides, can undergo degradation by biotic and abiotic mechanisms. However, these processes may not suffice to reduce the concentrations of chlorinated phenoxy derivatives on many sites [115].

Regarding dipyridyl derivatives, the best-known compounds are diquat and paraquat, developed as herbicides and desiccants. Diquat is water soluble and persistent in the aquatic system. However, it can bind to soil, which reduces its mobility in the environment. Although

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herbicides are usually little toxic to animals, diquat is toxic to some aquatic organisms [116]. Soil adsorbs paraquat, which presents its leaching to ground water; soil microorganisms and photolysis degrade this herbicide [117]. The herbicide glyophosate bears glycine, which adsorbs to soil, undergoes degradation by bacteria, and has low potential for runoff. However, is it highly water soluble and emerges in surface waters. Glyphosate is little toxic to mammals, but the surfactants present in some formulations rise the toxicity of this chemical. Hence, some formulations, mainly those intended for aquatic vegetation control, can kill amphibians [5]. Many authors have demonstrated that glyphosate formulations can cause genetic damage in fish [97].

Dithiocarbamates (DTC) function mainly as fungicides that protect crops, but they also work as rodent repellents [118]. The intensive use of dithiocarbamates in agriculture often contaminates water bodies [119]. Ziram, one of the best-known dithiocarbamates, is toxic to aquatic organisms [120].

Other examples of chemical classes of pesticides exist. Alachlor and metolachlor belong to the group of chloroacetanilides. These herbicides and their degradation products have arisen in surface and groundwater [121]. Diuron, a urea derivative, can pollute freshwaters by leaching through the soil. It has appeared in marinas and coastal areas [122]. Additionally, trifluralin, a dinitroanilin, has emerged in Arctic air and seawater [102].

Therefore, a huge amount and variety of pesticides exist in the environment. Many chemicals that exist at low concentrations may not cause acute detectable effects in organisms, but they may induce other kinds of damage, like genetic disorders and physiological alterations that, in the long run, reduce the organisms life span [11].

7. Methods to detect pesticides

A wide range of methodologies exist to identify possible exposure to pesticides. When identification is necessary due to poisoning of a patient attended in the clinic, the general procedures include anamnesis, physical examination, evaluation of clinical signs, and diagnostic and toxicological analysis. If the investigation aims to qualify and/or quantify a possible pesticide, it is generally necessary to collect a sample and analyze it for the presence of pesticides and/or metabolites in biological samples (blood, liver, stomach contents) and/or the environment (air, water, ground). Selection of the test will depend on the purpose of the analysis. It is also essential to consider the financial costs of a method. Simpler tests are still important, – apart from been inexpensive, many offer high sensitivity, specificity, precision, and accuracy, all of which are factors that are crucial for reliable analysis [123, 124].

Prior to analyzes pesticides samples analysts have to go through similar steps: definitions of the analytical problem (target analyte and its properties), choice of detection methods (immunoassays spectrometry), sampling (how to collect and store the sample), sample preparation (solubilization, extraction, concentration, and separation), calibration (qualification and/or quantification of the analyte), calculation and evaluation of the results, and actions to complete the analysis [125].

Sample storage for long periods should ensure that no sample degradation or external contamination occurs. Well-sealed containers stored under refrigeration and protected from light are mandatory. To avoid any type of external interference during analysis, none of the employed materials should modify or degrade the pesticide in the sample. The analysis of pesticides, mainly in water, ambient air, and soil sediments, often requires a purification step to clean the sample and pre-concentrate the analytes, to improve the quality of the analytical results. The extraction process is a key analytical step – it extracts the desirable compounds for further separation and characterization. Liquid-liquid extraction, and pre-concentration procedures, such as solid-phase extraction and solid-phase microextraction, are the most commonly used methods, but other extraction methods are also applicable depending on the objective [126]. Extraction of residues from the sample matrix demands appropriate solvents for maximum extraction efficiency and minimal co-extraction of interfering substances. The extraction solvents must be highly pure. Blank tests help to prove that the matrix does not interfere in the analyzes. After extraction, a purification step removes the interfering substance with minimal loss of the analyte. The final solution should include an appropriate solvent for analyte determination by the selected method [127].

Below is a didactic description of the main separations and detection methods.

7.1. Physicochemical methods

Gas chromatography (GC), Liquid Chromatography (LC), and Capillary Electrophoresis (CE) constitute physicochemical separation methods.

When the analyzed pesticide is volatile or semi-volatile, GC still is the method of choice: it offers higher resolution and lower detection limits. GC is usually associated with multiple detectors whose choice will depend on the characteristics of the target analytes. GC is based on sample volatilization and introduction into a chromatographic column coated or packed with a solid or liquid stationary phase. A gaseous mobile phase elutes the analyte; this phase is inert, and does not interact with the analyte. The carrier gases should be pure and chemically inert, too, and the choice will depend on the detector. The commonest carrier gases are helium, argon, nitrogen, carbon dioxide, and hydrogen [128].

LC has emerged as a great separation tool. It allows for effective separation of nonvolatile and thermally unstable pesticides that are incompatible with GC. During LC, extracts pass through multiple adsorbent columns that can discriminate between the components of the matrix and target analyte. The degree of selectivity will vary according to the adsorbent present in the column (alumina, silica gel, or Florisil), mesh size, and activity levels. Columns can be used separately or in combination [129].

CE is a powerful tool to separate and identify a wide range of molecules. EC provides high resolution, and large separation efficiency. It requires small sample size and low solvent consumption analyzes is faster and operational coats are low [130].

An ideal detector should ensure adequate sensitivity, good stability and reproducibility, and linear response to various concentrations of the analytes. It should also operate in a wide range of temperature, have reduced response time (independent of the flow), and be easy to handle.

The detector response should be equivalent for all the analytes or selective to certain classes of compounds. Ultimately, the detector should not destroy the sample. Unfortunately, a switch that exhibits all these characteristics does not exist, so it is necessary to select the detector according to the desired goal [128].

Several types of detectors are commercially available. They can come coupled to the separation device. These detectors use photometric or fluorimetric methods, thermal conductivity, diode array detection, electrons capture, atomic absorption, or pesticides mass/charge evaluation. The latter method is currently in evidence due because it is highly sensitive, offers autonomy, and performs a variety of functions. Electron capture and mass spectrometry are the most often used to detect pesticides.

The electron capture detector (ECD) is usually employed to search for organic pesticides, because it is highly sensitive and selective toward molecules containing electronegative functional groups. It also detects masses in the order of pictograms and can analyze traces of pesticides. However, ED cannot detect compounds with low electron affinity. Its excellent properties are useful for analysis of pesticides in both the environmental area and hospitals. A detector called μECD is also available in the market. It is advantageous over ECD in term of sensitivity, stability, and robustness [131].

Mass spectrometry (MS) is based on the ionization, acceleration, and separation of the generated molecules and ions according their mass/charge (m/z) ratio. This Provides a typical spectrum that gives the relative mass abundance of the different ionic species as a function of m/z so, which permits unambiguous identification of molecules. Mass spectrometry is a confirmation technique that is less subject to misunderstanding. Nevertheless, it has a drawback – it destroys the analyte [132].

As mentioned previously, the choice of method will depend on the case. LC-MS and GC-MS are the methods that generally separate and detect pesticides most suitable. These methods play a very important role in the analysis of pesticides and related compounds and are applicable in several areas like environmental analysis, food safety, and occupational toxicology, among others. Because they can serve various purposes, these methods also help to detect compounds in different samples, such as water, soil, sediment, sludge, vegetables and fruits, and animals and humans tissues and fluids [124, 126]. Obviously, method will based on the needs and characteristics of the target pesticide, and each sample will have their own features, which will depend on their physicochemical properties.

7.2. Biological

Chemical analysis of isolated compounds is commonly used to monitor environmental pollution, but such analyses can be limited and expensive and cannot indicate the biological effects. In contrast, biological tests indicate the toxicity of a ride range of compounds or environmental samples, and are therefore essential to determine the environmental impacts of the presence of these chemicals [133]. Immunoassays and biosensors are methods related to the biological factor. Immunoassays are a powerful tool in clinical laboratories and one of the most widely applied analytical techniques.

The reagents kits and the equipment necessary to perform immunoassays are commercially available and rely on fluorescent, chemiluminescent or other detection methods. Immunoassays can detect a wide range of compounds including drugs, proteins, and hormones; they can also identify and quantify the presence of pesticides residues in various samples such as natural water, food, and blood, among others [129].

Regarding biosensors, organisms such as *Drosophila melanogaster* fly species may aid the detection of pesticides in food samples and other matrixes such as water, soil, plants, and animal tissue. This test model is advantageous, because these insects have low tolerance to toxic substances with insecticidal character, besides being experimental models of easy creation, manipulation, and maintenance. In addition, they require few financial resources and can remain under laboratory conditions. However, this method only serves to detect the presence of pesticides, but it cannot identify the detected compound. Therefore, after using this probe, the analyst has to employ a chromatographic, for example, to identify the group of pesticides in that sample [123].

8. Summary of important points and perspectives

The chapter begins with an introduction about pesticides, citing the Second World War and the publication of the book "Silent Spring" by Rachel Carson. Even in the introduction, it is mentioned the Integrated Pest Management (IPM) and the risks and benefits of pesticides use.

Subsequently, the chapter presents the topic "physicochemical properties and stages of intoxication." This topic cites the physicochemical properties, the exposure, toxicokinetic, toxicodynamic and clinical phase of organophosphorous, carbamates, organochlorines, pyrethrins and pyrethroids, triazines, phenoxy derivatives, dipyridyl derivatives, glycine derivatives, dithiocarbamates, and others. In the latter group, the nanopesticides are mentioned.

The chapter also discusses the pesticides as inducers of oxidative stress and endocrine disruptors action of two important issues. Beyond, adress three topics differences: pestidas and human health, pesticides and environmental health, and methods of detection of these compounds. In the first, there are examples of intoxication from occupational, accidental and intentional exposure, besides decontamination methods. The second topic shows how a pesticide reaches the environment, and how it behaves. In other words, if hits the water, soil, and / or are biodegraded. Finally, the third topic addresses methods of detection of pesticides. Gas chromatography (GC), Liquid Chromatography (LC), and Capillary Electrophoresis (CE) constitute physicochemical methods. Immunoassays and biosensors are methods related to the biological factor.

Currently, there is a pursuit of a sustainable society, generating huge concern for human health just like the environment, this occurs due to action/persistence of pesticides in the environment, as well as its toxic effects to humans and other living beings. This pursuit for a healthier society tries to combat the toxic effects of pesticides, as they have caused a large reduction in

biodiversity (mainly insects pollinators), and affect humans causing genetic mutations, Mutagenicity and carcinogenicity, reproductive damages as well as disturbances behavioral (depression and suicides). Faced with this problem, many governments have sought to measures to limit access to these compounds, aimed at protecting human and environmental health, such as work done by the governments of India, Western Samoa and Finland, which restricted access to pesticides and reduced cases of suicides in their countries [42, 134].

This concern can also be viewed on the growing interest of researchers and regulatory agencies regarding research related to biopesticides and biological control of pests, also seeking the quality of environmental and human health mainly in the near future [135].

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