Chapter

Insect Resistance to Neonicotinoids - Current Status, Mechanism and Management Strategies

Shrawan Kumar Sahani, Vikas Kumar and Subhajit Pal

Abstract

Pesticides are any substance used for controlling, preventing, destroying, repelling, or mitigating of pests. Neonicotinoids have been the most commonly used insecticide since the early 1990s, current market share of more than 25% of total global insecticide sales. Neonicotinoid insecticides are highly selective agonists of insect nicotinic acetylcholine receptors (nAChRs) that exhibit physicochemical properties, rendering them more useful over other classes of insecticides. This includes having a wide range of application techniques and efficacy in controlling sucking and biting insects. Although neonicotinoids are applied as foliar insecticides with possible direct exposure risks to honeybees, a large part of neonicotinoid use consists of seed coating or root drench application. There are three major detoxification enzymes involved in the development of resistance against insecticides viz., cytochrome P450 monooxygenases, carboxylesterases, and glutathione S-transferases. The repeatedly used use of compounds of the same active ingredients and application of excessive organophosphates (OPs) and pyrethroids in *Bemisia tabaci*. Resistance to insecticides resulting in loss of efficacy of many older insecticides has placed excessive pressure on novel products. One of the major limitations to resistance management is the occurrence of cross-resistance. This review briefly summarizes the current status of neonicotinoid resistance, the biochemical and mechanisms involved, and the implications for resistance management.

Keywords: insect resistance, neonicotinoids, overuse, nicotinic acetylcholine receptors, management strategies

1. Introduction

Chemical control remains the most important and widely used strategy against noxious insect pests around the world. It is used to kill, harm, repel, or mitigate one or more species of an insect by disrupting the nervous system and damaging their exoskeletons. Insecticides have not only controlled insects, but it also used to control diseases carrier agents and helps in the economy and social benefits through better health and increase food production [1, 2]. After the introduction of neonicotinoids in the 1990s, most widely used against the sap-feeding insect. Among these imidacloprid is the most widely used insecticide in the world. Neonicotinoids

currently account for approximately 25% of the total insecticide market and are increasing in use as they replace the organophosphate (OP) and carbamate insecticides, causing less toxicity in birds and mammals than insects. Overwhelming evidence has risen over the past decade regarding potentially harmful risks to humans, nontarget insects, aquatic invertebrates, and side effects on the natural environment following usage of specific classes of insecticides [3, 4].

There is various kind of factors that helps the occurrence and initial successful establishment of neonicotinoids to control, mitigate the especially soft body insect pests. At that time there was no known pesticide resistance in target pests, mainly because of recently synthesized nicotine contain plants, their physicochemical properties included many advantages such as selectivity, target-specific, less residual effect on soil, and metabolism rate fast over previous generations of insecticides (i.e., organophosphates, carbamates, pyrethroids, etc.) they shared an assumed reduced operator and consumer risk [5, 6]. But after some time, due to large and indiscriminate use of the same mode of action insecticides have been responsible for developed resurgence and insecticide tolerance ability increased. The first report of neonicotinoid resistance was published in 1996, describing the low efficacy of imidacloprid against Spanish greenhouse populations of cotton whitefly. There are three major detoxification enzymes involved in the development of resistance against insecticides viz., cytochrome P450 monooxygenases, carboxylesterases, and glutathione S-transferases [1, 7].

Several field problems such as poor selection of chemicals and substandard application practices exacerbated the control failures of insecticides against *Bemisia tabaci* in India. The repeated use of compounds of the same active ingredients and application of excessive organophosphates, carbamate, pyrethroids, and neonicotinoids against insect pests cause the development of resistance. Resistance to insecticides resulting in loss of efficacy of many older insecticides has placed excessive pressure on novel products. One of the major limitations to resistance management is the occurrence of cross-resistance [8].

2. Landmark to development of neonicotinoids and their mode of action

- In 1970, first-time nithiazine was precursor by Henry Feuer, a reputed chemist at Purdue University [4, 9].
- Shell (oil refinery company) researchers found in screening that this precursor showed insecticide activity on insect pest management and refined it to develop nithiazine.
- In 1984, the mode of action of nithiazine was found to be as a postsynaptic acetylcholine receptor same as nicotine.
- In 1985, Bayer patented imidacloprid as the first commercial neonicotinoid, and till 1990 used at large scale.
- The early 2000s, two other neonicotinoids, clothianidin, and thiamethoxam, entered the market, which is drastically changing the thinking of people.
- During 2013, virtually all corn planted in the United States was treated with one of these two insecticides. Thiamethoxam among the neonicotinoids has less residual effect and persistence in nature.

- Beginning of 2014, about a third of US soybean acreage was planted with neonicotinoid-treated seeds, usually imidacloprid or thiamethoxam [3].

- Electrophysiological studies on identified cockroach neurons, and the binding to cockroach nervous system membrane.

2.1 Neonicotinoid groups Vs Older groups

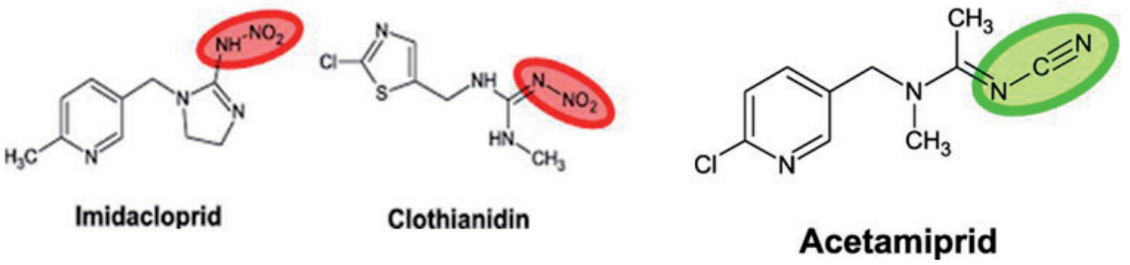
Neonicotinoids have been the most commonly used insecticides since the early 1990s as an alternative to older organophosphate and carbamate insecticides. Neonicotinoids are insecticides that exhibit physicochemical properties, rendering them more useful over other classes of insecticides [10]. Over the last few years, neonicotinoids have been combined with pyrethroids in formulated products, and with diatomaceous earth (e.g., Alpine dust insecticide, with dinotefuran) for the control of insect pests. Moderate to high levels of tolerance/resistance to various neonicotinoids showed by insect pests. Romero and Anderson reported that resistance to neonicotinoids may likely be conferred by the increased enzymatic activities found in these populations. Those findings showed that tolerance or even resistance to neonicotinoids is now present in field and storage pest populations [1, 11].

Neonicotinoids show high acute toxicity to honeybees. The neonicotinoid family includes imidacloprid, clothianidin, and thiamethoxam (the latter is metabolized to clothianidin in the plant and the insect). Recently, imidacloprid has been replaced by thiamethoxam and clothianidin in some parts of the world. To date, neonicotinoids have proved the development of resistance, such as *Myzus persicae* and *Phorodon humuli*. The effects of imidacloprid on *Nilaparvata lugens*, tebufenozide on *Plutella xylostella* and *Spodoptera exigua,* thiamethoxam on *Bemisia tabaci,* trichlorphon on *Bactrocera dorsalis*, imidacloprid on *Spodoptera litura*, and emamectin benzoate on *Chrysoperla carnea* have been reported [12].

The first report of neonicotinoid resistance was published in 1996, describing the low efficacy of imidacloprid against Spanish greenhouse populations of cotton whitefly. Later-generation, show stronger resistance (up to 17-fold in the first 15 generations, but >80-fold resistance after 24 generations, which has been confirmed in some populations of the whitefly (*Bemisia tabaci*) and the Colorado potato beetle (*Leptinotarsa decemlineata*) [13]. Although neonicotinoids are applied as foliar insecticides with possible direct exposure risks to honeybees, a large part of neonicotinoid use consists of seed coating or root drench application [14, 15].

2.2 Mode of action of neonicotinoid

All neonicotinoids act on the insect central nervous system as agonists of the postsynaptic nicotinic acetylcholine receptors (nAChRs). Neonicotinoids act as agonists on the postsynaptic insect nicotinic acetylcholine receptors (nAChRs), biodegradable substituents which have a much higher affinity on insects than mammals [16, 17]. Neonicotinoid insecticides are highly toxic to many invertebrates, including honey bees, bumblebees, and solitary bees. The neonicotinoids (including imidacloprid, dinotefuran, clothianidin, and thiamethoxam) are nitro functional group ($-NO_2$) instead of a cyano functional group ($-C{=}N$) in their molecular structure. This slight difference in their molecular structure affects the toxicity level of neonicotinoids, which bind to an insect receptor site. The nitro-group neonicotinoids are much more toxic to bees than the cyano-group neonics, which include acetamiprid and thiacloprid [11, 13, 18].



3. Global growth, status, and uses of neonicotinoid insecticide

During 1990, the global insecticide market was dominated by carbamates, organophosphates, and pyrethroids. In 2008, one-quarter of the insecticide market was neonicotinoid to 27% in 2010 and nearly 30% in 2012. The Overuse of chemical products in different spheres of life not only brings benefits for humanity but also presents a large number of threats against the environment and in consequence to human health. The present graph indicates the maximum use of neonicotinoids insecticide and its application in different countries. Here, thiamethoxam shares maximum contribution in the market (37.6) followed by imidacloprid (33.5), clothianidin (14.7), acetamiprid (7.2), thiacloprid (3.8), dinotefuran (2.9), nitenpyram (0.3), and the area

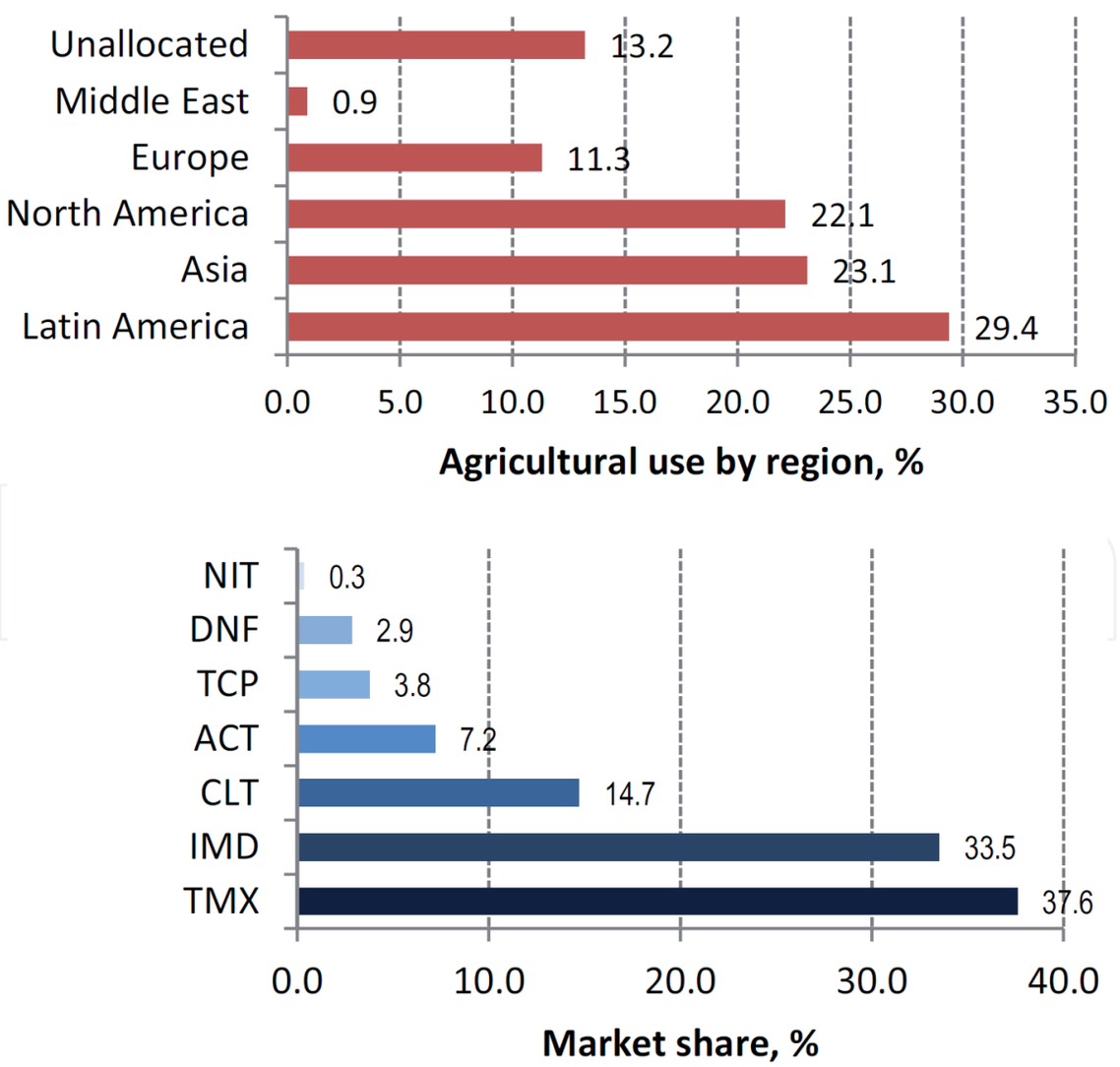


Figure 1.
Agricultural use by region and market share of individual neonicotinoids in percent. Abbreviations: TMX (thiamethoxam), IMD (imidacloprid), CLT (clothianidin), ACT (acetamiprid), TCP (thiacloprid), DNF (dinotefuran), NIT (nitenpyram).

uses maximum in agriculture production in Latin America (29.4), Asia (23.1), and North America (22.1) followed by others unallocated areas (**Figure 1**).

3.1 The use of neonicotinoids covers four major domains

The uses of neonicotinoid are to protect crops and ornamentals against polyphagous insects and mites, urban pest control to target harmful organisms such as cockroaches, ants, termites, wasps, flies, etc., apart from the agricultural uses, it is also applicable in veterinary sciences to reduce the chances of occurrence (fleas, ticks on pet animals) and fish farming infestations. In agriculture as well as horticulture crop, neonicotinoid can be functional in many different ways such as foliar spraying, seed dressing, soil drenching, furrow application, trunk injections in trees, mixing with irrigation water, drenching of flower, soil treatment, granular application, dipping of seedlings, bulbs and application with a brush on the stems of fruit trees. Seed and soil applications denote approximately 60% of their uses globally [16, 19]. The usage of neonicotinoid insecticides has grown considerably since the forerunner of this group, it is first introduced among neonicotinoids in the year 1991 followed by acetamiprid and thiamethoxam. Till now, seven insecticides be in the right place to this chemical class are available to farmers all over the world and classified as Group A within the Insecticide Resistance Action Committee (IRAC) and Mode of Action Classification Scheme. All neonicotinoids are agonists of insect nicotinic acetylcholine receptors [18]. In 1941, the first case documented by insects demonstrated resistance to an inorganic resistance; 1987—first reported in First reported on tobacco in vaeck, and later on tomato in Bischoff district. Insect resistance genetically modified crops (primarily cotton and maize), are toxic to certain insects. They are often called Bt crops because the introduction genes were originally identified in a bacterial species called *Bacillus thuringiensis* (**Figure 2**).

3.2 Insecticide resistance to neonicotinoid

Resistance is quickly developed due to the selection of highly effective compounds with kill or mitigate to insect, long residual effect, and is regular use of single biochemical target site. The toxicant is converted into a nontoxicant form in the body of an insect by various enzymes. All these enzymatic changes are carried forward and transmitted through genes. Resistance in B- and Q-type has been noticed in *Bemisia tabaci* to enhanced oxidative detoxification of neonicotinoids due to overexpression of monooxygenases. No evidence for target-site resistance has been found in whiteflies [18, 19]. Biotic and abiotic degradation processes contribute to the environmental persistence of neonicotinoids. The half-life of neonicotinoids varies depending on physiochemical

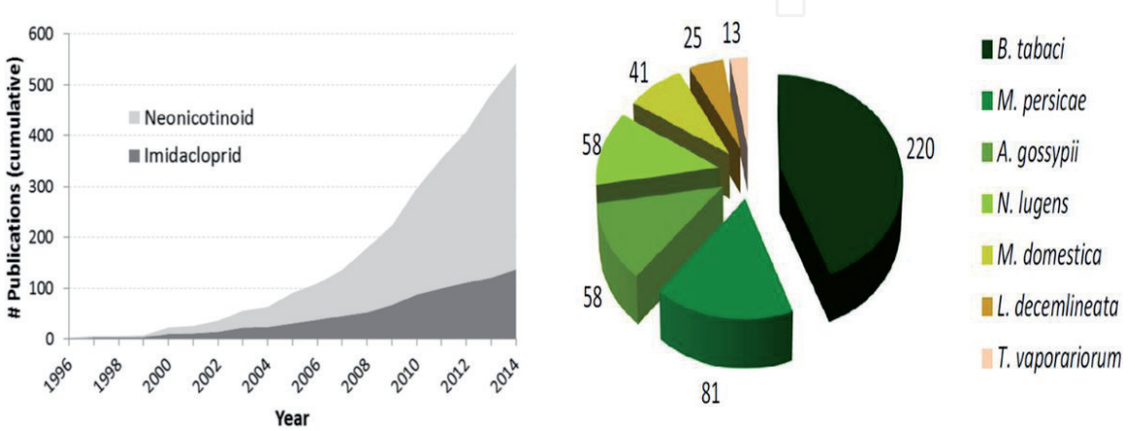


Figure 2.
Several reported cases of neonicotinoid resistance up to 2014. Only those pests with >10 (fold) reported cases are shown.

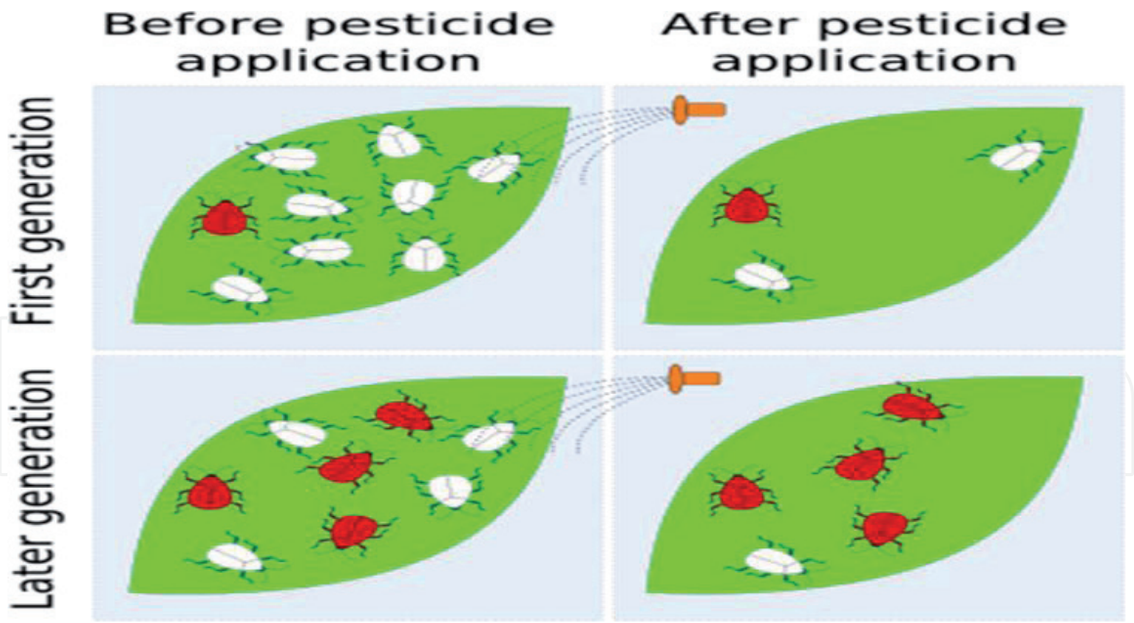


Figure 3.
Pesticide resistance can build up in the pest population when a change in the genetic characteristic of the pest population is inherited from one generation to the next.

conditions (i.e., organic matter content, soil texture, residence time) before undergoing complete degradation. The development of resistance is a complex and dynamic process and depends upon many factors. As per the IRAC, resistance is well-defined as a heritable change in the sensitivity of a pest population, that is reflected in the constant failure of a product to attain the expected level of control when used according to the label endorsement for that pest species [20]. The environmental protection agency (EPA) is divided into two classes of toxicity agents i.e., II and III. Accumulation (increase the level of pesticides) of those pesticides into the soil affects the pollen quality of sprayed plants, especially due to their toxic effects, against pollinators the consequences of the occurrence of these insecticides have been discussed [10, 21]. It is determined that the transfer of vertical gene (a particular gene) from the microorganism, higher plants, animals into a host plant for crop improvement and researches are called transgenic plant or insects, virus, fungus resistance plant. It gives us facts for future research. Mutation (can build up in the pest population when a change in the genetic characteristic of the pest population is inherited from one generation to the next) in nAChR subunits and in most cases, metabolism is also responsible for the development of resistance (**Figure 3**). The brown planthopper, *Nilaparvata lugens*, was selected with imidacloprid treatment at a sublethal dose to obtain resistant mutation. Both *Bemisia tabaci* (sweet potato whitefly) and *Trialeurodes vaporariorum* (greenhouse whitefly) have been shown to have a high possibility for resistance development and characterize some of the main targets for which IRAC specific strategies have been developed [8, 22]. Global resistance management guiding principles were designed by the Neonicotinoid Working Group of the Insecticide Resistance Action Committee and are based on guidelines published and updated earlier [9].

4. Mechanism of resistance and factors that influence resistance development

4.1 Resistance mechanisms

The various mechanisms that enable insects to resist the action of insecticides can be grouped into several categories:

4.1.1 Single resistance

Resistance to Dichloro diphenyl trichloroethane (DDT) amounts to resistance to several DDT analogs such as methoxychlor, but not to hexa chloro cyclohexane (HCH). Due to excessive and continuous use of the insecticides.

4.1.2 Cross-resistance

It occurs when resistance to one insecticide or within a group. Eg: organophosphate insecticides, fungicides etc.

4.1.3 Multiple resistance

It involves multiple, independent resistance mechanisms, which often lead to resistance to chemicals from different families (i.e., organophosphate and carbamate insecticides) [23].

4.1.4 Metabolic resistance

It plays one of the significant roles, in the development of resistance which helps to change the activity of enzyme systems that all insects possess to help them detoxify naturally occurring foreign materials. Enzymes are classified viz., esterases, monooxygenases, and glutathione S-transferases typically fulfill this function. These enzyme systems are often enhanced in resistant insect strains enabling them to metabolize or degrade insecticides before they can exert a toxic effect. Metabolic resistance appliances have been noticed in whitefly, aphid, and Colorado potato beetle populations for all major classes of insecticides, currently also used for soft body insect control including neonicotinoids insecticide [24].

4.1.5 Target site resistance

Insecticides generally perform on a specific site within the insect, especially within the nervous system (e.g., OP, carbamate, and pyrethroid insecticides). The site of action can be reformed in resistant strains of insects such that the insecticide no longer binds effectively. This results in the insects being unaffected, or less affected, by the action of insecticide than susceptible insects.

4.1.6 Reduced penetration

Changes in the insect cuticle or digestive tract linings that avoid or slow the absorption or diffusion of insecticides can be found in some strains of resistant insects. This resistance mechanism can affect a broad range of insecticides. Examples of reduced penetration mechanisms are limited and are often considered a contributing factor to reduced susceptibility.

4.1.7 Behavioral resistance

This resistance illustrates any adjustment in insect behavior that helps to avoid the lethal effects of insecticides [22]. Insecticide resistance in mosquitoes is not always based on biochemical mechanisms such as metabolic detoxification or target site mutations, but may also be conferred by behavioral changes in response to prolonged exposure to an insecticide.

Mechanism	Species
Resistance to neonicotinoids	
Enhanced expression of CYP6G1	*Drosophila melanogaster*
Enhanced expression of CYP6AY1, CYP6ER1, CYP4CE1, and CYP6CW1	*Nilaparvata lugens*
Enhanced expression of glutathione *S*-transferase (MdGST) and galactosyltransferase (MdGT1)	*Musca domestica*
Mutation of Dα1/Dβ2 subunits	*Drosophila melanogaster*
Deletion of Dα1 subunit	
Y151 mutation in Nlα1/Nlα3 subunits	*Nilaparvata lugens*
Reduced expression of Nlα8 nicotinic acetylcholine receptor (nAChR) subunit	
R81T mutation in Mpβ1 subunit	*Myzus persicae*
	Aphis gossypii
Tolerance to neonicotinoids	
Reduced sensitivity to thiacloprid and acetamiprid due to metabolism by CYP9Q3	*Apis mellifera*
Reduced sensitivity to thiacloprid and acetamiprid due to metabolism by CYP9Q4 and CYP9Q6	*Bombus terrestris*
Reduced sensitivity to thiacloprid due to metabolism by CYP9BU1 and CYP9BU2	*Osmia bicornis*

Table 1.
Mechanisms of neonicotinoid resistance and tolerance in insects.

4.1.8 Genetic basis of resistance

It occurs naturally, genetic mutations allow a small proportion of the population to resist and endure the effects of the insecticide. This occurs due to continually using the same insecticide and horizontal genes. Resistance insects will reproduce and the genetic changes that confer resistance are transferred from parents to offspring so that eventually they become numerous within the population (**Table 1**).

5. Factors influence in the development of resistance

5.1 Frequency of application

However, usually pesticide or management measures are used, one of the important factors that influence resistance development. With every use, an advantage is given to the resistance insects inside a population. The speed of increase of resistance in any population can usually be faster within the presence of a lower applicable value.

5.2 Dosage and persistence of effect

The period of pesticide persistence remains effective, additionally referred to as its persistence, relies upon the chemical science of the pesticide, the short of formulation, and also the application rate. The product that gives a persistent impact equally gives continuous selection pressure to multiple species. As an example, an area spray can persist for short time and can choose solely against one generation of mosquitoes [22]. In addition, a residual wall application or a bed

net treatment can persist for months or years providing choice pressure against several generations of an equivalent insect. It is so vital to frequently follow manufacturer and United Nations agency recommendations once victimization such pesticides.

5.3 Rate of reproduction

As we have got identified that usually, insects that have a short life cycle, and high reproductive rate are possible to develop resistance earlier than species that have a lower reproductive rate, as any resistance generation will quickly unfold throughout the population. The homopterans insect has an associate in nursing account for pesticide resistance and is considered by a comparatively short life cycle and high fecundity, with female laying a huge number of eggs throughout their reproductive life. However, the tse-tse fly have shorter life cycle and fecundity comparatively less than hemipterans and comparatively low rate of reproduction, females produce in total fewer approximately 10 offspring.

5.4 Population isolation

With vectors of sickness, the goal is common to get rid of all or the bulk of the population, but the larger the choice pressure that is placed on a population, the quicker status could also be lost. Immigration of people possessing susceptible genes from untreated areas can beneficially dilute and contend with the resistance genes within the overall population. Associate in nursing early step during a vector management program should therefore to be to estimate the importance of immigration of untreated insects. As an example, associate in nursing island wherever the whole space was treated would have the next risk of developing resistance as few untreated mosquitoes would be part of the treated population. The hazard of pesticide resistance rising out to be measured once designing resistance management ways [25, 26]. Awareness of and coordination with neighboring vector management programs and agricultural activities should be excited, so the regional impact on the target population is deliberated.

- Prolonged exposure to a single insecticide
- High selection pressure
- Large coverage area
- Insects multiplying by asexual means
- The selection at every stage of the insect life cycle

6. Neonicotinoid resistance management

- Always use products at the recommended label rates and spray intervals with the appropriate application equipment.
- Rotation of insecticide group against the rapid selection of resistant population.
- Use suitable integrated pest management (IPM) approaches.

- Neonicotinoids are used against different pests in the same cultivars.

Repeatable uses of different chemistry of neonicotinoids against more than one pest species in the same crop are less susceptible but need at the local level, to take into account the pest populations dynamics, overlapping of the various species, their relative importance, and each species' potential risk for developing resistance [2].

- Do not control a multigeneration pest exclusively with neonicotinoids.
- The use of nonspecific products helps to prevent the development of resistance.
- Plan to use neonicotinoid insecticides in such a way that they do not affect the beneficial organisms.
- Good agricultural practices should be applied alongside physical and biological pest control methods.
- Judicious use of insecticides (need-based and recommended dose).
- The use of insecticide synergists.
- Window system of pesticide application.
- Area-wide management.
- Crop pest host management.
- Monitor problematic pest populations to detect first shifts insensitivity.

6.1 Alternative prospects

- Use other synthetic or naturally occurring chemical insecticides
- Biological control with microorganisms
- Biological control through farming practices
- Use of semiochemicals for mass trapping, mating disruption, repulsion, antifeeding effects, push-and-pull or attract-and-kill techniques
- Use other techniques like physical and mechanical methods to minimize insecticidal loads
- Genetically improved plant varieties
- We used four criteria to rank the alternatives to neonicotinoids—efficacy (E), applicability (A), durability (D), and practicability (P)

7. Summary

The widespread use of synthetic insecticides has given rise to the serious problem of insecticide resistance all over the world. The problem of insecticide resistance

is growing in magnitude is no doubt steadily diminishing the choice of effective insecticides for vector control. The frequent change in insecticides involves a substantial increase in cost. The practice with neonicotinoid develops harmful possible impacts on nontarget species and the environment worldwide. This review provides a beneficial means for categorizing regions that may need improved development of best management practices (BMPs) to mitigate the adverse consequences associated with extensive use of insecticides in surface and groundwater. Pesticides must be used judiciously in an IPM program to preserve cost-effective pesticides and maintain susceptible individuals in a pest population. The recent finding that nAChR subunit composition can be switched in insects exposed to sublethal concentrations of neonicotinoids is of considerable interest. To manage pest species effectively while minimizing conditions that lead to the onset of resistance, we need to know how messenger ribonucleic acids (mRNAs) encoding, nAChR subunits, and their associated proteins, as well as enzymes involved in metabolism, are dynamically modified. The challenge of optimizing and implementing such tactics for specific pests depends on a suite of ecological, genetic, operational, and socioeconomic.

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