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Chapter

Neurotoxic Effects of Insecticides Chlorpyrifos, Carbaryl, Imidacloprid, in Different Animal Species

Alejandra Mora-Gutiérrez, Carmen Rubio, Ángel Alonso Romero-López and Moisés Rubio-Osornio

Abstract

Insecticides are pesticides used to control insects in agriculture, ornamental gardens, homes, and veterinary medicine. Although the toxic effects on the environment and the health of living beings are not fully understood, these pesticides have become the first options for crop protection in agriculture. After herbicides, insecticides are the most extensively used pesticides in agriculture, with large quantities consumed on every continent, primarily in America. Chlorpyrifos, carbaryl, and imidacloprid are among the top ten most used insecticides. Amidst organophosphates, chlorpyrifos has been reported to be used in over fifty food crops. Carbaryl is a carbamate employed as an insecticide, fungicide, herbicide, and nematicide. Similarly, neonicotinoids are the most used insecticide on a global scale. Neonicotinoids include imidacloprid, the second most frequently used pesticide, surpassed only by glyphosate. It is used because it is less toxic to humans. However, insects appear to be less resistant to its compounds. Evidence suggests that these insecticides persist in soils for a long time and have neurotoxic effects in animal species not intended to receive its consequences. Thus, this chapter's aim is to describe these three pesticides effects and contrast them with the most recent findings regarding their neurotoxic effects in various animal species.

Keywords: insecticides, chlorpyrifos, carbaryl, imidacloprid, neurotoxicity

1. Introduction

Pesticides are substances that exist in our daily lives. Their most widespread use is in agriculture, where they are used to protect crops from pests caused by plants and animals. They are also used to prevent diseases caused by ectoparasites in farm animals and pets. These substances are used in gardening and brought into our homes to protect us from mosquitoes and other insects. Pesticides come into intimate touch with all forms of life through drinking water and eating food. However, the use of these substances is so widespread and poorly controlled that environmental contamination is inevitable.

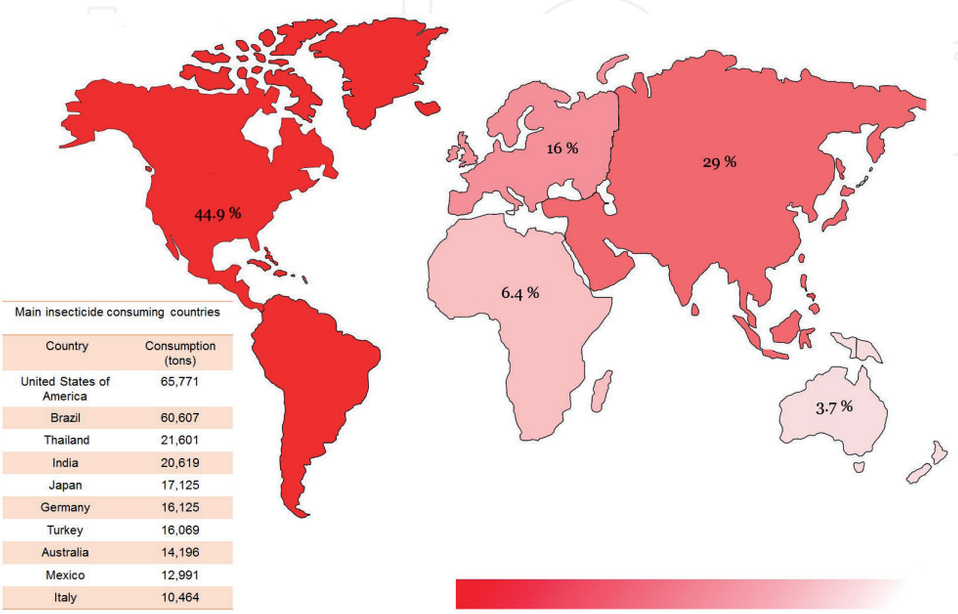
Pesticide exposure occurs in a variety of ways. Not all living organisms are exposed to the same periods or the same dose, or not even to a single type of pesticide or to the same mixtures. The above may have yet unknown, synergistic, or potentiating effects on organisms.

Insecticides are a class of pesticides used to kill or control insects. It is not only used in agriculture, but also in ornamental gardens, homes, and veterinary medicine. Although the hazardous effects on the environment and the health of living beings are not yet fully understood, they have become one of the primary solutions for crop protection in agriculture. Regardless of the fact that pesticides come in a wide variety of families, the major goal of this chapter is to highlight the effects of imidacloprid (neonicotinoid), chlorpyrifos (organophosphate), and carbaryl (carbamate), insecticides widely used in agriculture, despite recent findings of their neurotoxic effects on several animal species.

2. Worldwide use of insecticides

After herbicides, insecticides are the most extensively used pesticides in agriculture [1]. The principal insecticide consumers by continent were America (44.9%), Asia (29%), Europe (16%), Africa (6.4), and Oceania (3.7%), with the United States being the country with the highest insecticide consumption worldwide (**Figure 1**) [2]. Recently collected data, dating from 1998 to 2014, indicates that chlorpyrifos was the third most used organophosphate pesticide in the United States, only for corn cultivation, with a total of 1,122kg/ha. In the same country, the most widely used carbamate was carbaryl with a total of 1,024 kg/ha; while imidacloprid was the most used neonicotinoid, with 0.057 kg/ha. During the same time period, chlorpyrifos, carbaryl, and imidacloprid were among the top 10 most widely used insecticides in the United States [3]. Currently, these same pesticides are used in agriculture and are included among the principal insecticides for each insecticide family aforementioned [4–6].

Furthermore, organophosphate insecticides account for roughly half of all insecticides used worldwide, and chlorpyrifos is one of the most widely used. This insecticide is approved for use on more than 50 food crops in both developed and



Main insecticide consuming countries

Country	Consumption (tons)
United States of America	65,771
Brazil	60,607
Thailand	21,601
India	20,619
Japan	17,125
Germany	16,125
Turkey	16,069
Australia	14,196
Mexico	12,991
Italy	10,464

Figure 1.
Highest to lowest insecticide use by continent.

developing countries [7]. About 50 chemicals belong to the carbamate family, which are utilized as fungicides, herbicides, and nematicides in addition to having insecticidal properties. Carbaryl was the first carbamate to be commercialized, and it is now more widely used than all other carbamates combined [8]. Neonicotinoids, on the other hand, appear to be the most widely employed insecticides worldwide, according to the literature. In fact, imidacloprid is the world's second most widely used pesticide, after only the controversial herbicide glyphosate [9, 10]. Neonicotinoids have largely replaced carbamates and organophosphates because they are considered less toxic to humans and insects, and they appear to be less resistant to neonicotinoids compared to other conventional insecticide classes [11].

3. Of the molecule, its structure, and mechanism of action

3.1 Chlorpyrifos

Organophosphates are compounds of organic nature that contain phosphorus. Chlorpyrifos (O, O-diethyl-O-3,5,6-trichloropyridin-2-yl phosphorothioate) is an organic thiophosphate of the chloropyridine class [12]. The latter is one of the most widely used organophosphate insecticides in agriculture, primarily used on corn, soy, fruit trees, walnut trees, brussels sprouts, blueberries, broccoli, and cauliflower, among others. This pesticide is also used on golf courses, on ornamental plants, for treating wood, and in homes to combat mosquitoes, cockroaches, and ants [13]. Chlorpyrifos act by irreversibly inhibiting the acetylcholinesterase enzyme activity, which causes acetylcholine accumulation in the synaptic cleft, causing overstimulation of postsynaptic receptors and the consequent signs of intoxication [14].

3.2 Imidacloprid

Imidacloprid [1-[(6-chloropyridin-3-yl) methyl] imidazolidin-2-ylidene] nitramide is a neonicotinoid of the chloropyridinyl class [15], which like the insecticides of the same family, acts as an agonist of nicotinic cholinergic receptors (nAChRs) of insects and mammals [16, 17]. IImidacloprid is used in agriculture for corn, cotton, soybean, potato, wheat, and some vegetable seeds, as well as for soil treatment and foliar application on crops like orange, potato, and cotton. It is also utilized in the treatment of decorative plants and residential areas, industrial vegetation and forestry management [18]. Additionally, it is used as veterinary medicine in presentations such as pipettes or collars for direct application on dogs and cats to prevent infestations by internal and external parasites [19].

3.3 Carbaryl

Carbaryl (1-naphthyl methylcarbamate) is a carbamate-based pesticide. It's a carbamate ester made up of 1-naphthol and methylcarbamic acid. On plants, this pesticide is insecticidal, acaricidal, and even growth retardant when used in plants. It is currently used to treat corn, soybean, cotton, nuts, fruit, and vegetable crops in agriculture [20]. It is mostly used on apple, nut, and soybean crops in the United States. However, it is found in more than 40 crops around the world, including asparagus, squash, and potatoes. Its non-agricultural uses include ornamental plants, lawns, grass, roads, and buildings [21]. Carbaryl acts by inhibiting acetylcholinesterase. Nevertheless, unlike organophosphates, carbamates do it reversibly [22].

4. Persistence in soil and water

When pesticides are manually or aerially sprayed on seeds, soil, or even directly on plants, they can last for days, months, or even years. They might also filter through the soil into surface and deep waterways, polluting food and water sources for living beings by coming into contact with animal and plant life. **Table 1** illustrates the soil-water partition coefficients (Koc) and octanol–water partition coefficients (Kow), which are used to characterize the mobility and bioaccumulation properties of pesticides, respectively. While these coefficients are not the only indicators used to determine pesticide behavior in the environment and in organisms, they do serve as referents for pesticide toxicity.

The Koc is a coefficient that is used to determine the pesticide concentration "attached" to soil particles as well as the phase present in the solution, i.e., dissolved in the same soil's water. As a result, the lower the temperature, the higher the Koc of the pesticide in solution, and the greater the likelihood of it leaching into groundwater. The Kow is a coefficient that is used to calculate pesticide concentrations in octanol and water. Pesticides having a high Kow, which are more soluble in octanol and less soluble in water, have been found to accumulate in organisms [23]. Chlorpyrifos accumulates greater in organisms than carbaryl and imidacloprid, as shown in **Table 1**. It does, however, have a lesser tendency to leak into the soil as compared to them. In this sense, imidacloprid would pose a greater risk as a groundwater pollutant.

To estimate a substance's environmental fate in diverse environments, scientists must first determine its degradation half-life, or DT_{50}, which is the time it takes for

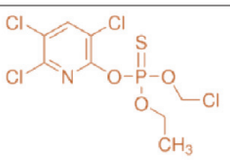
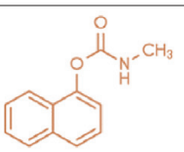
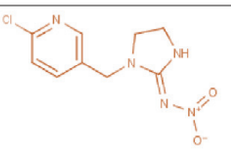
	Chlorpyrifos	**Carbaryl**	**Imidacloprid**
Structural formula			
Chemical name	O, O-dietil-O-3,5,6-trichloropyridin-2-il fosforotioato	1-naphthyl methylcarbamate	1-[(6-chloropyridin-3-yl) methyl]imidazolidin-2-ylidene]nitramide
Color and form	White granular crystals	Colorless to light tan crystals	Colorless crystals
Odor	Mild mercaptan	Odorless	Slight characteristic odor
Melting Point	42 °C	145°C	144°C
Boiling Point	Decomposes before boiling	Decomposes before boiling	Decomposes before boiling
Molecular Weight	350.6	201.22	255.7
Water solubility (mg/L)	1.4	110 (at 22°C)	610 (at 20 °C)
Vapor pressure	2.49 x 10^{-3} mmHg at 25°C	1,36x10^{-6} mmHg at 25° C	3.99 x 10^{-10} mmHg at 20°C
Octagonal-water coefficient (K_{ow})	4.7	1.59 at 2.3	0.57 at 21°C
Soil sorption coefficient (K_{oc})	360 at 31000	290	249 at 336

Table 1.
Crucial physicochemical characteristics for insecticides are chlorpyrifos, carbaryl, and imidacloprid.

50% of a chemical to degrade or disappear from water or soil [7]. For the purposes of this review, the three pesticides DT_{50} examined will be provided below, depending on their average persistence in soil and water,

Chlorpyrifos can have a long persistence even in arctic regions, where its presence has been assessed in samples of ice, snow, a microcosm of water, sediments, air, and flora. The persistence of this pesticide (due to its high resistance to hydrolysis) has been reported to be greater in aquatic habitats than in soil. However, the LD_{50} in soil, has a wide range of values as reported in the literature, ranging from a few days to four years. It is also suggested to be more stable in low-pH soils, dark settings, and cold environments [7]. Chlorpyrifos DT_{50} has been found to last from 1 to 120days in the field and up to 180 days in the soil in the absence of light. It is worth noting that in organic soils, the half-life is longer than in mineral soils. A DT_{50} of 150 to 200 days has been documented in anaerobic pond sediments, while 106 + 54 days has been reported in experimental circumstances of wetland and anaerobic sediments. Chlorpyrifos has a DT_{50} of 18.7 days in freshwater and 49.4 days in seawater at 10°C, which decreases with increasing temperature [24].

In the case of carbaryl, its DT_{50} in the soil ranges from 17 to 28 days. It is considered to have low persistence, where it is degraded mainly by the action of light and bacteria. In sandy soil conditions, its half-life is 7 to 14 days, while in clay soil it ranges from 14 to 28 days, hydrolyzing itself rapidly in alkaline soils. The DT_{50} in water is highly variable, increased in acidic conditions; for example, in acidic water with a pH of 5, degradation is slow and can persist for up to 1500 days [23]. The DT_{50} of carbaryl in soil has recently been reported to be 16 days, while it can reach 12 and 5.8 days in water and sediments, respectively [25].

Neonicotinoids have a high DT_{50}, which means they can last a long time in the soil, with values in the range from 6.7 to 1230 days, while imidacloprid has the highest DT_{50}, with a value of 35.9 to 1230 days. Though it should be noted that the degradation of neonicotinoids and other pesticides in soil is dependent on pH, temperature, humidity, chemical concentration, and even the presence of microorganisms [26]. As evidence, imidacloprid has been found to remain for 42 to 129 days in vegetated soils and more than 180 days in soils free of vegetation [27]. The data on this insecticide's water persistence is varied, with half-lives ranging from 1 to 3 hours, 48 hours, and even 31 to 43 days [28].

5. Neurotoxic effects in different animal species

The lethal dose 50 or LD_{50}, is a measure that in toxicology is used to estimate the dose of a test substance that produces 50% of death in a certain animal species. It is used as a reference to determine how toxic it is to humans [29]. The LC_{50} or lethal concentration 50, corresponds to the concentration of a chemical substance in the

Class		**LD_{50} for rat (mg / kg body weigth)**	
		Oral	**Dermal**
Ia	Extremely dangerous	<5	<50
Ib	Highly dangerous	5–50	5–200
II	Moderately dangerous	50–2000	200–2000
III	Slightly dangerous	>2000	>2000
U	Acute hazard unlikely	5000 or more	

Table 2.
Toxicological classification for pesticides with moderate toxic effects.

Insecticide	Class	Nerve target	LD_{50} or LC_{50} in different species				Toxicological classification (WHO)
			Rat	Honey bee	Fish	Bird	
			Acute oral LD_{50} (mg/kg)	Acute contact LD_{50} (mg/bee)	Acute exposure LC_{50} (mg/L)	Acute oral LD_{50} (mg/kg)	
Chlorpyrifos	Organophosphate	AChE	182	0.072	108	27.36	Ia
Carbaryl	Carbamate	AChE	230	0.84	3470	1870.5	II
Imidacloprid	Neonicotinoid	nAChR	439.8	0.061	229,100	35.36	II

Table 3.
Effect of LD_{50} or LC_{50}: chlorpyrifos, carbaryl, and imidacloprid in different animal species.

air or in the water that causes half of the exposed animals to die [30]. According to the WHO toxicological classification for pesticides (**Table 2**) [31], both imidacloprid and carbaryl are in class II, which includes those pesticides with moderate toxic effects, while chlorpyrifos is located in class 1b since its LD_{50} is below 200 mg. Therefore, it is considered highly dangerous. In **Table 3**, the LD_{50} or LC_{50} for chlorpyrifos, carbaryl, and imidacloprid in different animal species are illustrated.

6. Neurotoxic effects of chlorpyrifos, carbaryl, and imidacloprid

Although insecticides are substances designed to kill some kinds of insects that cause pests, for decades it has been documented that they can also kill insects that should not be the target of their toxic effects and that overall, are essential for life on planet Earth. The most documented case is the decrease in pollinator populations and its possible association with insecticides utilization. In recent reviews, information supporting that insecticides can interfere with localization capacity, alteration of foraging and motor behavior, olfactory learning, and flight ability has been gathered. Additionally, they negatively impact the immune system and increase the death rate, among other toxic effects in bees [32–35], bumblebees [36–38], butterflies and moths [39–42], ants [43, 44], earthworms [39, 45] and various aquatic invertebrates [46–48]. They have also been associated with neuronal and colony performance alterations in bumblebees [32]. Insecticides such as dichlorvos, imidacloprid, and malathion, among others, can harm butterfly populations, resulting in decreased survival and changes in feeding and oviposition patterns [49].

Therefore, the effects on non-target insects have received special attention. According to studies on these species, an environmental emergency has been declared due to the decline in their populations. It is worth noting that insecticides have effects not confined to insects, which exacerbates the existing problem because all living beings are exposed to varying degrees of insecticides, making humans vulnerable to their toxic effects. Following, there is a brief overview of the effects identified in the last five years for each of the insecticides that have been the subject of this chapter, grouped into three different types of effects: behavioral, neurochemical, and cellular (**Tables 4–6**). However, for more detailed information, consider the present bibliography.

6.1 Chlorpyrifos

The recent literature regarding chlorpyrifos toxic effects in different species is extensive. However, this chapter has focused on those that are associated with effects

Behavioral effects			
	Chlorpyrifos	**Carbaryl**	**Imidacloprid**
Insects	Alters caste differentiation in *Plebeia droryana* bees [50]. Alters the formation and recovery of olfactory memories in bees [51]. It alters the locomotor activity of the cockroach *Nauphoeta cinerea* [52]. Alteration of olfactory learning and memory retention in *Apis mellifera* and *Apis cerana* bees [53]. Impaired locomotor performance manifested with altered swimming activity in Diamesa zernyi larvae [54].	It causes alterations in the percentage of copulations in adults of *Rhynchophorus palmarum* (Coleoptera: Curculionidae) [55]. No more recent studies for the review period in the literature.	Paralysis, tremors, prostration, and death in *Scaptotrigona postica* Latreille bees [56]. Decreased food consumption, digging, and foraging behavior in the red ant *Solenopsis Invicta* [57]. Alterations in sexual behavior and search for hosts in parasitic wasps Nasonia vitripennis [58]. It affects the queen selection behavior of the stingless bee *Plebeia droryana* [59]. Reduced visual movement and deterioration in-flight behavior in the migratory locust Locusta [60]. Disruption of copulation in adults of *Rhynchophorus palmarum* (Coleoptera: Curculionidae) [55].
Aquatic organisms	Alterations in the straightening of the gastropod *Gibbula umbilicalis* [61]. Irregular hatching patterns in shrimp *Artemia salina* [62]. Alteration of swimming activity, such as hypoactivity and spasms in the *Physalaemus gracilis* tadpole [63] Alterations in the swimming pattern in the catfish *Heteropneustes fossilis* [64].	General hypoactivity, decrease in escape swim, and feeding behavior in tadpoles of the terrestrial Anaxyrus toad [65]. Decrease in hatching speed of shrimp *Artemia salina* [62]. Delay in the ocular peduncle retraction speed in the blue crab *Callinectes sapidus* [66]. Hypoactivity, alterations in exploratory, social and feeding behavior in zebrafish exposed during embryonic life [67]. Decreased shell closing time and increased mucus secretion from the gills in the *Unio pictorum* mussel [68]. Decreased startle behavior and habituation in zebrafish larvae [69].	It decreases exploratory behavior, swimming activity and increases the sensorimotor response to startling stimuli in zebrafish [70]. It alters the swimming behavior and avoidance behavior of the predators of the tadpole Limnodynastes tasmaniensisy [71]. Decreased response to predators in the *Lithobates sylvaticus* frog [72]. Alterations in swimming and feeding behavior in the *Farfantepenaeus aztecus* shrimp [73]. Locomotor alterations and decreased aggressive behavior in the *Procambarus clarkii*es crab [74]. Hypoactivity in the zebrafish *Danio rerio* [75]. Lethargy is followed by hyperactivity and spasms in the tadpole *Leptodactylus latrans* [76].

Behavioral effects			
	Chlorpyrifos	**Carbaryl**	**Imidacloprid**
Birds	Salivation, tearing, panting, frequent defecation, tremors, and seizures in broilers [77]. Alteration in migratory orientation in the white-crowned sparrow *Zonotrichia leucophrys* [78].	Difficulty walking, weak legs, dizziness, frequent defecation, less food consumption, decrease in aggressive behavior [79].	Alteration in migratory orientation in the white-crowned sparrow *Zonotrichia leucophrys* [78]. Hypoactivity, decreased flight behavior, spasms, drooping wings, ataxia, prostration in the pigeon *Zenaida auriculata* [80]. Decrease in food consumption and delay in migration in the white-crowned sparrow *Zonotrichia leucophrys* [81]. Muscle tremors, ataxia, and depression in domestic chickens *Gallus gallus* domesticus [82].
Non-human vertebrates	Anxiety affects exposure in fetal life in male Wistar rats [83]. Alterations in social behavior and recognition memory in C57Bl6 / J mice [84]. Decreased locomotor activity and muscle strength in Sprague–Dawley rats [85] Alteration of the reference memory; Anxious behavior in male Wistar rats [86]. Catalytic behavior decreased motor coordination and gait disturbances in Swiss mice [87]. Piloerection, tremors, seizures, hypoactivity, among other neurological signs after administration in mice [88]. Impairment of social behavior and sensorimotor reflexes in PON 1/1 mice [89].	Memory and learning deficits. As well as habituation behavior alterations in NMRI mice [90]. Hypoactivity in Norwegian gray rats [91]. Hypersalivation, miotic pupils, lethargy, coma in bats *Eidolon helvum* [92].	Hypoactivity increased grooming behavior and behaviors associated with anxiety and depression in male Sprague–Dawley rats [93]. Decreased exploratory behavior, a deficit in sensorimotor functions, and depression in male Sprague–Dawley rats [94]. It alters the vocal, auditory, orientation, and memory systems in bats *Hipposideros armiger terasensis* [95].
Humans	Arm tremors in prenatally exposed children [96]. Alterations in the social and motor function of 3-year-old children are exposed postnatally [97]. Neurobehavioral deficits in exposed Egyptian workers [98].	Semi-conscious state due to acute intoxication [99].	Coma, dyspnea, and sweating in acute poisonings [100]. Drowsiness, confusion, incoherence, lack of orientation, and unconsciousness after acute poisoning [101]. Somnolence, Glasgow Coma Scale with a score of 10/15 and Miotic pupils after acute poisoning [102].

Table 4.
Behavioral effects of chlorpyrifos, carbaryl and imidacloprid on five animal species.

Neurochemical effects			
	Chlorpyrifos	**Carbaryl**	**Imidacloprid**
Insects	Decreased acetylcholinesterase activity and oxidative stress in *Nauphoeta cinerea* cockroaches' heads [52]. Lipid peroxidation and protein carbonylation in Diamesa zernyi larvae [54]. Increased levels of acetylcholinesterase in *Apis mellifera* bees' heads [103].	Inhibition of carbonic anhydrase in the bee *Apis mellifera* [104]. Decreased levels of acetylcholinesterase in the head of the bee *Apis mellifera* [103].	Increased levels of acetylcholinesterase in the heads of the bee *Apis mellifera* [103]. It decreases the activity of acetylcholinesterase and 8-hydroxy-2-deoxyguanosine, increases the levels of antioxidant enzymes in the brain tissue of the rainbow trout *Oncorhynchus mykiss* [105].
Aquatics organisms	Cholinesterase inhibition in the protobrain of shrimp *Artemia salina* [62]. Inhibition of acetylcholinesterase in the gastropod *Gibbula umbilicalis* [83]. Oxidative stress and acetylcholinesterase inhibition in common carp *Cyprinus carpio* brain tissue [106]. Decreased acetylcholinesterase activity and oxidative stress in *Physalaemus gracilis* tadpoles [63]. Cholinesterase inhibition in Chilina gibbosa [107].	Decreased levels of acetylcholine, GABA, choline, tryptophan, and phenylalanine in *Danio rerio* zebrafish larvae [108]. Cholinesterase inhibition in the protobrain of shrimp *Artemia salina* [62]. Inhibits acetylcholinesterase activity in the brain of tropical fish Phalloceros harpagos, *Pterygoplichthys pardalis*, and *Astyanax altiparanae* [109]. Inhibition of cholinesterase and carboxylesterase in Chilina gibbosa [107].	It increases acetylcholinesterase activity and causes oxidative stress in *Gobiocypris rarus* fish brain tissue [110]. Inhibition of brachial acetylcholinesterase in Sydney rock oyster [111]. Oxidative stress and acetylcholinesterase inhibition in zebrafish *Danio rerio* [75]. Inhibition of acetylcholinesterase in the muscle of *Astyanax altiparanae* fish [112].
Birds	Decreased acetylcholinesterase activity in blood, serum, and plasma of broilers [77]. Inhibition of acetylcholinesterase and butyrylcholinesterase; oxidative stress in the brain of the Coturnix japanica quail [113].	Inhibition of plasma acetylcholinesterase in the vulture *Gyps fulvus* [114].	It increases the levels of monoamines in the cerebral cortex of the *Coturnix coturnix* quail [115]. Alteration of acetylcholinesterase and glutathione-S-transferase activity in the muscle and brain of the gray bay-wing bird Agelaioides baduis [116].

Neurochemical effects			
	Chlorpyrifos	**Carbaryl**	**Imidacloprid**
Non-human vertebrates	Decreased activity of acetylcholinesterase; down-regulation of genes related to Parkinson's disease, synaptic transmission, plasticity, and dopaminergic and GABAergic signaling [117]. Acetylcholinesterase increased activity; increased levels of nitric oxide and reactive oxygen species in the amygdala and hippocampus of male Wistar rats [86]. Decreased acetylcholinesterase activity in the brain and cerebellum of Sprague Dawley rats [85]. Decreased dopamine levels and acetylcholinesterase activity in the striatum of Swiss mice [87]. Decreased brain levels of dopamine, serotonin and the activity of monoamine oxidase, acetylcholinesterase, and sodium-potassium ATPase in rats [118].	Acetylcholinesterase inhibition in Norwegian gray rats [91].	Increased acetylcholinesterase activity and calcium levels in the hypothalamus and pituitary of the Wistar rat [119]. Increased levels of epinephrine, norepinephrine, and cortisone in the serum of male Sprague–Dawley rats [93]. Reduction of serotonin, GABA, and dopamine levels, as well as oxidative stress in the brain of male Sprague–Dawley rats [94]. Reduction of GABA and glutathione levels, as well as a decrease in SDH in the albino rat brain [120].
Humans	Humans Decreased intracellular ATP levels and mitochondrial dysfunction in induced pluripotent stem cells [121].	Binding to human melatonin receptors [122]. Inhibition of plasma acetylcholinesterase after acute poisoning [99].	Increases intracellular calcium levels in LUHMES and SH-SY5Y neurons [123].

Table 5.
Neurochemical effects of chlorpyrifos, carbaryl and imidacloprid on five animal species.

Effects on the cellular level			
	Chlorpyrifos	**Carbaryl**	**Imidacloprid**
Insects	No recent studies for the review period in the literature.	No recent studies for the review period in the literature.	Induction of apoptosis by increased levels of caspase-3 and caspase-1 mRNA in the bee *Apis mellifera* [124]. Apoptosis and autophagy in neurons of the brain of the bee *Apis mellifera* [124]. Decreased density of synaptic units in the fungal bodies of the bee *Apis mellifera* [125]. Decreased driving speed in locusta migratoria [60].
Aquatics organisms	Increased expression of BNDF and c-fos in brain tissues of the zebrafish *Danio rerio* [126]. Degeneration and vacuolization in neurons of the dorsal pars medialis in the catfish *Heteropneustes fossilis* [64].	No recent studies for the review period in the literature.	Increased expression of BDNF and c-fos in brain tissues of the zebrafish *Danio rerio* [126].
Birds	Necrosis and degeneration in the brain of broilers [77]. Neurodegeneration, infiltration of mononuclear cells in the brain, and congestion of blood vessels of the meninges of broilers [127]. Neurodegeneration, liquefactive necrosis, vacuolar degeneration, glia cell enlargement, and satellitosis in the broiler brain [128].	No recent studies for the review period in the literature.	Pyknosis, karyolysis, perineuronal edema, reactive astrocytosis, among other histopathological findings in the white Leghorn hen embryos cerebellum [129]. Neurodegeneration, axonal degeneration with demyelination, congestion, perivascular edema, neuronal vacuolization in the *Columba livia* domestica pigeon [130].
No humans vertebrates	Histological alterations in the brain and cerebellum of Sprague Dawley rats [85]. Lewy body formation and neurodegeneration in the substantia nigra of Swiss albino mice [131]. Gliosis and Purkinje cell degeneration in male Wistar rats [132].	Alterations in normal brain development due to changes in important protein levels during neonatal exposure in NMRI mice [90]. Alterations in the electroencephalogram of the visual and frontal cortex of the male Long Evans rat [133]. Neuroinflammation in the hippocampus of male Wistar rats exposed during pregnancy and lactation [134].	Neurodegeneration and increased GFAP expression in the brain of male Sprague–Dawley rats [94]. Absence of the cellular band of the hippocampal formation in mice [135]. Decreased proteins related to echolocation in different brain regions of the bat *Hipposideros armiger terasensis* [95]. DNA damage of male Wistar rat brain cells [136].

Effects on the cellular level			
	Chlorpyrifos	**Carbaryl**	**Imidacloprid**
Humans	Inhibition of voltage-gated calcium channels in human PC12 cells [137]. Inhibition of neurite length, number of neurites, and branch points per neuron in human neural progenitor cells [138]. Apoptotic cell death in human neural stem cells [139]. Alterations in the morphology of different brain regions in exposed children [140].	Associated with meningiomas in people involved in agriculture [141].	Brain edema after acute poisoning [101]. Cell death in neurons of SH-SY5Y human neuroblastoma [142].

Table 6.
Effects on the cellular level of chlorpyrifos, carbaryl and imidacloprid on five animal species.

on the nervous system. For example, in non-target insects, such as bees, it has been observed that it can have adverse effects on caste differentiation [50], as well as on olfactory learning and memory retention [51, 53]; in cockroaches [52] and mosquito larvae [54] has been associated with locomotor alterations (**Table 4**) [143]. It has also been documented that chlorpyrifos can cause alterations in acetylcholinesterase activity and induce oxidative stress in different insects [52, 54, 103] and annelids (**Table 5**). On the other hand, in aquatic organisms such as mollusks, crustaceans, amphibians, and fish, it has been reported that it can cause alterations in locomotor activity [61, 63, 64, 144], inhibit acolinesterase in shrimp [62, 144], copepods [145], common carp [106], tadpoles [63] and snails [61, 107], as well as causing neuronal degeneration in catfish [64]. In toxicity studies carried out in broilers, it has been described that it can cause nervous signs such as salivation, tearing, panting, frequent defecation, tremors, and seizures [77], in sparrows, it can alter the migratory orientation [78] and inhibit acetylcholinesterase activity in broilers [77] and quail (**Tables 4** and **5**) [113]. Regarding its cellular effects, in repeated studies, chlorpyrifos has been reported to be associated with neurodegeneration in broilers [127, 128]. The neurotoxic effects of chlorpyrifos scale to small mammal species. In fact, in rodents under experimental conditions, it has been seen that it can have anxiogenic effects [83, 86] and cause alterations in the memory of recognition [84] and reference [86] in locomotor activity [85, 87], in social behavior (**Table 4**) [84, 89].

While, acute poisonings are associated with signs of piloerection, tremors, seizures, and hypoactivity, among other neurological manifestations [88]. Regarding brain neurochemistry in experimental rodents, it has been reported that chlorpyrifos can alter the activity of acetylcholinesterase. It participates in the downregulation of genes related to Parkinson's disease, causes oxidative stress and decreases dopamine and serotonin levels [86, 87, 117, 118]. Overall, it has also been associated with neurodegeneration in rodents for experimentation [85, 131, 132]. In humans, it has been reported that chlorpyrifos can alter social and motor function in children (**Table 5**) [96, 97]. As well as having fallout related to neurobehavioral deficits in workers exposed to the insecticide [98]. At the neurochemical level, in an in vitro study with human cells, it was shown that it can decrease intracellular levels of ATP and cause mitochondrial dysfunction [121]. Finally, at the cellular level, it has been reported to cause inhibition of activated calcium channels by voltage [137], alter

morphology [138], and induce apoptosis in vitro [139]. In human cells exposed to chlorpyrifos, a recently published study reported that it may be associated with alterations in the morphology of different brain regions in children exposed to the substance (**Table 6**) [140].

6.2 Carbaryl

Recent studies on the neurotoxic effects associated with carbaryl are scarce. However, it has been reported that in bees, it can inhibit carbonic anhydrase [104] and decrease acetylcholinesterase levels [103], as well as its negative effect on isopod growth and survival (**Table 5**) [146]. In aquatic organisms, it has been discovered that carbaryl can cause embryonic deformities and growth inhibition in crustaceans [147], affect hatching speed in shrimp [62], locomotives alterations in blue crabs [66], mussels [68], and zebrafish [69]. Besides, in this same species, it has been associated with alterations in exploratory, social, and feeding behavior [67]. Likewise, in tadpoles, it causes hypoactivity, reduction in escape swimming, and feeding behavior (**Table 4**) [65]. Regarding the effects on brain chemistry, it has been reported that carbaryl may be related to the decrease in the levels of acetylcholine, GABA, choline, tryptophan, and phenylalanine in zebrafish [108]. Additionally, it inhibits acetylcholinesterase in shrimp [62], in some species of tropical fish [109], and also in mollusks (**Table 5**) [107]. On the other hand, it has been documented that in broilers, acute poisoning can cause walking difficulty, weakness in the legs, dizziness, frequent defecation, less food consumption, and a decrease in aggressive behavior (**Table 4**) [79]. Overall, acetylcholinesterase inhibition has been reported, particularly in the vulture [114]. Simultaneously, in experimental rodents, it has been associated with deficits in memory and learning. As well as alterations in habitual behavior [90] and hypoactivity [91]. Furthermore, in a supposed carbaryl poisoning in bats, signs such as hypersalivation, miotic pupils, lethargy, and coma were reported [92]. This substance can also inhibit acetylcholinesterase in Norwegian gray rats [91] and in experimental rodents. The above has been related to neurodevelopmental alterations [90], as depicted in the visual and frontal cortex electroencephalogram [133] and hippocampal neuroinflammation [134]. In humans, it has been linked to a semi-conscious state and acetylcholinesterase inhibition after acute poisoning in a 3-year-old child, without further details on other associated neurological signs (**Table 4**) [99]. Moreover, in an in vitro study, it was observed that carbaryl could bind to human melatonin receptors [122]. Carbaryl was recently associated with meningiomas in people agriculturally involved in an epidemiological investigation [141].

While, acute poisonings are associated with signs of piloerection, tremors, seizures, and hypoactivity, among other neurological manifestations [88]. Regarding brain neurochemistry in experimental rodents, it has been reported that chlorpyrifos can alter the activity of acetylcholinesterase [86, 87, 117, 118]. It participates in the downregulation of genes related to Parkinson's disease [117], causes oxidative stress [86] and decreases dopamine and serotonin levels [87, 118]. Overall, it has also been associated with neurodegeneration in rodents for experimentation [131, 132]. In humans, it has been reported that chlorpyrifos can alter social and motor function in children [96, 97]. As well as having fallout related to neurobehavioral deficits in workers exposed to the insecticide [98]. At the neurochemical level, in an in vitro study with human cells, it was shown that it can decrease intracellular levels of ATP and cause mitochondrial dysfunction [121]. Finally, at the cellular level, it has been reported to cause inhibition of activated calcium channels by voltage [137], alter morphology [138], and induce apoptosis in vitro [139]. In human cells exposed to chlorpyrifos, a recently published study reported that it may be associated with

alterations in the morphology of different brain regions in children exposed to the substance (**Table 6**) [140].

6.3 Imidacloprid

Despite being considered harmless for most living organisms, neonicotinoid insecticide have been the focus of extensive investigation, as their toxicity has been proven to extend beyond insects [148], to humans. Imidacloprid poisoning in bees has been associated to neurological symptoms such as paralysis and tremors [56], and fire ant exposure has been linked to decreased consumption, foraging, and digging behavior, as well as parasitic wasps with alterations in host-seeking behavior (**Table 4**) [57, 58]. Reduced visual mobility and degradation in in-flight behavior in lobsters, in addition to influencing queen selection behavior in stingless bees have been other reported consequences of the exposure to this insecticide [59, 60]. Imidacloprid has been linked to a decrease in the density of synaptic units in fungiform bodies [125] and a decrease in driving speed in lobsters [103]. It can also increase acetylcholinesterase levels [103] and induce apoptosis and neuronal autophagy [60, 124]. In edaphic invertebrates, imidacloprid causes diverse effects on the survival, growth, and reproduction of earthworms, springtails, mites, and isopods based on LC_{50}, EC_{50}, and EC_{20} toxicity tests [149]. In aquatic organisms, a decrease in acetylcholinesterase levels in mollusks has been reported [150], as well as varied effects on exploratory behavior, swimming activity, and sensorimotor response to startling stimuli in zebrafish (**Tables 4** and **5**) [70].

Moreover, exposure to imidacloprid has been associated with alterations in swimming behavior in tadpoles [71] and shrimp [73], decreased response to predators in frogs [72], and locomotor alterations in crabs [74], zebrafish [75] and tadpoles (**Table 4**) [76]. At the neurochemical level, it has been proposed that imidacloprid can alter acetylcholinesterase activity and cause oxidative stress in fish [75, 105, 110]. It also inhibits brachial acetylcholinesterase in oysters [111] and in fish muscles (**Table 5**) [112]. At the cellular level, it has been documented that the above may be associated with increased expression of BNDF and c-fos in the brain tissues of zebrafish (**Table 6**) [126]. In birds, it has been reported that exposure to imidacloprid can cause hypoactivity, decreased flight behavior, spasms, drooping wings, ataxia, and prostration in pigeons [80]. It has also been stated that it can alter the migratory orientation and delay the time of starting migration in the white-crowned sparrow [151]. In one of the most recently published studies, it was reported that in chickens, it can generate neurological signs such as muscle tremors, ataxia and depression (**Table 4**) [82]; in quail, it can increase monoamine levels in the cerebral cortex [115] and alter the activity of acetylcholinesterase in the muscles and brain of the gray laurel wing bird (**Table 5**) [116]. At the cellular level, it has been associated with neurodegeneration in chicken embryos' cerebellum [129] and pigeons [130]. In experimentation rodents, it has been associated with hypoactivity, increased grooming behavior, and conduct associated with anxiety and depression [93, 94]. While in bats, it may be associated with alterations in the vocal, auditory, orientation, and memory systems (**Table 4**) [95]. Also, in rodents, it can increase acetylcholinesterase activity [119], adrenaline, norepinephrine, and cortisone levels [93], and reduce serotonin, GABA, dopamine, and glutathione (**Table 5**) [120, 152]. Regarding the cellular effects, exposure to imidacloprid can also cause neurodegeneration, an increase in the expression of GFAP [152], and DNA damage in neurons [136]. In bats, it has been related to a decrease in proteins related to echolocation in different brain regions [95]. Moreover, in humans, acute imidacloprid poisonings have been associated with neurological signs such as dyspnea, coma, sweating, drowsiness, confusion, incoherence, lack of orientation, and miotic pupils, among others [100–102].

In an in vitro study with LUHMES and SH-SY5Y cells, an increase in intracellular calcium levels was found [123] (**Table 5**) On the other hand, after acute poisoning, cerebral edema has been reported as a necropsy finding [101], while in an in vitro study it was revealed that it can cause the death of SH-SY5Y cells [135].

On the other hand, acute poisonings are linked to piloerection, tremors, seizures, and hypoactivity, among other neurological manifestations. Regarding brain neurochemistry in experimental rodents, it has been reported that chlorpyrifos can alter the activity of acetylcholinesterase [86, 87, 117, 118]. It participates in the downregulation of genes related to Parkinson's disease [117], causes oxidative stress [86] and decreases dopamine and serotonin levels [87, 118]. Overall, it has also been associated with neurodegeneration in rodents for experimentation [85, 132]. In humans, it has been reported that chlorpyrifos can alter social and motor function in children [96, 97]. As well as having fallout related to neurobehavioral deficits in workers exposed to the insecticide [98]. At the neurochemical level, in an in vitro study with human cells, it was shown that it can decrease intracellular levels of ATP and cause mitochondrial dysfunction [121]. Finally, at the cellular level, it has been reported to cause inhibition of activated calcium channels by voltage [137], alter morphology [138], and induce apoptosis in vitro [139]. In human cells exposed to chlorpyrifos, a recently published study reported that it may be associated with alterations in the morphology of different brain regions in children exposed to the substance [140].

7. Conclusions and perspectives

Insecticides are pesticides commonly associated with neurotoxic effects [153] and although the general population is exposed on a daily basis to low doses through water and food [154–156] the highest risk is presented by agricultural workers, their families and people who live in the areas surrounding the fields, unfortunately, these people are the most exposed and also the least informed about the toxic effects, which leads to bad practices of use, handling and disposal of these substances, which put wildlife and the environment at risk. Since the effects that cause the greatest impact are usually those that directly affect human health, in conclusion some neurotoxic effects associated with the use of insecticides are revealed. In epidemiological studies in humans, organophosphates have been linked to effects such as cholinergic syndrome, polyneuropathy and neuropsychiatric disorders such as cognitive deficits, anxiety, depression, peripheral neuropathy, extrapyramidal symptoms such as dystonia, tremor at rest, bradykinesia, postural instability and rigidity of facial muscles, among others, and have even been associated with neurodegenerative diseases such as Parkinson's and Alzheimer's disease [157, 158]; neonicotinoids have been linked to developmental diseases such as autism and anencephaly and in acute poisonings with neurological signs such as memory loss, finger tremors, muscle spasms, coma and dilated pupils [159–161]; On the other hand, with regard to epidemiological studies on neurotoxicity of carbamates in humans, the literature is limited, however, in the most recently published article, it has been reported that after acute poisoning, these pesticides can cause signs such as coma, drowsiness, seizures, disorientation, tremors and fasciculations, among others [157]. However, although there are epidemiological studies in which the possible relationship between exposure to pesticides and neurological disorders has been determined, to date they remain limited and in fact most of the toxic effects of many pesticides used in the field are unknown. agriculture and therefore it is difficult to determine how we can protect ourselves from them, although there are studies in which the neuroprotective effect of various substances has been experimentally demonstrated, which could counteract the neurotoxic effects of pesticides, for example in the case of pesticides.

Organophosphates it has been documented that the flavonoid kaempferol may have protective effects on chlorpyrifos-induced neurotoxicity [162] and that crocin and citric acid may also have the same effect on malathion-induced toxicity [163, 164]; in the case of neonicotinoids, reduced glutathione, curcumin, resveratrol, ascorbic acid, and aqueous ginger extract have been shown to act as neuroprotectors against imidacloprid-induced toxicity [165–168], as well as curcumin and N-acetylcysteine can protect against acetamiprid-induced neurotoxicity [169, 170]; In the case of carbamates, it has been described that naringenin can combat oxidative stress induced by exposure to carbaryl [171]. Previous studies offer alternatives as possible neuroprotectors, therefore, it is necessary to continue investigating the mechanisms of toxicity and target species of pesticides that exist on the market, before thinking of creating new, more powerful and, of course, more toxic pesticides ; In addition to banning those that pose a high risk to living beings and the environment and making strict policies to control their distribution and sale, since it is clear that it is difficult to live without pesticides, however, it is our duty to use them responsibly.

Acknowledgements

The present work has been possible thanks to Grant from Consejo Nacional de Ciencias y Tecnología (CONACYT) México, registry number 287959.

Conflict of interest

The authors declare no conflict of interest.

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