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Review

The global status of insect resistance to neonicotinoid insecticides

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ABSTRACT

The first neonicotinoid insecticide, imidacloprid, was launched in 1991. Today this class of insecticides comprises at least seven major compounds with a market share of more than 25% of total global insecticide sales. Neonicotinoid insecticides are highly selective agonists of insect nicotinic acetylcholine receptors and provide farmers with invaluable, highly effective tools against some of the world's most destructive crop pests. These include sucking pests such as aphids, whiteflies, and planthoppers, and also some coleopteran, dipteran and lepidopteran species. Although many insect species are still successfully controlled by neonicotinoids, their popularity has imposed a mounting selection pressure for resistance, and in several species resistance has now reached levels that compromise the efficacy of these insecticides. Research to understand the molecular basis of neonicotinoid resistance has revealed both target-site and metabolic mechanisms conferring resistance. For target-site resistance, field-evolved mutations have only been characterized in two aphid species. Metabolic resistance appears much more common, with the enhanced expression of one or more cytochrome P450s frequently reported in resistant strains. Despite the current scale of resistance, neonicotinoids remain a major component of many pest control programmes, and resistance management strategies, based on mode of action rotation, are of crucial importance in preventing resistance becoming more widespread. In this review we summarize the current status of neonicotinoid resistance, the biochemical and molecular mechanisms involved, and the implications for resistance management.

1. Neonicotinoid insecticides

Neonicotinoids are one of the most important chemical classes of insecticides globally due to their high efficacy against a range of important insect pests and their versatility of use [1,2]. They are registered in more than 120 countries worldwide [2] and are particularly active against numerous sucking pests, and also several coleopteran, dipteran, and lepidopteran pest species by foliar, soil and seed treatment applications [3]. Neonicotinoids are selective agonists of the insect nicotinic acetylcholine receptor (nAChR), a pentameric cys-loop ligand-gated ion channel located in the central nervous system of insects [1]. The mode of action classification scheme of the Insecticide Resistance Action Committee (IRAC) lists seven commercial neonicotinoids in Group 4A (nAChR agonists) (Sparks and Nauen, in this issue). The first neonicotinoid launched was imidacloprid in 1991, followed by nitenpyram and acetamiprid in 1995, and others such as thiamethoxam in 1998 (Fig. 1). Based on total global insecticide sales the market share of neonicotinoids was greater than 25% in 2014, with thiamethoxam, imidacloprid and clothianidin accounting for almost 85% of the total neonicotinoid sales in crop protection in 2012 (Fig. 2). The main regions of neonicotinoid use are Latin America, Asia and North America (75%), with Europe accounting for 11% of total global sales (Fig. 2). Increases in use have inevitably led to a mounting selection pressure for resistance to neonicotinoids. This review summarizes the global status of neonicotinoid resistance in a range of important insect pests with a particular focus on the biochemical and molecular mechanisms underlying resistance, and on information reported since the last comprehensive review of this subject published ten years ago [4].

2. Neonicotinoid resistance: from mechanisms to field failure

The first report of neonicotinoid resistance was published in 1996, describing low efficacy of imidacloprid against Spanish greenhouse populations of cotton whitefly, *Bemisia tabaci* [5]. Since then more than 500 peer-reviewed papers have been published on neonicotinoid resistance issues (SciFinder® 2014, American Chemical Society) in different pest insects (Fig. 3). A substantial proportion

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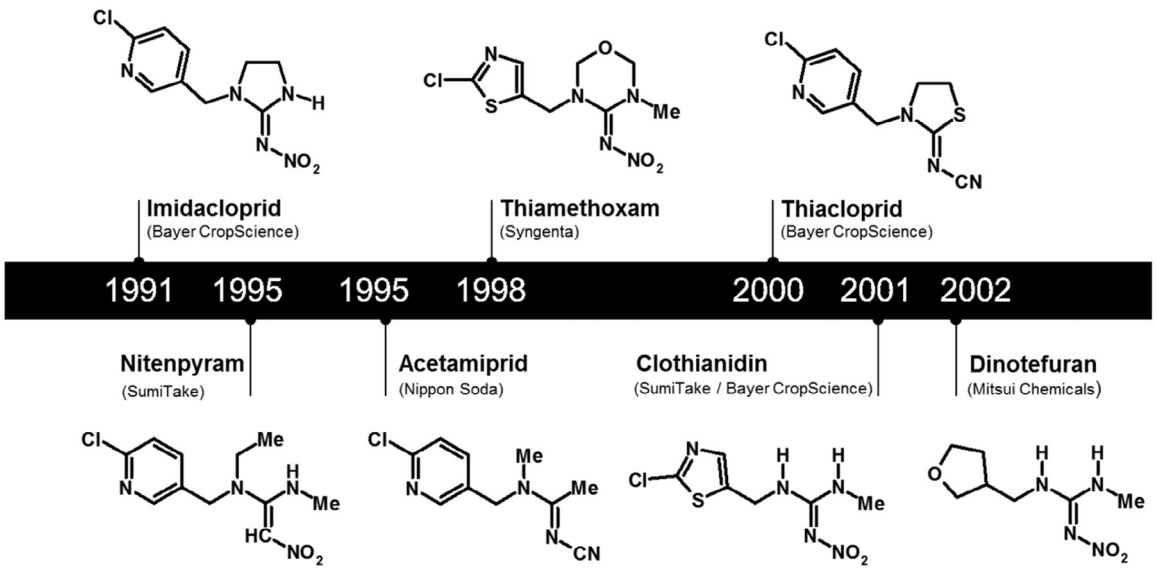

Fig. 1. Important neonicotinoid insecticides (manufacturers) and year of market introduction.

of these refer specifically to imidacloprid resistance. The Arthropod Pesticide Resistance Database (APRD) [6] lists more than 330 cases of imidacloprid resistance, followed by ca. 130 and 50 cases of thiamethoxam and acetamiprid resistance, respectively. Unsurprisingly, the number of arthropod species with resistance to neonicotinoids has increased with time (Fig. 4). However, most cases of neonicotinoid resistance (all compounds combined) concern *B. tabaci* followed by the green peach aphid, *Myzus persicae*, the cotton aphid, *Aphis gossypii*, and the rice brown planthopper, *Nilaparvata lugens*. Other pests targeted by neonicotinoid insecticides with at least 10 assigned cases of resistance in the APRD are houseflies, *Musca domestica*, Colorado potato beetle, *Leptinotarsa decemlineata* and glasshouse whitefly, *Trialeurodes vaporariorum* (Fig. 5). In the sections below we treat each of these seven species separately, but then combine others with fewer than 10 cases reported.

2.1. Bemisia tabaci

The cotton whitefly, *B. tabaci* (Gennadius) is a highly destructive and invasive sucking pest, damaging plants by direct feeding, honeydew excretion (as a nutritional source for sooty mold) and transmission of numerous plant viruses [7]. At least 24 cryptic and morphologically indistinguishable *B. tabaci* biotypes have been identified by recent phylogenetic comparisons based on DNA sequencing [8,9]. However, two widespread biotypes, the Middle East–Asia Minor 1 biotype (MEAM1, also referred to as biotype B) and the Mediterranean biotype (MED, also referred to as biotype Q), are of particular importance as crop pests [10]. Both biotypes have developed resistance to multiple classes of insecticide [11,12] including neonicotinoids [4]. Neonicotinoid resistance has been widely reported in both B and Q type *B. tabaci* from several geographic regions [4,12–19] particularly against imidacloprid. Resistance ratios for neonicotinoids in *B. tabaci* often exceed 1000-fold and lead to serious control failures [4].

Neonicotinoid resistance in *B. tabaci* is mainly conferred by enhanced detoxification by microsomal monooxygenases [17,20], and recently a single, constitutively overexpressed, cytochrome P450, CYP6CM1, was shown to be highly correlated with imidacloprid resistance in B- and Q-type whiteflies [21]. Functional expression of CYP6CM1 revealed its capacity to detoxify imidacloprid by hydroxylation of position 5 of the imidacloprid imidazolidine ring system [22], but also its inability to metabolize other neonicotinoids such as acetamiprid [23]. Resistance to imidacloprid in cotton whiteflies was shown to be age-specific [24] and correlated with the expression of CYP6CM1 in different life stages [25]. Recently it was shown that CYP6CM1 also detoxifies pymetrozine by hydroxylation, an insecticide with a different mode of action and chemically very different from neonicotinoids [26]. These results provided the molecular basis for the observed cross-resistance between neonicotinoids and pymetrozine in *B. tabaci* [27]. Transgenic lines of *Drosophila melanogaster* expressing CYP6CM1 were shown to be

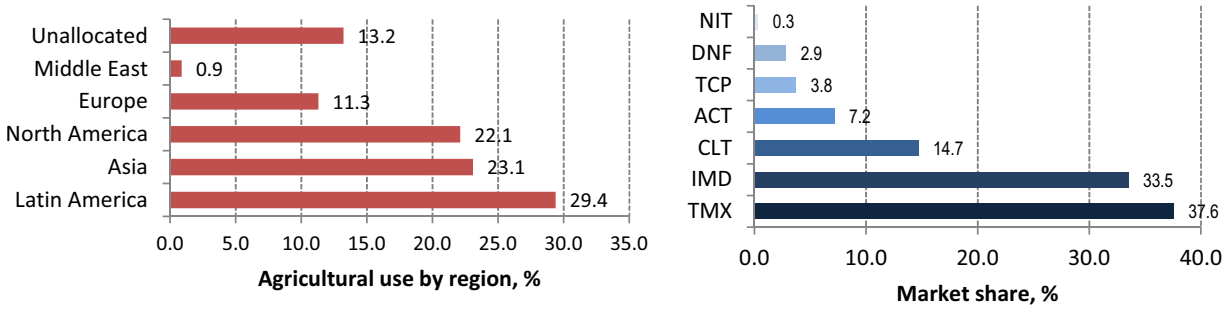

Fig. 2. Agricultural use by region and market share of individual neonicotinoids in percent (total market share 2012: 3.192 bn US$; Source: Wood Mackenzie). Abbreviations: TMX (thiamethoxam), IMD (imidacloprid), CLT (clothianidin), ACT (acetamiprid), TCP (thiacloprid), DNF (dinotefuran), NIT (nitenpyram).

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