CHAPTER-I

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1.1 General introduction

Modern crop production cannot be developed without use of chemicals for the pest control referred to as the pesticides. The crop yields have been raised about one third by the use of pesticides. Insects become susceptible due to continues use of these insecticides hence should be continuously renewed, by the new insecticides having novel mode of action.¹

Neonicotinoid insecticides have many common molecular features. The notable feature is that these compounds contain four sections like aromatic heterocycle, flexible linkage, hydroheterocycles or guanidine/amidine and electron-withdrawing group. Another interesting feature is the configuration, the electron-withdrawing groups of NO₂ or CN linked to a CdC (Carbon double bond Carbon) or CdN (Carbon double bond Nitrogen) bond can exist in either of the two configurations (trans or cis), but X-ray crystallographic study showed that the heteroaromatic moiety in neonicotinoids was only in the trans configuration relative to the electron-withdrawing tip. The related calculation also revealed that the trans E-isomeric form is also predominant in both gaseous and aqueous phases. In addition, the previous study of binding model presumed by Casida and Sattelle was based on trans configuration.¹⁰

Other names of neonicotinoid insecticides present in the literature based on the names of given molecule structure fragments e.g. chloronicotinyls, chloropyridyls, thianicotinyls, nitromethylenes, nitroguanidines, cyanoguanidines etc. For the development of nicotinoid insecticides the crucial turning-point was work done by scientists from Nihon Tokushu Noyaku Seizo KK. and Nippon Bayer (Japan, 1984). By introducing heterocyclic ring 3-methyl pyridyl groups, particularly 6-chloropyridyl-3-methyl they achieved an essential improvement in the insecticidal activity.¹⁴

1.2 Market Status of neonicotinoids

The neonicotinoids represent one of the most important groups of insecticides on the current market of plant protection products. Imidacloprid is one of the largest selling
insecticides worldwide and get distributed in more than 120 countries. In the year 2006 the worldwide annual sales of neonicotinoids was about 1.56 billion USD. Neonicotinoids is a promising new class of pesticides for an effective and long-lasting protection of agricultural crops. The outstanding development of neonicotinoid insecticides has been achieved for the modern crop protection, consumer products and animal health markets between 1990 and today reflects the enormous importance of this chemical class. The unique success of neonicotinoid insecticides have reflected in their turnover figures in 1990 as compared with 2008. In 1990, before the launch of the first neonicotinoid insecticide, imidacloprid, the agrochemical market (total volume of €7.942 billion) was dominated by organophosphates (OPs) (43%), pyrethroids (18%) and carbamates (16%). In 2008, neonicotinoids gained a 24% share of a slightly decreased total market of €6.330 billion, mainly at the expense of OPs (13.6%) and carbamates (10.8%). On the other hand, the turnover figures for seed treatments are very impressive. A so-called niche market of €155 million for insecticidal seed treatment in 1990 was dominated by carbamates (77.4%). It was then reached to a €957 million market shell, with a share for neonicotinoid insecticides 80% in 2008.

In addition to the common neonicotinoid spectrum, the commercial products differ considerably with respect to soil and seed treatment uses, as soil stability is limited for some of them such as nitenpyram, acetamiprid and dinotefuran. The first neonicotinoid imidacloprid has registered for over 140 crop uses in more than 120 countries under the trade names Confidor, Admire for foliar use and Gaucho for seed treatment. The nitenpyram (Capstar, Takeda/Syngenta) as a fast-acting, adult Flea control product in cats and dogs for animal health controls. It was used for the control of sucking insects in rice, fruit, tea, vegetables and field crops. In Japan it was marketed under the trade name Bestguard. Acetamiprid has been marketed, under the trade name Mospilan and is registered for cotton, vegetables (Assail), potato, orchards for codling moth control, vines, citrus, tea and ornamentals (Chipco,Tristar). In addition, acetamiprid is also of interest for the control of termites and household pests. Thiamethoxam is marketed as Actara for foliar applications, as Platinum for the soil applications and Cruiser for the seed treatment. Thiamethoxam was registered for 115 crop uses in at least 65 countries on a wide range of crops such as vegetables, potatoes, rice, cotton, fruit, tobacco and
cereals. Its pest spectrum includes all major sucking insects, as well as some chewing and soil-living pests. Thiacloprid is available in the market under the trade name Calypso and is active against sucking and chewing insect pests on crops such as fruit, cotton, vegetables, oilseed, cereals, potato, rice and ornamentals and also for various species of beetles, lepidopteran leafminers and *C. pomonella* (L.). It has also been applied on flowering crops because it is safe for Bee. Therefore, thiacloprid and clothianidin covers a broad pest spectrum, which resulted in applications as insecticide for seed treatment (Poncho), for soil (Dantotsu) and for foliar use (Dantop). Dinofuran available in market under the trade name Starkle and is marketed in the United States as Safari on ornamentals and as Venom in fruit, cotton, potatoes and vegetables.\(^7\),\(^{11}\)

Worldwide annual sales of neonicotinoids, including imidacloprid with the largest sales volume among all insecticides, are approximately $1 billion, accounting for 11–15% of the total insecticide market.\(^{12}\) The discovery of imidacloprid has been referred to as a milestone in the past three decades of insecticidal research. The unprecedented high insecticidal potency and supreme systemic properties were immediately recognized and through the following additional finding of activity against strains resistant to the prevailing insecticides and low mammalian toxicity, imidacloprid soon took over the lead in the world insecticidal market and has been the frontrunner. The neonicotinoids class share heralded by imidacloprid 20% of the current insecticide market.\(^{13}\) Neonicotinoids being one of the most important, groups of insecticides. Beside influence of the insecticidal activity the pharmacophore is also responsible for some of its specific properties, as photolytic activity, the rate of degradation in soil, metabolism in plants and toxicity to honeybees and other beneficial insects.\(^ {14}\)

### 1.3 History of neonicotinoids

1930’s era brought about the development and the use of synthetic organic compounds for insect pest management.\(^4\) The scientist Shell described, first time the insecticidal properties of some simple nitromethylene heterocycles to discover the nithiazine as a neonicotinoid lead structure in 1972. After thirteen years Nihon Bayer achieved an important breakthrough in this Chemistry, to synthesize the imidaclorprid and found increased insecticidal activity by more than 100 factors against green rice leafhoppers.
The first patent application for this new invention was reported in 1985 and started extensive research activities by other companies. Ciba (since 1996 Novartis), Takeda, Nippon Soda, Agro Kanesho, Mitsui Chemicals and others related to this research area. After imidacloprid was launched in 1991, nitenpyram and acetamiprid were brought to the market. Thiamethoxam was discovered which represented the second-generation of neonicotinoids, which was marketed under the trade names Actara for foliar and soil treatment and Cruiser for seed treatment.² Neonicotinoids showed an excellent chemical and biological properties. The first successful member of this family is imidacloprid, having a subclass chloronicotinyl compounds, nitenpyram from Takada Chemical Industries, acetamiprid from Nippon Soda and thiacloprid from Bayer Crop Science and brought to the market in the year 1995, 1996 and 2000, respectively. In the development of novel insecticide, 2-chloro-5-thiazolyl compound, named thiamethoxam, was developed by Novartis Crops Protection in 1998. Another insecticide clothianidin was introduced in the market by Bayer Crop-Science in 2002. Dinofuran with a tetrahydro-3-furylethyl group instead of an aromatic heterocyclic ring was developed by Mitsui Chemicals and was first registered in Japan in 2002.³ Once optimized to imidacloprid and its analogs, the neonicotinoids joined the earlier chlorinated hydrocarbons, organophosphorus compounds, methylcarbamates and pyrethroids to constitute the five principal types of active ingredients, all of which are neuroactive insecticides. These developments were possible because of the selective toxicity of the neonicotinoids nithiazine, a nitromethylene heterocycle discovered by Soloway and colleagues of the former Shell Development Company in California, was the first prototype of the highly insecticidal neonicotinoids. The lead compound was 2-(dibromonitromethyl)-3-methylpyridine, recognized by Shell scientists in 1970 having unexpected modest insecticidal activity. The nithazine (hydrothiazine ring) was replaced with other N-heterocycles and the substituents were introduced on the nitrogen atoms. Activity was enhanced first with the N-(4-chlorobenzyl) and then the N-(3-pyridinylmethyl) moieties. The replacement of the nitromethylene by nitroimine to give imidacloprid reported in February, 1985 with 62 to more than 3000 fold-higher insecticidal activity, than that of nicotine. The physicochemical properties of neonicotinoids played an important role in the development. The principal target pests of these compounds are Aphids, Leafhoppers,
Whiteflies and other sucking insects due to their excellent systemic property and water solubility. Thiacloprid, acetamiprid and the nitromethylene-thiazolidine analogs of imidacloprid with relatively high hydrophobicity showed lepidoptericidal activities. Photostability is an important factor in the field of performance of the neonicotinoids. The nitromethylene chromophore of nithiazine and imidacloprid analogs ($\lambda_{\text{max}} > 320$ nm) absorbs strongly in the sunlight range of 290-400nm and rapidly decompose to the non insecticidal compounds. Replacing nitromethylene with a nitroimine or cyanoimine substituent ($\lambda_{\text{max}} < 270$ nm) avoids the absorption of sunlight and consequently confirmed the prolonged residual activity.\(^5\)

The first generation of the neonicotinoids contains four substances that is acetamiprid, imidacloprid, nitenpyram and thiacloprid (first generation) contain the heterocyclic 6-chloro-3-pyridyl group. Second generation of neonicotinoids contain two substances clothianidin and thiamethoxam (second generation) the 2-chloro-5-thiazolyl group thiamethoxam and clothianidin. Third generation neonicotinoids contain only one substance dinotefuran (third generation) the 3-tetrahydrofuranyl group (Fig. No. 1).\(^6\)
First Generation Neonicotinoids

Second generation Neonicotinoids

Third generation Neonicotinoids

Fig. No. 1. List of neonicotinoid compounds.
1.4 Discovery of neonicotinoids

Researchers have started the project by pursuing nithiazine in 1979, which Shell announced as a new insecticide in 1978. Electrophysiological studies clarified that nithiazine acts on the nicotinic acetylcholine receptor (nAChR) in the same fashion as nicotine. It seemed to us there were no obvious structural similarities between the two compounds. There were several possible variations from nithiazine to explore, the tetrahydrothiazine ring, the N or S atom in the central ring or the push-pull olefin part. Researchers have explored the transformation of the perhydrothiazine framework to diazacycloclokanes. The screening test was done with the Green rice leafhopper (Nephotettix cincticeps). One of the most important pests for rice culture, showed the concentrations for 90% mortality, LC_{90}. The activity was dependent on the ring size and the five-membered ring compound showed the highest activity. As the ring size increases, the activity decreases. Seven and eight membered ring compounds had a severe loss of activity and acyclic compounds have completely lost the activity. At the time, researchers concluded that the active molecule must be a cyclic structure and preferably a plain ring such as a five-membered ring. This assumption may have facilitated the research, but it caused a strategic error in the product development. Introduction of the various substituents on the five-membered ring and found that only the benzyl group enhanced the activity. From these result, they first thought that the pharmacophore of this class may be the nitromethylene-imidazolidine itself and the activity would emerge when the benzyl group dissociated metabolically. However, when substituents were introduced to the benzylic benzene ring, the activity depends upon the kind and position of the substituent. The p-chloro and m-cyano derivatives gave the best results. The benzylic displacement is not likely affected so much by the kind and position of the substituents, therefore, researchers had to think that the active moiety is not the nitromethylene-imidazolidine but the whole molecule containing the benzyl group with these substituents. This may be a sign for the possible existence of active structures expanding from nithiazine, but they could not explore so far as this idea and above all the efficacies of their products. After two years, the Bayer researchers took up nithiazine again in work. This time researchers introduced heteroaromatic rings to the nitromethylene imidazolidine skeleton. After a few trials, they found that 3-pyridylmethyl and 4-pyridylmethyl derivatives showed
insecticidal activity superior to that of nithiazine. A similar enhancement was observed in other heteroaromatic rings with the nitrogen atom at the corresponding position. At this stage they felt that this might be able to develop something in this class. Soon after that, they found that a 6-chloro-3-pyridylmethyl group enhanced the activity extraordinarily. LC\textsubscript{90} of 6-chloro-3-pyridylmethyl-2-nitromethylene-imidazolidine was 0.32 mg liter\textsuperscript{-1}. This finding was the epoch-making event in the entire research road. Researchers have keenly realized the miracle of nature whereby a molecule can change the properties dramatically with the addition of only one atom. Researchers continued work on the structure-activity relationship study (SAR). For the functional group researchers had a belief that nitromethylene was the best. However, unexpectedly, the cyanoimine derivative was highly insecticidal at 0.32 mg litre\textsuperscript{-1}, but other imino variants such as carbamate or sulfonyl imine were lower in activity. Researchers continued working on the functional group variation and finally found that the nitroimino derivatives have the highest activity. Thus, the imidacloprid was discovered on February 20\textsuperscript{th}, 1985. When researchers look back that they did not conclude a nitromethylene derivative was the best candidate but continued their work on the SAR for the functional group variations. Later, they found out why nithiazine was canceled. It has a high photolability showing clearly that the longer absorption wavelength of nitromethylene chromophores as compared with nitroimines or cyanoimines and consequently, essentially shorter half-lives under sun-lamp radiations. This indicates that the stability under practical conditions is crucial for the pesticide development. However the Bayer researchers started with modifying the nithiazine and reached imidacloprid on this development flow. In the early stage researchers assumed that the active molecule had to consist of a cyclic structure, preferably a five-membered ring and conducted research in this direction. However, this was a hasty conclusion. Later, they noted that the activity was not the ring size but the push-pull olefin substituted with a chloronicotinyl group. When they realized this and started to work on the open of ring structures, other companies along with Bayer started research in acyclic molecules and can be looked at as the acyclic variants derived from cyclic prototypes. In the course of trials of various structural modifications to obtain the new active compounds, less attention seems to have been paid to the variation of the substituents on the pyridine ring. Discovery of a new compound leading to a new
chemical class with a novel mode of action happens only once or twice in the time-span of one's career.\textsuperscript{13}

1.5 Site of action of neonicotinoids

Neonicotinoid insecticides act as antagonists on the post-synaptic nicotinic acetylcholine receptor of the insect’s central nervous system. In the same manner as acetylcholine, the binding of a neonicotinoid causes the opening of connected ion channels and leads to the depolarization. The crucial difference between the binding of acetylcholine and neonicotinoids to the receptor is that acetylcholine leaves the receptor after cleavage through the enzyme acetyl cholinesterase, whereas neonicotinoids remain bound to the receptor. Therefore, neonicotinoids in high dosages provoke an ongoing depolarization and finally lead to the blocking of signal transmission. In insects the actions of neonicotinoids causes excitations of the nerves and finally paralysis leading to death. Nicotinic acetylcholine receptors exist not only in the insects but also in the vertebrates. However, the corresponding neuron pathway is more abundant in insects. There are at least 17 subtypes of nicotinic acetylcholine receptors characterized by the differences in the subunits of the receptors. Neonicotinoid insecticides show a high selectivity for the certain subtypes of receptors and exhibit differences in the actions on the insects as compared to the vertebrate receptors. This unique selectivity regarding the molecular target site is one key factor for the limitation of adverse effects on the beneficial organisms and also for the assessment of risks posed by the presence of neonicotinoid residues in food.\textsuperscript{6}

Okazawa et al. (2000), described a set of 25 ring systems and noncyclic neonicotinoids used in a comparative molecular field approach (CoMFA) study of the binding affinity to House fly \textit{M. domestica} against nAChR.\textsuperscript{7} Neonicotinoids have low toxicity toward mammals and no teratogenic or mutagenic effects.\textsuperscript{12}

1.6 Utilization of neonicotinoids

Neonicotinoid insecticides are active against a wide range of sucking, biting and some chewing insects. The main reasons for the success of the neonicotinoids in plant
protection are their high efficacy, selectivity, plant systemicity as well as long-lasting effect and versatile applications. Clothianidin, imidacloprid and thiamethoxam are used as the active substances in seed dressings. These neonicotinoids protect the crops in several ways. The neonicotinoids are used to protect the seeds from being destroyed by insects in the soil and the uptake of the neonicotinoids through the roots and their systemic distribution leads to the entire protection of plants from biting, sucking and chewing insects during growth. Through, these two modes of actions the neonicotinoids are applied in seed dressings. In contrast, thiacloprid and acetamiprid are applied as sprays onto agricultural plants and supply directly with short time protection. In addition to its use in seed dressing’s thiamethoxam can also be applied in the form of a spray.6

The biological activity and agricultural uses of neonicotinoid insecticides are enormous and numerous overviews, articles and book chapters have been published over the past decade. Due to their unique physicochemical properties, neonicotinoids can be used in a variety of crops. Besides a high intrinsic acute and residual activity against sucking insects and some chewing species, a high efficacy against Aphids, Whiteflies, Leafhoppers and Planthoppers, the neonicotinoids showed an excellent rapid translocation in plants. The agricultural uses of these compounds against Aphids (e.g., *Aphis gossypii*, *Myzus persicae*, *Phorodon humilii*, *Rhopalosipham padi*) on vegetables, sugar beet, cotton, pome fruit, cereals and tobacco; Leafhoppers and Planthoppers (e.g., *Nephotettix cincticeps*, *Nilaparvata lugens*); Beetles on potatoes (e.g., *Leptinotarsa decemlineata*); Water weevil on rice (*Lissorhoptrus oryzophilus*); Whiteflies (e.g., *Bemisia tabaci*, *Trialeurodes vaporarium*) and Thrips (e.g., *Thrips tabaci*) on vegetables, cotton and citrus; Micro-lepidoptera (e.g., *Cydia pomonella*, *Phyllocnistis citrella*) on pome fruit and citrus and Wireworms (*Agriotes spp.*) on sugar beet and corn.

The crop protection, applications of neonicotinoid insecticides in nonagricultural fields have been expanded in the recent years, the household sectors, lawn and garden for controlling termites (e.g., *Reticulotermes spp.*) and turf pests such as White grubs and Cockroaches (e.g., *Blattella germanica*). New bait gel formulations containing imidaclorpid such as Maxforce Prime (Bayer Environmental Sciences), for the control of Cockroaches and thiamethoxam, such as Optigard (Syngenta), for broadspectrum control of Ants, are now on the market.
On the other hand, neonicotinoid insecticides can also be used to control veterinary pests from cat and dog Fleas (e.g., *Ctenocephalides felis*, *Ctenocephalides canis*), Lice (e.g., *Linognathus setosus*, *Trichodectus canis*) and Flies (e.g., *Musca domestica*) in animal health.

Recently, several new neonicotinoid insecticide combinations with other active ingredients from different substances were launched such as Advantage Multi (or Advocate; Bayer Animal Health) as spot-on formulation of the imidacloprid and the Macrolactone moxidectin, which showed efficacy against Ear mites (*Otodectes cynotis*) and Fleas (*C. felis*). K9 Advantix (Bayer Animal Health) as spot-on topical solution of imidacloprid and the pyrethroid permethrin for dogs, which work synergistically against the most common and important external parasites such as the Long star tick, *Amblyomma americanum*. Finally, Vectra 3D (Summit VetPharm) is a new topical spot-on ectoparasiticide containing a combination of dinotefuran, permethrin and pyriproxyfen against *A. americanum* and the Gulf Coast against Tick *A. maculatum* on dogs.

Due to the plant systemic properties, neonicotinoid insecticides such as imidacloprid, thiamethoxam and clothianidin are important for vectors control of plant virus diseases, thereby suppressing the secondary spread of viruses in various crops. For imidacloprid this control has been discovered during its early development supported by antifeedant effects of sublethal dosages of imidacloprid concentrations on *B. tabaci* and was later observed, for the persistent of barley yellow dwarf virus (BYDV) transmitted by *R. padi* and *Sitobion avenae*. Outstanding crop protection was achieved with seed treatment or a foliar applications in the cereals against aphids and BYDV, in tobacco against thrips and tomato spotted wilt virus (TSWV), Whiteflies, yellow leaf curl virus (TYLCV) and in citrus against Glassy winged sharpshooters as the vector for the bacterium *Xylella fastidiosa*.

Today approximately 60% of all neonicotinoid applications are soil/seed treatments and most spray applications are especially targeted against pests attacking crops such as cereals, corn, rice, vegetables, sugar beet, potatoes, cotton and others. However, the increasing success of neonicotinoid insecticides also relies on versatile application methods such as irrigation water in drip or drench systems for vegetables or in floating box systems for tobacco seedlings (e.g., Confidor S), which offer long-lasting control of
Aphids and Whiteflies. Seedling box application in rice gives on excellent control of rice pests such as Hopper species and Rice water weevil. Soil drenching in permanent crops protects young citrus trees against Citrus leafminer (*P. citrella*). Applications to the base of the trunk result in an efficient control of *Eriosoma lanigerum* (Hausmann) in apple trees. In addition, drench and drip applications are well suited for the control of *Perileucoptera coffeella* in coffee and *Planococcus sp.* and other Mealy bug species in grapevines. Soil injection to protect emerging vegetable seedlings against soil inhabitation and sucking pests is common practice in the United States. On the other hand, Banana weevil and Thrips are controlled via trunk and bud injection.

An important aspect is an excellent fit of neonicotinoid insecticides for integrated pest management (IPM) systems. Depending on the application method and timing, non target organisms are not affected by neonicotinoids. Safety for beneficial and pollinators insects has especially been optimized by its selectivity. The application of neonicotinoid with seed treatment, a new opportunity has been opened up in modern crop protection. Besides seed dressing, also film coating, pelleting and multilayer coating is an environmentally safe and perfect protection of young plants against insect pest attack. This method, of application of the active ingredient is virtually independent of the weather and can be applied directly to the site of action. Today, the plant systemic neonicotinoids imidacloprid, thiamethoxam and clothianidin are widely used for the seed treatment in different crops such as cotton, corn, cereals, sugar beet, oilseed rape and others, demonstrates the spectrum of activity of clothianidin seed treatment (Poncho) for the control of early and midseason corn pests in the United States against a broad range of soil-inhabitating, root, stem and leaf-feeding pests from different orders such as Coleoptera, Lepidoptera, Diptera, Homoptera, Hemiptera and Hymenoptera. As a corn seed treatment, clothianidin (Poncho) protects young plants against the entire early season pest complex (soil and leaf pests) and especially Wireworms, *Agriotes spp.* and Cicadas in many crops. Chlothianidin is very effective against different species of *Diabrotica* (Termis corn rootworm) such as the Western (*D. virgifera* virgifera), Northern (*D. barberi*), Southern (*D. undecimpunctata* howardi) and Mexican (*D. virgifera* zeae) corn root worms. Larvae feed on primary and secondary corn roots. Excessive loss of root tissues from larval feeding can cause instability of the corn plants that result in
lodging. Massive lodging reduces the harvest efficiency and therefore, causes severe losses in yields. Feeding damage on roots will also reduce water and nutrient uptake, root and plant growth and ultimately yield, under the favorable soil conditions. Key crops for neonicotinoid insecticides are vegetables, pome, stone, citrus fruits, rice, cotton, corn, potato, sugar beet, oilseed crop, soybean and many others.\(^7\)

### 1.7 Environmental fate of neonicotinoids

All of them have a polar character and showed moderate to high solubility in water ranging from 185 mg litre\(^{-1}\) to 840 g. litre\(^{-1}\). From the investigations it is revealed that the neonicotinoids are converted into numerous and variable metabolites in plants as well as in mammals. The metabolism of the parent compounds included various reactions such as nitro reduction, cyano hydrolysis, demethylation, sulfoxidation, imidazolidine and thiazolidine hydroxylation, olefin formation, oxadiazine hydroxylation, ring opening and chloropyridinyl dechlorination. In this context, it is interesting to note that clothianidin has been applied in time as neonicotinoid insecticide along with a metabolite of thiamethoxam.\(^6\)

According to Jeschke and Nauen (2008) neonicotinoid insecticides provides a relatively low risk for the environment as well as for mammals and other nontarget organisms due to their high selectivity. The results of those study showed that the oxidation of cytochromes P450 to be an important mechanism for the detoxification of acetamiprid and thiacloprid that is the reason for their low toxicity towards Honey bees.\(^6\)

The metabolism of neonicotinoids such as imidacloprid is strongly influenced by the method of application where as in foliar applications most of the residues on the leaf surface display unchanged parent compound. Most of the imidacloprid administered to plants by soil application or seed treatment is metabolized more or less completely, depending on plant species and time.\(^7\) However, concerns of wind drift, pollution of surface water and groundwater due to high solubility in water and toxicity to honey bees and other beneficial organisms require more study.\(^9\)
1.8 Development of Pest resistance to neonicotinoids

In addition, there is a tangible threat of resistance development, especially the major markets where loss of neonicotinoids would have severe negative consequences to insect and disease control. Therefore, a global strategy for neonicotinoid insecticides will be focused on efficient resistance management according to IRAC (International Research Advisory Committee) guidelines. Combined with an active lifecycle management such as new formulation concepts, innovative developments on a new product combinations and the search for additional unique selling points and target-site investigations by using modern techniques, neonicotinoids will be the most important chemical class in modern crop protection for insect control. As first member, imidacloprid became generic (off-patent) in many countries in 2006, since, it has been used on broader scale. However, this will definitely facilitate the development of resistance to neonicotinoid insecticides, because it has been shown that in many cases the neonicotinoid class is affected as a whole once resistance to imidacloripid develops. In addition, patent protection on nitenpyram, thiacloprid, acetamiprid and clothianidin is starting to expire as well resulted recently in generic manufacture and increasing price erosion. Generic versions of expired neonicotinoid insecticides are already manufactured and established in numerous markets such as India and China. After 18 years of use, several insect pests that are the core targets for neonicotinoids have been shown to possess a high potential for resistance development such as Whiteflies *B. tabaci* (Gennadius) and *T. vaporariorum* (Westwood), the Brown planthopper *N. lugens*, the Colorado potato beetle *L. decemlineata* (Say) and a few others such as the Mango leafhopper *Idioscopus clypealis* (Lethierry).
1.9 References


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