Brief Overview about Neonicotinoid insecticides; Acetamiprid Toxic effects

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Abstract

Background

Pesticides are natural or synthetic chemicals of public health concern. They are used to prevent, repel, destroy, and mitigate pests and vectors causing human and animal diseases as well as pests that grow on and harm plants. Although the application of pesticides has advantages of improving agricultural productivity and reducing insect-borne diseases, pesticides may pose threats due to their nonbiodegradability. Persistence of pesticides in the environment leads to unavoidable exposure of human and animals to these toxic compounds that contaminate air, water, soil, and food, resulting in incidence of toxicological hazards in mammals. The discovery of imidacloprid by Shinzo Kagabu, and its subsequent market introduction in 1991, started the era of the neonicotinoid class of insecticides. followed in 1999 by thiamethoxam and its metabolite, clothianidin, Over the following two decades, neonicotinoids have become the most widely used insecticides on the global market. Nicotinic acetylcholine receptors (nAChRs) are involved in rapid neurotransmission in both insect and mammalian nervous systems and play major roles in learning and memory. Acetamiprid is a widely used second generation neonicotinoid of outstanding systemic action and potency. It is used for control of insects on several crops and sucking insects like aphids, bees and mosquitoes. Acetamiprid, a member of neonicotinoid synthetic chlorinated insecticide family is a new insecticide that has been introduced in the market. It is used against insects that have gained resistance to organophosphate, carbamate and synthetic pyrethroids. Homicide or suicide cases using acetamiprid are also expected to increase in the future.

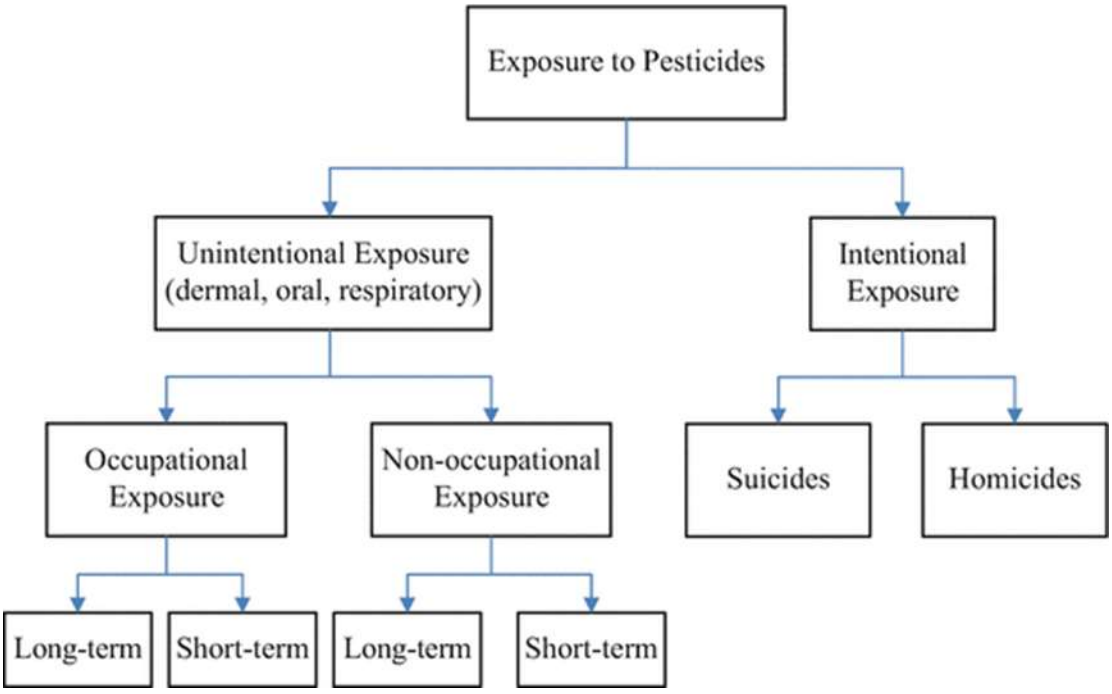
Keywords: Neonicotinoid insecticides, Acetamiprid

INTRODUCTION

Pesticides are natural or synthetic chemicals of public health concern. They are used to prevent, repel, destroy, and mitigate pests and vectors causing human and animal diseases as well as pests that grow on and harm plants. Although the application of pesticides has advantages of improving agricultural productivity and reducing insect-borne diseases, pesticides may pose threats due to their nonbiodegradability. Persistence of pesticides in the environment leads to unavoidable exposure of human and animals to these toxic compounds that contaminate air, water, soil, and food, resulting in incidence of toxicological hazards in mammals (***1)***

Mode of Exposure to Pesticides:

Most deaths result from self-poisoning by ingestion, rather than occupational or accidental exposures, which are typically topical or inhalational. Severe pesticide poisoning is more common in the rural developing world where pesticides are widely used in agriculture and therefore freely available.



Dependent by the mechanism of action in a plant, we can

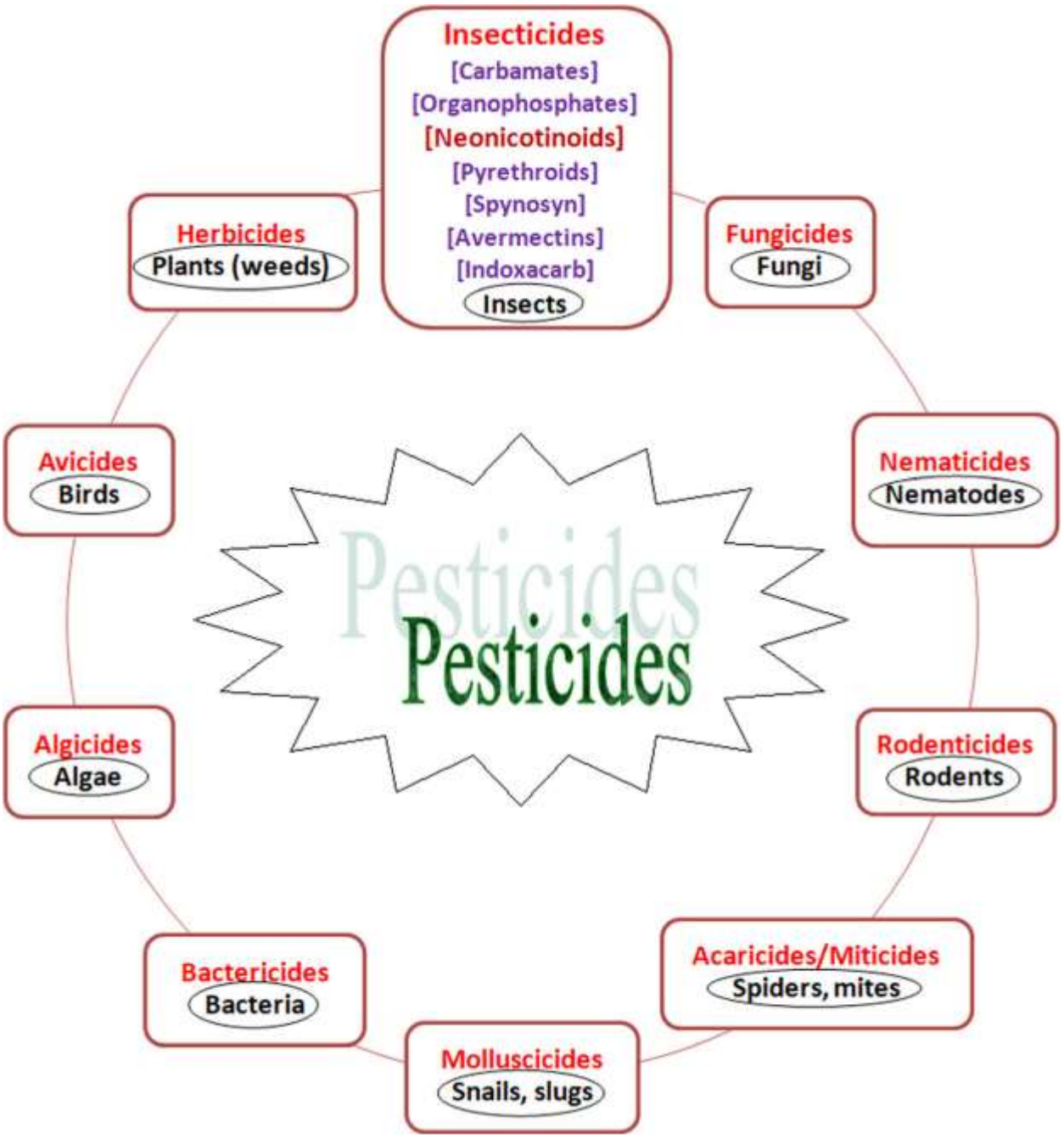
distinguish between contact (surface) insecticides—which remain and act on the external plant surface—and systemic insecticides that enter into the plant system and are transported with sap to the whole plant parts.

(2).

Classification:

Pesticide' is the term used to describe a range of chemicals utilized as insecticides, fungicides, herbicides and rodenticides.

Organophosphorus (OP) and carbamate insecticides and the herbicide paraquat are the most important cause of death from pesticides; the rodenticide aluminium phosphide is a major problem in parts of rural Asia. Newer agents (e.g. pyrethroids, glyphosate, neonicotinoids) cause far fewer deaths ***(3).***



(4)

Dependent by the mechanism of action in a plant, we can distinguish between **contact (surface) insecticides**—which remain and act on the external plant surface **systemic insecticides** that enter into the plant system and are transported with sap to the whole plant parts. **(2).**

Use of Pesticide:

Pesticides are used to protect agricultural land, stored grain, flower gardens as well as to eradicate the pests transmitting dangerous infectious diseases

Benefits of Pesticides *(5)*

1.To control pests and plant disease vectors, thus to improve yield and quality of crop.

2. To control human/livestock disease vectors and nuisance organisms, thus to save lives of

human and animal as well as reduce suffering control of insect-borne diseases and illnesses, such as malaria.

3. To control organisms that could harm other human activities and structures, thus to help preventing tree/brush/leaf hazards, and to help protecting wooden structures

4.To save crops yields of four dollars ($4) against every dollar ($1) spent on pesticides.

Hazards of Pesticides:

Due to the lack of particular awareness and understanding of growers regarding pesticide use, different adverse effects caused by pesticides and pesticide residues ***(6)***, such as:

- pest resistance to pesticides,
- degeneration of beneficial organisms such as predators, pollinators and earthworms, resurgence of pests,
- diversity in soil microbial,
- toxic residues in food, water and air,
- the disruption of ecosystem,
- acute and chronic human illnesses, are gradually increasing.

Health hazards:

Organophosphorus insecticides

OP insecticides are estimated to cause more than 100,000 deaths and 2 million hospital admissions every year, nearly all in developing countries.

Mechanisms of toxicity

OP insecticides phosphorylate multiple enzymes and proteins throughout the body. Inhibition of the synaptic enzyme acetylcholinesterase that is thought to be responsible for toxicity ***(7)***

Clinical features

Acute poisoning is characterized by widespread muscarinic and nicotinic effects caused by inhibition of acetylcholinesterase at autonomic nerve endings and neuromuscular junctions, and in the central nervous system (CNS). Muscarinic symptoms include salivation, bronchorrhoea, bradycardia as well as pinpoint pupils.

Nicotinic effects include profuse sweating, fasciculation, progressive flaccidity and weakness of proximal muscle groups, in particular the neck flexors followed later by the extraocular muscles and muscles of respiration. Respiratory failure is common in severe poisoning and is the major cause of death.

Diagnosis is confirmed by measuring plasma or, preferably, red cell acetylcholinesterase activity .

Management

Initial treatment: the initial aims are to resuscitate and stabilize the patient with support of the airway, ventilation and circulation. Decontamination of the patient should await patient stabilization with administration of antidotes (see below) as necessary.

Antidotes: the specific antidotes are atropine and oxime reactivators ***(8).***

Long-term health effects

Neuromuscular symptoms (lethargy, irritability, poor concentration, mood swings, depression, insomnia, paraesthesia, muscle aches and pains) are thought to be caused by chronic exposure to organophosphorus insecticides ***(9).***

Carbamate insecticides

Carbamate insecticides act in the same manner as OP insecticides and features of poisoning are similar. However, carbamate poisoning is generally less severe and of shorter duration because carbamate-inhibited acetylcholinesterase reactivates comparatively rapidly. Chronic effects are less reported.

Resuscitation and supportive measures should be implemented as required, together with administration of oxygen, fluids and atropine. Oximes are seldom needed ***(10).***

Neonicotinoid insecticides

These compounds are synthetic nicotine analogues that were developed in the 1970s–1990s and include acetamiprid, imidacloprid and thiamethoxam. Imidacloprid is now the best-selling insecticide worldwide. Neonicotinoids cause their effects by stimulation of nicotinic acetylcholine receptors in CNS, predominantly α4β2 subtype ***(11).***

Organochlorine and N-phenylpyrazole insecticides

Both organochlorine (e.g. endosulfan, lindane) and the more recent N-phenylpyrazole (e.g. fipronil) insecticides inhibit γ-aminobutyric acid (GABA) receptors, resulting in seizures.

Therapy is supportive with incremental administration of benzodiazepines, barbiturates and thiopental general anaesthesia ***(12).***

Bipyridyl herbicides (paraquat, diquat)

Paraquat is now banned in Europe; however, poisoning remains common in parts of Asia. Paraquat poisoning is often fatal causing deaths within a few hours from acute renal failure and pulmonary fibrosis.

Diquat poisoning is less common and can be less severe due to the lower concentration formulations, although it can produce multiple organ failure as well ***(13).***

Pyrethroid Pesticides

Pyrethroid pesticides are potent neuro poisons, endocrine disruptors, and may cause paralysis. Pyrethroids are a synthetic version of pyrethrin, like Deltamethrin and cypermethrin ***(14).***

Neonicotinoids

History:

By the 1980s, many pest insects had developed resistance to the organophosphates, carbamates, and pyrethroids then on the market. In the beginning of 1990s, a new group of active compounds was introduced, including neonicotinoid compounds ***(15).***

The discovery of imidacloprid by Shinzo Kagabu, and its subsequent market introduction in 1991, started the era of the neonicotinoid class of insecticides. followed in 1999 by thiamethoxam and its metabolite, clothianidin,. Over the following two decades, neonicotinoids have become the most widely used insecticides on the global market ***(16).***

Moreover, the commercialization of neonicotinoids is more profitable for the companies that make them than nicotine because it is easily extracted from tobacco leaves at lower cost. They

can be easily dissolved in water and slowly break down in the soil, so they are easily absorbed by plants and provide protection during plant growth ***(17)***

(e.g., imidacloprid, acetamiprid, nitrosoguanidine, dinotefuran, clothianidin, thiacloprid, and thiamethoxam); all of them are insecticides **(18)**

Chemical Structure:

Chemically, neonicotinoids are related to nicotine. Nicotine itself has insecticidal properties and in the past it was used for

many years as infusions meant to eliminate some species of pests. Good results in controlling aphids and various greenhouse crop pests were achieved by fumigating greenhouse by burning nicotine, mainly used as nicotine sulfate resistance process developed by insects to this substance **(19).**

N-[(6-chloro-3-pyridyl)methyl]-N'-cyano-N-methyl- acetamidine135410-2-7

compared with nicotine that result in enhanced selectivity for insect nAChRs. Also, the amino nitrogen atom in nicotine is ionized, while in the neonicotinoids, the corresponding nitrogen atom is not ionized but bears a partial positive charge ***(20)***

Classification:

Seven neonicotinoid insecticides are currently used for agricultural production. These are imidacloprid and thiacloprid (developed by Bayer CropScience), clothianidin (Bayer CropScience and Sumitomo), thiamethoxam (Syngenta), acetamiprid (Nippon Soda), nitenpyram (Sumitomo), and dinotefuran (Mitsui Chemicals). An eighth compound, sulfoxaflor , has recently come onto the market in China and the USA. In China, new neonicotinoid compounds are being developed and tested (e.g., guadipyr and huanyanglin) ***(21)***

The first generation of neonicotinoids included nitenpyram, imidacloprid and thiacloprid. They act as partial agonist of the nicotinic nAChRs

The second-generation neonicotinoid like Thiamethoxam act as a poor agonist of insect nAChRs . However, it is a full agonist at cercal afferent/giant interneuron synapses where it induces a strong depolarization ***(22).***

The third-generation neonicotinoid dinotefuran can interact with insect nAChRs.The insecticidal activity of dinotefuran and its derivatives is better correlated to nerve-blocking activity than to nerve-excitatory activity,

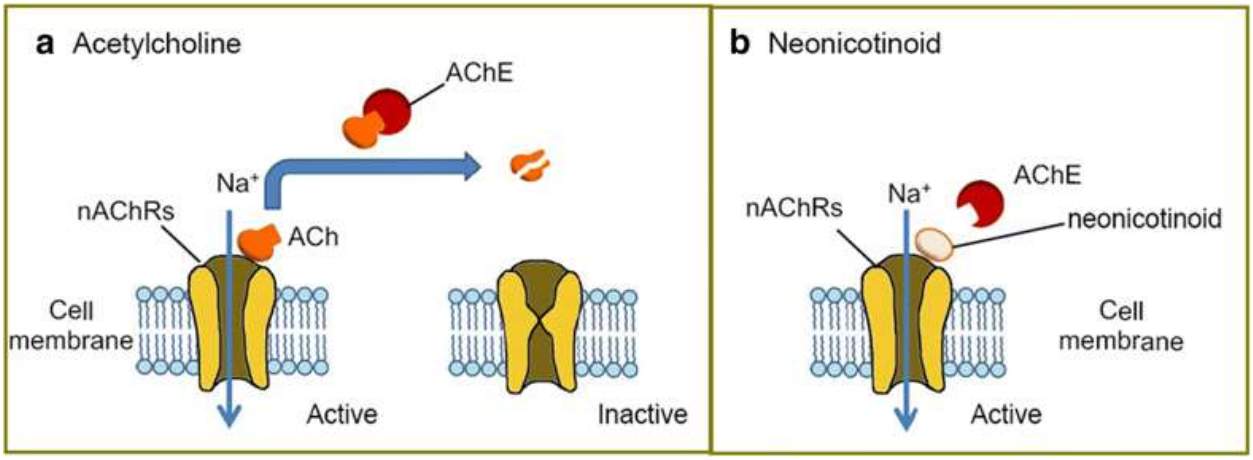
fourth-generation neonicotinoid includes Sulfoxaflor that exhibits a high insecticidal activity against a broad range of sap-feeding insects. It can also act on nAChRs and may be considered as a neonicotinoid. Its action involves receptor desensitization, receptor selectivity.

Mechanism of action:

Nicotinic acetylcholine receptors (nAChRs) are involved in rapid neurotransmission in both insect and mammalian nervous systems and play major roles in learning and memory. Neonicotinoids are acting as agonists of nicotinic acetylcholine receptors (nAChRs) in the postsynaptic neuron. This causes continuous activation of the receptor, leading to symptoms of neurotoxicity**.(23)**

- the agonistic action on the α4β2 subunits, which elicits a neuronal impulse in the organism;
- the competition of neonic molecules with the natural neurotransmitter acetylcholine and
- the persistence of the stimulus, as the neonic is not deactivated by the enzyme acetylcholine-esterase, which leads to overstimulation and eventual death of the neurons ***(24).***

It Was proved that imidacloprid and other neonicotinoids directly activate and change the α4β2 subtype of nAChR in humans. It is the best known subtype of nAChR in mammal brain, with the greatest density of receptors in diencephalon (*thalamus*). This subtype is involved in a range of brain functions such as cognition, memory, and behavior and have been proven to change in neurodegenerative disorders as Alzheimer's or Parkinson's disease, schizophrenia, and depression.



Schematic presentation of action of neonicotinoid acetylcholine receptors in the presence of acetylcholine and a neonicotinoid substance,

uses:

The use of neonicotinoids covers four major domains:

- plant protection of crops and ornamentals against herbivorous insects and mites
- urban pest control to target harmful organisms such as cockroaches, ants, termites, wasps, flies, etc.,
- veterinary applications (against fleas, ticks, etc. on pets and cattle, and fleas in cattle stables)
- fish farming (to control rice water weevil (*Lissorhoptrus oryzophilus* Kuscel) infestations in rice-crayfish (*Procambarus clarkii*) rotation ***(24)).***

Neonicotinoids are active against a broad spectrum of economically important crop pests, including Aphidae (aphids), Aleyrodidae (whitefly), Cicadellidae (leafhoppers), Chrysomelidae (among others western corn rootworm), Elateridae (wireworms), Fulgoroidea (planthoppers), Pseudococcidae (mealybugs), and phytophagous mites ***(25)***. Some of these groups (e.g., aphids) can also transmit viruses, so neonicotinoids can also contribute to the control of insect vectors of crop viral diseases.

Pharmacokinetics:

Absorption:

Neonicotinoids have rapid and efficient intestinal absorption

Distribution:

Metabolism:

Metabolism of the seven major commercial neonicotinoids can be divided into two phases.

Phase I metabolism depend on cytochrome P450, includes reactions such as demethylation, nitro reduction, cyano hydrolysis, hydroxylation of imidazolidine and thiazolidine accompanied by olefin formation, hydroxylation of oxadiazine accompanied by ring opening, and chloropyridinyl and chlorothiazolyl dichlorination. For some neonicotinoids, cytosolic aldehyde oxidase together with cytochrome P450 is responsible for nitro reduction in mammals ***(26).***

Phase II metabolism is mainly responsible for conjugate formation. Several metabolites are common to different neonicotinoids but others are compound specific ***(26).***

Excretion:

Ueyama et al., (27) successfully detected seven neonicotinoids (acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, thiacloprid, and thiamethoxam) in human urine samples collected from 52 Japanese people.

Environmental fate of neonicotinoids:

Recent studies have shown that neonicotinoids may have a longer biological half-life in the environment, therefore neonicotinoids may be more prevalent than previously thought. In the Danube River Basin, more than 50% of the water samples were detected the presence of NIT **(27).**

Air:

neonicotinoids used in seed treatments were consistently found in pollen stored in affected hives. Exposure to contaminated dust could pose risks for nontarget organisms whether they are exposed to insecticides by contact or through the ingestion of contaminated plant products (pollen, nectar, etc.) **(27).**

Soil:

insecticides can be applied directly to soils for uptake by plants or to the plants themselves by stem injections. The subsequent breakdown of plant material containing insecticide residues can release concentrations back into the soils, thereby providing a further route of soil contamination **(27).**

Neonicotinoid concentrations in soils decrease rapidly after application, by hydrolytic, photolytic, and microbial degradation, by plant uptake while persistence occurs under cool, dry conditions **(27).**

Water:

water on the soil surface of treated fields may contain high concentrations of systemic pesticides ***(28).***

Health effects:

Reproductive toxicity:

Neonicotinoids have detrimental effects on reproductive systems and embryonic development,

Female:

It causes dose dependent pathomorphological changes in follicles and ovarian weight decrease with alteration in the levels of LH, FSH, and progesterone ***(28).***

Male:

It decreases weights of the epididymis, sperm count, and testosterone.

In addition, it was also found a dose dependent seminiferous tubule apoptosis and DNA fragmentation ***(28).***

Renal toxicity:

Ayse and Okkes, (28).revealed nephrotoxicity in infant and adult male rats after imidacloprid and clothianidin in the form of increased levels of fatty

acids, cholesterol and vitamins in kidney tissues.

Hepatotoxicity:

The liver is the principal target organ of neonicotinoids damage. Neonicotinoids was found to cause hepatotoxicity and hepatocarcinogenicity including pathological changes and abnormal liver enzymes ***(29).***

Genotoxicity:

Different neonicotinoids can alter the integrity of DNA causing DNA damage, chromosomal abberation and also cause gene mutation ***(29).***

Neurotoxicity:

Several studies have shown neurotoxicity of neonicotinoids to nAChRs, causing significant decrease in the pain threshold and spontaneous locomotor activity in rats. Moreover, Behavioral changes in the form of anxiety and deterioration of cognitive functions when compared tocontrols ***(29).***

Immunotoxicity:

Neonicotinoid insecticides have potential immunosuppressive effect by suppressing cell-mediated immune response and induce histopathological changes in the spleen and liver ***(29).***

Endocrine toxity:

Some Neonicotinoid agents have endocrine-disrupting effects like thiacloprid ***(30).***

Park et al., (30).suggested that imidacloprid increased insulin resistance.

In addition, imidacloprid lead to fat accumulation through alteration of lipid metabolism.

Acetamiprid

Acetamiprid is a widely used second generation neonicotinoid of outstanding systemic action and potency. It is used for control of insects on several crops and sucking insects like aphids, bees and mosquitoes ***(30).***

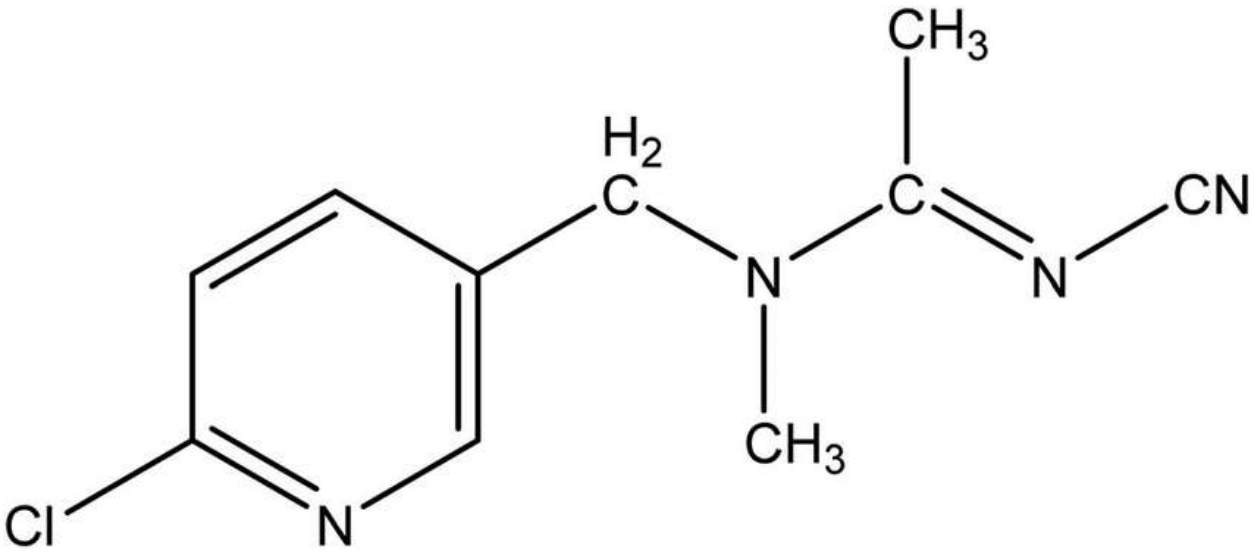
Acetamiprid (ACM) is a broad-spectrum insecticide used for the protection of vegetables and fruits from pest. The extensive use of this pesticide had led to contamination of environment including soil, water, as well as food products. However, there are few informations regarding the molecular mechanism by which ACM exerts its cytotoxic and genotoxic effects ***(30).***

Acetamiprid, a member of neonicotinoid synthetic chlorinated insecticide family is a new insecticide that has been introduced in the market. It is used against insects that have gained resistance to organophosphate, carbamate and synthetic pyrethroids. Homicide or suicide cases using acetamiprid are also expected to increase in the future.

It seems that a little work on the toxico-pathological effect of ACP in rats has been done. Thus, there is an urgent need to obtain more information regarding the manner in which ACP acts at cellular level.

Acetamiprid is a source of toxicities in humans. Its creation takes place during the thermal processing of foods that contain ACP. Where the majority of ACP was conjugated with glutathione, while a minimal amount was activated via glycidamide. Both ACP and glycidamide can form covalent adducts with DNA and hemoglobin, as well as induced gene mutation, chromosomal aberration and malignant neoplasm in rodents. Furthermore, ACP and its bio-transformed metabolite, glycidamide are hazardous to different organs ***(30).***

Physicochemical properties:



Absorbance 244-245 nm

Its molecular weight is 222.68 g/mol

Physical character: odorless powder must be dissolved in water.

The oral median lethal dose (LD50) was in the range of 146–217 mg/kg body weight ***(31).***

Trade names:

It is available in the market in the form of acetamiprid 20% in the following trade names: Cezar, Hekplan, Mospildate, Shark, Tenaz, Vapcomore, Mortal, Profil, Assail, Intruder, Tri-star, Mospilan according to ***Polish Ministry of Agriculture and Rural Development***

Uses:

Agricultural plants: potato, sugar beet, folder beet, winter oilseed rape, spring rape, tobacco.

Fruit trees: apple tree, berry plants: raspberry, blackcurrant, strawberry.

Vegetable plants (in ground and under cover): brassica, onion (from sowing and seedling),

tomato, cucumber, paprika, eggplant.

Ornamental plants (in the ground and under the covers).

Pharmacokinetics:

Absorption:

Acetamiprid is very rapidly absorbed orally and transported through the brush border of the intestinal cells via both passive and active transport systems. Acetamiprid uptake is pH-insensitive and temperature and sodium sensitive ***(31).***

Distribution:

Acetamiprid is rapidly and almost completely absorbed and is widely distributed into the tissues, being found at highest concentrations in GI tract, adrenal gland, liver and kidney, following oral administration to the rat.

http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Report11/Acetamiprid.pdf

Metabolism:

In mammals, N-demethylation is the main metabolization pathway for acetamiprid

Other pathways are also involved like cyano hydrolysis, cleavage of 6-CAN, cleavage of N-CN linkage from acetamiprid, which yields the N-descyano compound (ACE-NH) ***(31).***

Main metabolites: Acetamiprid-D-desmethyl, N-desmethyl acetamiprid, IM-2-1, ACE-dm, N-(6-Chloro-3-pyridylmethyl)-N′-cyano-acetamidine

The metabolite 6-CNA remains stable for more than 72 h in all biological compartments, except gut-free abdomen, which could explain the toxicity of acetamiprid ***(32).***

Excretion:

The major route of elimination was via the urine and bile. It Was reported that N-[(6-chloro-3-pyridyl)methyl]-N′-cyano-acetamidine (acetamiprid-N-desmethyl) is the most dominant urinary metabolite of acetamiprid and that 6-chloronicotinic acid was found in the urine of patients suspected of subacute exposure to Acetamiprid.

Environmental fate:

Soil:

Acetamiprid half-life is known to depend strongly on soil conditions, being almost 10 times longer under dry conditions ***(32).***

Water:

In seven major river basins in China, ACET was detected in 80% of samples ***(32).***

This evidence suggested that the human is increasingly exposed to neonicotinoids.

Toxic effects:

Hepatotoxicity:

Acetamiprid causes hepatotoxicity measured in increased levels of AST and ALP. As well, it causes altered liver structure and through induction of oxidative stress-mediated cellular damage and apoptosis ***(33).***

Renal toxicity:

Acetamiprid induced nephrotoxicity takes place through decreasing the expression of inflammatory cytokines, apoptosis and alteration of renal function parameters ***(34).***

Immunotoxicity:

It Was Reported That suppression of both humoral and cell mediated immunity in mice. Immunosuppression leads to change in span of life, increased susceptibility to infectious diseases and decreased immune response to foreign antigen.

Neurotoxicity:

The brain is particularly vulnerable to oxidative stress because of its high-energy demands, high level of peroxidable fatty acid and its relatively low antioxidant capacity. This irreversible molecular damage is the leading cause of

neurodegenerative diseases ***(35).***

Conclusion

Acetamiprid belongs to a relatively new class of insecticide that developed in the late 1980s, the 'neonicotinoids'. The precise structure of acetamiprid is that of a chloronicotinyl compound and it has been shown to be a potent agonist at the nicotinic acetylcholine receptors in insects. The primary use for acetamiprid is to control insects such as aphids, which have been known to attack and damage leafy plants. Acetamiprid is available as a ready-to-use formulation in addition to wettable powders and water-dispersible granules. Although acetamiprid has shown to have higher affinity for nicotinic receptors in insects compared to mammals, there have been some reports of imidacloprid (another neonicotinoid) undergoing biotransformation in rodents resulting in a compound that has higher affinity for then the nicotinic receptor compared to (−)-nicotine. This could potentially lead to toxicity in mammals. There have been no reports of chronic toxicity or of bioactivation of acetamiprid so far in mammals. A recent report has shown that acetamiprid can undergo transepithelial absorption across intestinal cells, possibly resulting in toxicity if acetamiprid accumulates within the body. It is not thought that acetamiprid contamination of soil is persistence and the general thought is that acetamiprid presents low hazard risks to human/vertebrate populations under normal conditions.

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