Environmental Research 218 (2023) 114953

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Environmental occurrence, toxicity concerns, and biodegradation of neonicotinoid insecticides

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ARTICLE INFO

Keywords:
Neonicotinoid toxicity
Bioaugmentation
Degradation pathways
Remediation

ABSTRACT

Neonicotinoids (NEOs) are fourth generation pesticides, which emerged after organophosphates, pyrethroids, and carbamates and they are widely used in vegetables, fruits, cotton, rice, and other industrial crops to control insect pests. NEOs are considered ideal substitutes for highly toxic pesticides. Multiple studies have reported NEOs have harmful impacts on non-target biological targets, such as bees, aquatic animals, birds, and mammals. Thus, the remediation of neonicotinoid-sullied environments has gradually become a concern. Microbial degradation is a key natural method for eliminating neonicotinoid insecticides, as biodegradation is an effective, practical, and environmentally friendly strategy for the removal of pesticide residues. To date, several neonicotinoid-degrading strains have been isolated from the environment, including *Stenotrophomonas maltophilia*, *Bacillus thuringiensis*, *Ensifer meliloti*, *Pseudomonas stutzeri*, *Variovorax boronicumulans*, and *Fusarium* sp., and their degradation properties have been investigated. Furthermore, the metabolism and degradation pathways of neonicotinoids have been broadly detailed. Imidacloprid can form 6-chloronicotinic acid via the oxidative cleavage of guanidine residues, and it is then finally converted to non-toxic carbon dioxide. Acetamiprid can also be demethylated to remove cyanoimine (=N–CN) to form a less toxic intermediate metabolite. A few studies have discussed the neonicotinoid toxicity and microbial degradation in contaminated environments. This review is focused on providing an in-depth understanding of neonicotinoid toxicity, microbial degradation, catabolic pathways, and information related to the remediation process of NEOs. Future research directions are also proposed to provide a scientific basis for the risk assessment and removal of these pesticides.

1. Introduction

Fourth-generation neonicotinoids (NEOs) emerged after carbamates, organophosphorus, and pyrethroid insecticides in 1980s. Imidacloprid, the first commercial product of this class, is in use since 1990s (Goulson, 2013). During the last 30 years, neonicotinoid insecticides usage increased dramatically. Today, NEOs are the most commonly applied insecticides globally, accounting for approximately 25% of all the pesticides (Zhang et al., 2020; Zhao et al., 2020). It is a well-known fact that NEOs are used in sugar beet, vegetables, fruits, cotton, rice, and other industrial crops to counter mining and sucking pests, and seed treatment is the most common method (Katić et al., 2021). Neonicotinoids are also used in veterinary drugs against lice, flea, and fly in dogs and cats, and against household pests (Jeschke et al., 2011).

NEOs, including dinotefuran (DIN), athiamethoxam (THM), thiacloprid (THD), clothianidin (CLO), imidacloprid (IMI), nitenpyram, and cetamiprid (ACE), are synthetic compounds with a structure similar to that of nicotine (Fig. 1). The background information on neonicotinoid

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https://doi.org/10.1016/j.envres.2022.114953
Received 23 June 2022; Received in revised form 6 November 2022; Accepted 24 November 2022
Available online 28 November 2022

pesticides is shown in Table 1. Nicotinic acetylcholine receptor (nAChR) act as agonists and bind with acetylcholine receptors selectively, restricts insect acetylcholine (ACh), disturbs central nervous system leading to insect paralysis and death (Casida, 2018; Yue et al., 2003) (Fig. 2). Due to the unique mechanism of action, this type of insecticide does not have cross-resistance with conventional insecticides. In addition, compared to traditional insecticides, NEOs are effective against a wide variety of insects, act at low concentrations, provide long-term control, have a systemic effect, can be applied using several methods, and have a high degree of crop safety (Anderson et al., 2015).

NEOs are comparatively better than highly toxic organophosphorus pesticides, and cause less harm to the non-target organisms and environment (Thompson et al., 2020). However, literature depicts that NEOs also have varying degrees of toxicity to pollinators, aquatic insects, birds, mammals, and even human beings (Hladik et al., 2018; Pan et al., 2022).

On the one hand, NEOs are readily soluble in water (logKow 0.55–1.26; logKoc1.4–2.3), are slightly persistent in soil (the half-life of soil degradation is 3 to > 1000 d), and are non-volatile (<0.002 mPa at 25 °C) (Goulson, 2013; Hladik et al., 2018). On the other hand, plants uptake only 5% of their active ingredients (Sur and Stork, 2003), which are mostly dispersed in the environment (Goulson, 2014). Therefore, NEOs are commonly found in waterways including water runoff (streams and rivers), wetlands, and groundwater (Lamers et al., 2011; Starner and Goh, 2012; Hladik et al., 2014; Main et al., 2014; Sánchez-Bayo and Hyne, 2014; Vijver et al., 2014; Schaafsma et al., 2015b). This increases the possibility of non-target organisms being exposed to NEOs. Therefore, increasingly more scholars are beginning to pay attention to the adverse effects of NEOs. Two studies in 2012 showed that the NEOs in pollen and nectar can adversely affect honeybee navigation and individual survival, as well as bumblebee colony development and queen bee production (Henry et al., 2012; Whitehorn et al., 2012b). EFSA (European Food Safety Authority) carried out a risk assessment on the use of the three most common agricultural NEOs (imidacloprid, clothianidin, and thiamethoxam) and their effects on bees. These studies demonstrated the NEOs toxicity on flowering crops, which further poses a serious risk to the bees. Therefore, EFSA has recommended a moratorium on the use of NEOs in processed plants. European Commission implemented these recommendations in 2013 (Wood and Goulson, 2017). In addition to pollinators, NEOs are known to harm aquatic ecosystems, particularly non-target aquatic invertebrate communities (Morrissey et al., 2015). During planting, feeding birds may eat seeds coated with neonicotinoids, which may cause lethal or sublethal effects (Lopez-Antia et al., 2013; Eng et al., 2017). The sub-lethal effects include weight loss and impaired flight direction, which are critical in maintaining the correct direction of migration (Eng et al., 2017).

Furthermore, people are paying increasingly more attention to the toxicity of NEOs to mammals, especially humans. When using NEOs as a seed treatment or as granules, active ingredients partially (2%–20%) enter the plants through root absorption (Sánchez-Bayo and Hyne, 2014) whereas 80%–98% remains in the soil, environment, or lost in planting, or eventually enter surface water or groundwater (Tapparo et al., 2012). These facts increase the risk of exposure to NEOs. NEOs treatments could lead to oxidative stress, reproductive toxicity, hepatotoxicity, genotoxicity, and neurotoxicity, among others (Karabay and Oguz, 2005; Abou-Donia et al., 2008; El-Gendy et al., 2010; Kapoor et al., 2010; Mohany et al., 2012; Gu et al., 2013; Lonare et al., 2014; Gibbons et al., 2015; Annabi et al., 2015; Berheim et al., 2019).

Therefore, there is an urgent need to develop an effective and sustainable approach for the on-site degradation of NEOs. Oxidation during Fenton reaction photochemical degradation is known to remove NEOs from the water samples (Mitsika et al., 2013; Borges et al., 2016). However, chemical and physical degradation techniques are costly, require harsh conditions, and may result in pollution (Guo et al., 2019). Compared to physical and chemical methods, the use of microorganisms in the remediation of pesticides is considered an eco-friendly, cost-effective, and efficient method, as microorganisms have a strong degradation potential due to their genes and enzymes being naturally adapted to these sites (Cycoń et al., 2017; Mulla et al., 2018; Birolli et al., 2019). To date, several neonicotinoid-degrading strains, including *Stenotrophomonas maltophilia*, *Bacillus thuringiensis*, *Ensifer meliloti*, *Pseudomonas stutzeri*, *Hymenobacter latericoloratus*, *Variovorax boronicumulans*, *Phanerochaete sordida*, *Streptomyces canus*, and *Fusarium* sp., have been isolated and identified (Pang et al., 2020a; Zhang et al., 2022a; Gautam et al., 2022). These microorganisms exhibit superior degradation abilities through different mechanisms and metabolic pathways. However, neonicotinoid-degrading enzymes and corresponding genes related

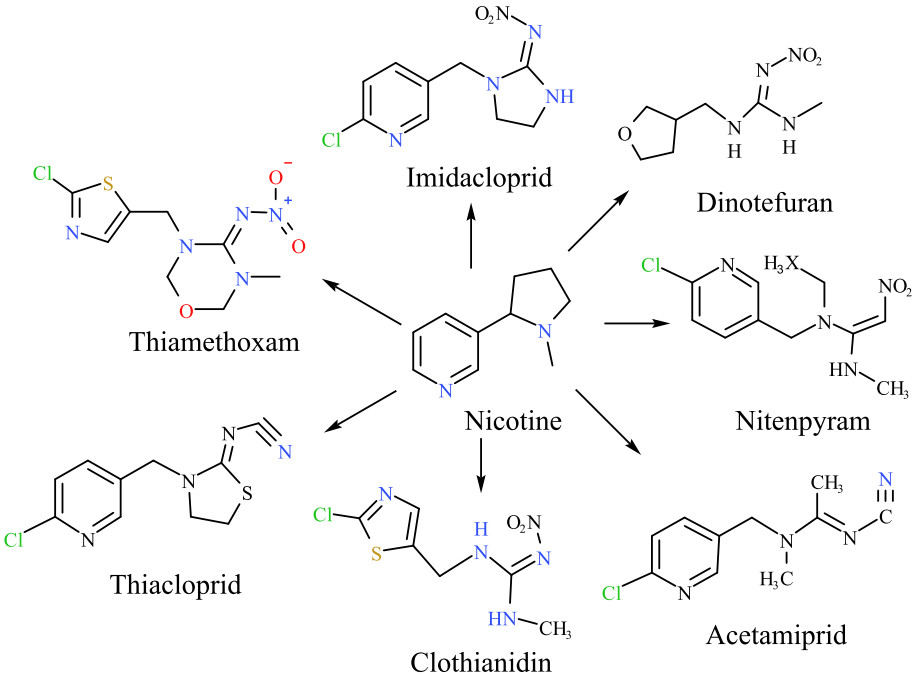

Fig. 1. The chemical structure of nicotine and seven neonicotinoids.

Table 1
Typical neonicotinoid insecticides and their basic characteristics.

Name	Chemical formula	Year	CAS number	IUPAC name	Molar mass
Acetamiprid	C10H11ClN4	1995	135410-20-7	*N*-[(6-chloropyridin-3-yl)methyl]-*N*′-cyano-*N*-methylethanimidamide	222.67
Thiacloprid	C10H9ClN4S	2001	111988-49-9	[3-[(6-Chloropyridin-3-yl)methyl]-1,3-thiazolidin-2-ylidene]cyanamide	252.72
Nitenpyram	C11H15ClN4O2	1995	150824-47-8	(E)-1-*N*′-[(6-chloropyridin-3-yl)methyl]-1-*N*′-ethyl-1-*N*-methyl-2-nitroethene-1,1-diamine	270.71
Imidacloprid	C9H10ClN5O2	1991	138261-41-3	(NE)-*N*-[1-[(6-chloropyridin-3-yl)methyl]imidazolidin-2-ylidene]nitramide	255.66
Clothianidin	C6H8ClN5O2S	2001	210880-92-5	1-[(2-Chloro-1,3-thiazol-5-yl)methyl]-3-methyl-2-nitroguanidine	249.68
Thiamethoxam	C8H10ClN5O3S	1998	153719-23-4	(NE)-*N*-[3-[(2-chloro-1,3-thiazol-5-yl)methyl]-5-methyl-1,3,5-oxadiazinan-4-ylidene]nitramide	291.72
Dinotefuran	C7H14N4O3	2002	165252-70-0	Hydroxy-[[*N*′-methyl-*N*-(oxolan-3-ylmethyl) carbamimidoyl]amino]-oxoazanium	203.22

Note: Information is from the following website: https://pubchem.ncbi.nlm.nih.gov/.

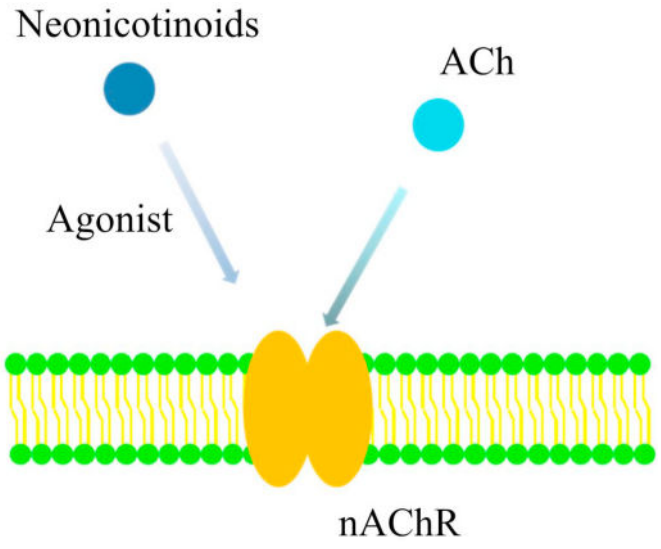

Fig. 2. The mechanism of action of neonicotinoid insecticides. Note: nAChR, nicotinic acetylcholine receptor; Ach, acetylcholine.

studies in microbes are limited. In addition, only a few review articles have discussed the neonicotinoid toxicity and microbial degradation in contaminated environments. Thus, this review is focused on providing an in-depth understanding of neonicotinoid toxicity, microbial degradation, catabolic pathways, and information related to the remediation process of NEOs.

2. Neonicotinoid residues in soil, water, and food

The benefits of neonicotinoid insecticides, such as their low vertebrate toxicity, high insect toxicity, flexible application, and systemic activity, quickly made them one of the extensively applied pesticides globally. Neonicotinoids are applied more widely today than any other type of insecticide and account for more than one-quarter of the pesticides used (Simon-Delso et al., 2015; Thompson et al., 2020). However, everything has two sides. Since only a small amount of neonicotinoid insecticides are absorbed by plants after application, most of the remainder will eventually enter the soil. Moreover, their soil half-life is longer and a high potential for leaching and runoff, which facilitate their sustainability and transportation of NEOs to the environment (Goulson, 2013; Bonmatin et al., 2015). Fig. 3 shows the transmission route of NEOs. Many studies have reported the concentration of NEOs in the environment around the world.

2.1. Soil

Neonicotinoid seed dressing revealed 1.6 and 20% absorption of the active ingredients by crops (Cheng et al., 2022; Sur and Stork, 2003). Of the 80–90% of the unabsorbed active ingredients, <2% is lost during sowing as dust (Tapparo et al., 2012). Several soil ecosystem factors are mediated biologically and pesticides could disrupt or delete non-target soil biotic communitiesrevealing potential risk of pesticides to soil ecosystem (Chagnon et al., 2015). Neonicotinoids can be retained in the soil for several years, and at a concentration that meets environmental requirements (Goulson, 2013; Pisa et al., 2015; Bonmatin et al., 2015), they will have a significant negative impact on some soil organisms, thereby posing risks to soil ecosystem services. The half-life of neonicotinoids in soil has been reported to range from 1 day to nearly 4 years under various conditions (Table 5).

Several studies have shown that neonicotinoid pesticides persist in soil for

many years after treated seeds are planted and that they accumulate in the soil after repeated use (Bonmatin et al., 2005b; Hladik et al., 2017). A study in the United Kingdom showed that, after treating seeds with imidacloprid, the soil content of imidacloprid increased from 6 to 8 ng g^{-1} to 18–60 ng g^{-1} in six years (Goulson, 2013). In addition, neonicotinoids concentrations rise with repeated applications, plateauing after 4–6 years, and after stopping the use of treated seeds, they can persist in the soil for many years (Goulson, 2013; Hladik and Kolpin, 2015; Hladik et al., 2018; Schaafsma et al., 2015a; Schaafsma et al., 2016; Xu et al., 2016). Given the long half-life of neonicotinoids and their soil accumulation, we can guess that most cultivated soils have higher neonicotinoid content. Bonmatin et al. tested 74 randomly selected samples of farmland soil in France, and they did not detect imidacloprid in 7 of the samples, whereas it was detected in the remaining 67 samples at different levels (Bonmatin et al., 2005a). There is a connection between adverse effects on organisms and the ecological functions of soil, but there is little empirical evidence on the effects of neonicotinoid pesticides on soil ecosystems; one reason for this is that they were not widely used until 10 years ago (Chagnon et al., 2015).

2.2. Water

Pesticide pollution is widely recognized as one of the greatest threats to global freshwater ecosystems (Bhatt et al., 2023; Zhan et al., 2018). Due to their high water solubility, neonicotinoids are often found in groundwater and surface water globally. As is well known, freshwater ecosystems play an important role in people's lives, including in cleaning, irrigation, industry, daily life, and aquaculture. Invertebrates account for a large biodiversity proportion of freshwater food chain. Thus, the presence of neonicotinoids in freshwater will affect the number, physiology, and life history of invertebrates and then the food chain relationship (Chagnon et al., 2015).

Neonicotinoid compounds can enter groundwater and wetlands through various pathways, such as spraying, drifting, and surface runoff (Thompson et al., 2020). He et al. measured the level of six neonicotinoid compounds in the tap water of 38 Chinese cities and found that at least one NEO has an overall detection rate of 100%, which shows ubiquitous presence of NEOs in Chinese tap water in China (He et al., 2021). During the same period, another study was conducted of a total of 884 drinking water samples from 32 provinces and Hong Kong in China. Ten NEOs and their major metabolites (6) have been identified in water samples (Mahai et al., 2021). In Canada, thiamethoxam, clothianidin, and imidacloprid, have been detected in more than 90% river water

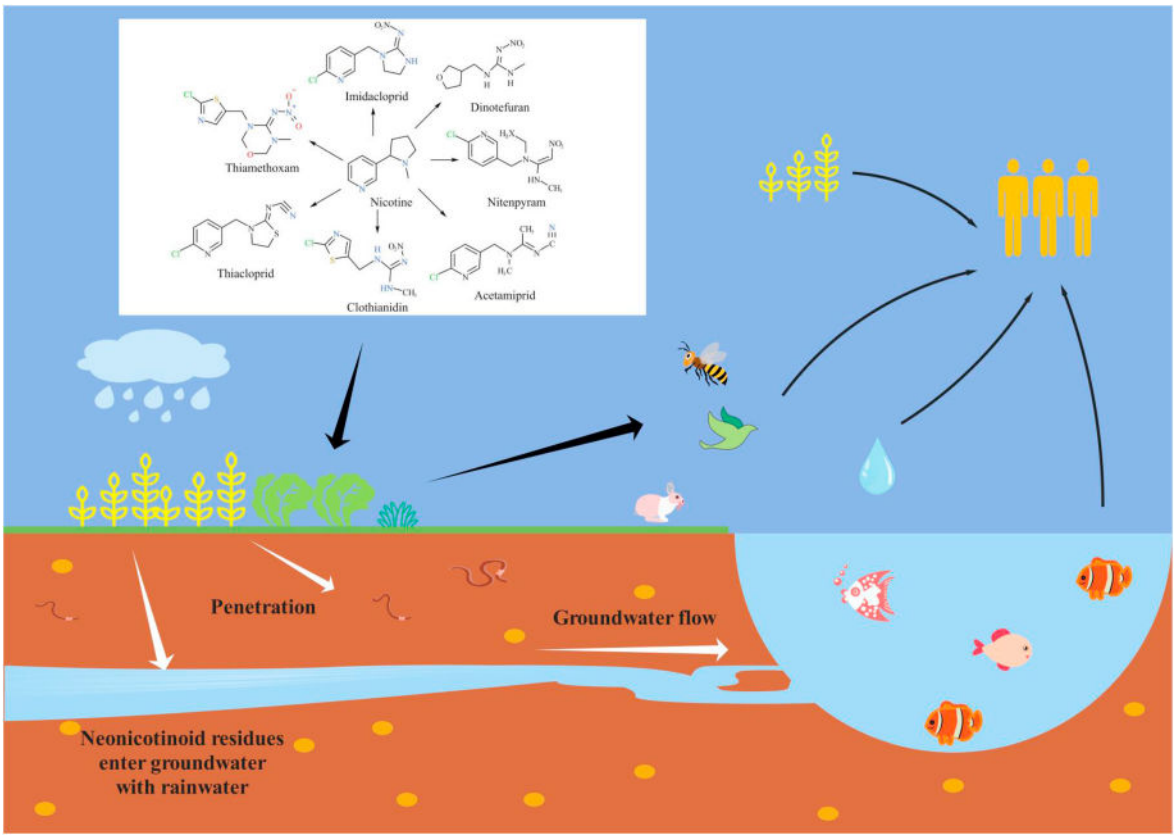

Fig. 3. Environmental dissemination and accumulation in non-target organisms of neonicotinoid insecticides.

samples over a three-year period (2012–2014); two locations exceeded the Canadian freshwater guidelines, and 75% of the samples showed a concentration of more than 230 ng L^{-1} (Struger et al., 2017). During the 2013 growing season, Hladik et al. collected water samples from nine stream sites in the midwestern United States and found clothianidin (75%) > thiamethoxam (47%) > imidacloprid (23%); the maximum individual concentration of the sample during the growing season was between 42.7 and 257 ng L^{-1} (Hladik et al., 2014).

2.3. Food

Neonicotinoid compounds have low molecular weights and high water solubility, which provide systemic properties for their entry into plant tissues (Magalhaes et al., 2009). Some studies have shown that neonicotinoids can be transferred to pollen, vegetables, fruits, and tea, and washing with water cannot completely remove neonicotinoids, so they are considered potential human exposure routes (Craddock et al., 2019a; Liu et al., 2010; Shi et al., 2019; Thompson et al., 2020). Chen et al. tested the residues of neonicotinoid in vegetables and fruits (Table 6). Among them, the detection rates of imidacloprid and acetamiprid were up to 100%.

All the vegetable and fruit samples, except for nectarines and tomatoes, and honey samples (90%) contained either one or more neonicotinoids. Among them, either two or more neonicotinoids were present in one sample of 45% of vegetables, 50% of honey, and 72% of fruit samples, and the detection rate of imidacloprid was the highest (Chen et al., 2014). The analysis of neonicotinoids conducted by the US Department of Agriculture's Pesticide Data Program from 1999 to 2015 revealed that neonicotinoids were detected in imported and domestic products (Craddock et al., 2019b). They reported that the annual maximum detection frequency of all neonicotinoids was generally less than 20%, and the total detection amount of imidacloprid was the highest (12%). The high test frequencies for specific foods were as follows: cherries with 45.9%, apples with 29.5%, pears with 24.1%, and strawberries with 21.3% for acetamiprid and cauliflower with 57.5%, celery with 20.9%, cherries with 26.3%, cilantro with 30.6%, grapes with 28.9%, collard greens with 24.9%, kale with 31.4%, lettuce with 45.6%, potatoes with 31.2%, and spinach with 38.7% for imidacloprid (Craddock et al., 2019b). Wang et al. (2022) have reported that thiamethoxam applied in the soil was easily absorbed by leeks and was subsequently transported upward to metabolize to the more toxic clothianidin, which had lasting dietary risk.

A study that analyzed 7 neonicotinoids in vegetables and fruits from two cross-sectional investigations, that is, one carried out in the U.S Congressional Cafeteria and one carried out in Hangzhou, China, further confirms the ubiquity of neonicotinoids in the global food supply (Lu et al., 2018). The results showed that thiamethoxam and imidacloprid are most commonly found in vegetables and fruits having detection rates of 66 and 51% in Hangzhou, and 52 and 53% in the U.S Congressional Cafeteria, respectively. Neonicotinoids are also frequently detected in honey (Blacquière et al., 2012; Jones and Turnbull, 2016; Kavanagh et al., 2021; Mitchell et al., 2017a). A global survey has depicted that honey contains 5 NEOs, and 75% of honey samples contained at least one NEO, with Europe, Asia, and North America having the highest detection rates (Mitchell et al., 2017a).

The ingestion of water and food is a crucial potential route of exposure compared to the inhalation of dust and air. At the same time, combined with the above studies, it is necessary to be alert to the potential health risks of NEOs, strengthen food safety management, and further evaluate the risk of human exposure to NEOs.

3. Toxicity to non-target organisms

NEOs are becoming more prevalent in terrestrial and aquatic environments due to the large-scale use of NEOs, resulting in them leaching into water and building up residues in soil (Bonmatin et al., 2015;

Sánchez-Bayo et al., 2016; Zhang and Lu, 2022). Without any doubt, most organisms living near cultivated land will be exposed to them. Multiple studies have investigated NEOs toxicity to non-target fish, birds, insects, mammals, and even humans. Table 2 shows the acute median lethal concentration (LC_{50}) or lethal dose (LD_{50}) of neonicotinoids to some non-target organisms.

3.1. Pollinators

The growing evidence shows that the number of pollinators, especially honeybees, is declining globally, which has drawn people's attention to biodiversity and ecological protection, and neonicotinoids have been identified as the main factors responsible for this decline (Mitchell et al., 2017b). On the one hand, NEOs are commonly used in the seeds of rape, sunflowers, and corn, which are the main feed sources for pollinators in cultivated land. However, a small amount of neonicotinoid compounds has been found in the crops' nector and pollen that have undergone seed treatment. On the other hand, the extensive foliar applications of NEOs in the gardens provides further exposure for pollinators.

In 2017, Mitchell et al. investigated the situation of neonicotinoid contamination in 198 bee samples from all the continents (excluding Antarctica) and many isolated islands (Mitchell et al., 2017b). 75% of the samples contianed one of the five NEOs (thiamethoxam, imidacloprid, acetamiprid, thiacloprid, and clothianidin), 45% samples poessessed two or more NEOs whereas 10% had 2 to 3 NEOs. This also confirms that honey bees are exposed to neonicotinoids in foods globally. Neonicotinoids and other pesticides could collectively be more harmful to the pollinators.

Bees exposed to neonicotinoids will have adverse changes in physiology, biochemistry, and behavior. Alburaki et al. conducted a study on 32 bee colonies to detect and determine the potential impact of NEOs on the bee health in cornfields (Alburaki et al., 2015). The data show that neonicotinoids induce physiological stress in bees and increase pathogen load, thereby weakening the health of bees. Cook et al. found that high-dose clothianidin can reduce the lipid and glycogen content of bees, while high-dose imidacloprid exposure can reduce the metabolic rate of bees when bees are exposed to sublethal clothianidin concentrations. This also proves that neonicotinoids can interfere with the endocrine neurophysiological pathways of honey bees (Cook, 2019).

Because neonicotinoid residues are often detected in pollen, it is reasonable that NEOs cause chronic toxicity to bees. Current studies have found that neonicotinoids mainly cause chronic toxicity to honeybees in the following ways: (1) they cause neurophysiological disorders in honeybees and influence the growth of honeybee larvae (Tavares et al., 2019); (2) they have a negative impact on the life span and foraging behavior of worker bees (Shi et al., 2020); and (3) they reduce the reproductive success rate of bees (Sandrock et al., 2013).

The mechanism behind the adverse consequences of NEOs on bees has drawn in extensive interest. Through Zhang's research, it was found that the digestive and regenerative cells of the midgut undergo morphological and chemical changes after bees are exposed to pesticides (Zhang et al., 2021). In addition, long-term exposure to pesticides also increases the degree of compaction of most of the nuclear chromatin, resulting in irregular nuclei (da Silva Cruz et al., 2010). Therefore, understanding the chronic toxicity of pesticides in sublethal doses is important to discover the mechanism of interaction between bees and pesticides.

In April 2018, European Union voted to ban outdoor applicaitons of three neonicotinoids, namely, clothianidin, thiamethoxam, and imidacloprid. From September 1st of the same year, France banned five neonicotinoids (thiamethoxam, clothianidin, acetamiprid, imidacloprid, and thiacloprid), and France became the first country in the EU to ban neonicotinoids in order to protect bee populations.

3.2. Birds

In the past, it was generally believed that neonicotinoids posed little harm to birds. However, neonicotinoids have also been reported to pose direct or indirect negative effects on birds at high environmental concentrations (Mineau and Palmer, 2013).

Millot et al. reviewed the reports of the French SAGIR network (1995–2014) (Millot et al., 2016). There were 103 wild animal death cases having residues of imidacloprid. The main species were grey partridges (*Perdix*) and white pigeons (*Columba oenas, Columba livia*, and *Columba palumbus*). Similarly, Hallmann et al. found that the average intrinsic growth rate of local (the Netherlands) farmland bird populations is negatively correlated with the concentration of imidacloprid; that is, imidacloprid may cause a decline in local bird populations (Hallmann et al., 2014). Further research found that, when the concentration of imidacloprid exceeds 20 ng per liter, the number of birds decreases by an average of 3.5% per year. In addition to the acute toxicity caused by directly drinking contaminated water, the reason for this phenomenon may be related to the reduction in bird food (insects) caused by the application of neonicotinoids. Moreover, the cumulative effect of birds eating contaminated insects may also cause a decline in bird populations.

Laboratory oral exposure experiments show that neonicotinoids have reproductive effects on birds. For example, after exposure to 1 mg $kg^{-1}{\cdot}d^{-1}$ clothianidin for 26 days, male quail developed testicular abnormalities, an increased DNA damage rate, and a decreased embryo length (Tokumoto et al., 2013). Clothianidin affects the reproduction of male quail by destroying germ cells and inhibiting or delaying embryonic development. Exposing red-legged partridges (*Alectoris rufa*) to high doses of imidacloprid can cause 58.3% mortality, and when exposed to 31.9 mg $kg^{-1}{\cdot}d^{-1}$ of imidacloprid for ten days, it can also reduce the fertilization rate and size of their eggs (Lopez-Antia et al., 2013). Gobeli et al. chose the eggs of bobwhite quail as a research object, injecting them with different concentrations of imidacloprid at different time points (Gobeli et al., 2017). After 19 days of incubation, the embryos were dissected, weighed, and staged, and they found that the embryonic development rate of bobwhite quails was affected and that the survival rate of chicks was reduced. Pandey and Mohanty exposed

Table 2
Acute median lethal concentrations (LC_{50}) or lethal doses (LD_{50}) for non-target organisms exposed to neonicotinoid insecticides.

Taxon	Research Object	LC50 or LD50	References
Non-target insect	Bees	Oral 3.7 ng·bee^{-1}; Contact 81 ng·bee^{-1} (IMI) Oral 5 ng·bee^{-1}; Contact 24 ng·bee^{-1} (TMX) Oral 3.8 ng·bee^{-1}; Contact 28 ng·bee^{-1} (CLO)	(EFSA, 2013a; EFSA, 2013b; EFSA, 2013c)
Aquatic vertebrates	Fish	1.2–241 mg L^{-1} (IMI) >93.6 mg L^{-1} (CLO)	Gibbons et al. (2015)
Birds	Mallards	283 mg kg^{-1} (IMI) 98 mg kg^{-1} (ACE) 576 mg kg^{-1} (TMX) >752 mg kg^{-1} (CLO)	(Mineau and Palmer, 2013)
	Grey partridge	15–41 mg kg^{-1} (IMI); 430 mg kg^{-1} (CLO)	
Mammals	Rats	Oral 450 mg kg^{-1} (IMI); 182 mg kg^{-1} (ACE) Oral 1563 mg kg^{-1} (TMX); >5000 mg kg^{-1}(CLO) Oral 640 mg kg^{-1} (THC); 2400 mg kg^{-1} (DIN)	(Sheets et al., 2016b)

Note: IMI, imidacloprid; ACE, acetamiprid; TMX, thiamethoxam; CLO, clothianidin; THC, thiacloprid; DIN, dinotefuran.

red plum finches (*Colinus virginianus*) to 0.5% LD_{50} of imidacloprid for 30 days and found that the weight, volume, and histopathology of their thyroids significantly changed, indicating that low-dose pesticide exposure may affect the homeostasis of the thyroids and the reproduction of birds (Pandey and Mohanty, 2017).

In addition to their effects on reproduction, neonicotinoids may also affect the migration and other behaviors of birds. After the injection of imidacloprid, the fat storage and body weight of birds decreased significantly (average loss: low-17%, high-25%), and they could not be correctly oriented. These results indicate that the consumption of four imidacloprid-treated rapeseeds by wild birds daily for more than 3 days may result in damage to their health, delayed migration, and an improper migration direction, resulting in an increased risk of death or the loss of reproduction opportunities (Eng et al., 2017).

3.3. Aquatic organisms

The migration of neonicotinoids to aquatic environments is usually caused by precipitation, snowmelt, and dust (Raby et al., 2018). For aquatic species, the known effects of NEOs on their biological, behavioral, genetic, and physiological toxicity levels have been described.

However, the toxicity of neonicotinoid insecticides to different types of aquatic organisms is different by up to several orders of magnitude. Finnegan et al. have reported chronic and acute thiamethoxam toxicity to over 30 freshwater species and 4 marine species, and they found that, in the test, fish and aquatic primary growers were insensitive and that, in all cases, the acute lethal concentration (LC_{50}) and the median lethal concentration (EC_{50}) were greater than or equal to 80 mg L^{-1}, which far exceeds the surface water exposure concentration (Finnegan et al., 2017). The EC_{50} of invertebrates (mollusks, worms, and rotifers) is greater than or equal to 100 mg L^{-1} (not sensitive). In general, the most sensitive organism in the chronic test is the chironomid larva with a 30 d NOEC (emergence) of 0.01 mg L^{-1}.

Acute exposure to concentrations of 1 μg L^{-1} or lower and long-term exposure to concentrations of 0.1 μg L^{-1} will negatively affect the emergence, growth, survival, migration, and behavior of various sensitive aquatic invertebrates (Morrissey et al., 2015). Under the actual concentration of neonicotinoid thiacloprid in the field, the number and biomass of the main orders of newborn aquatic insects (Coleoptera, Diptera, Mayfly, Odonata, and Trichoptera) decreased significantly (Barmentlo et al., 2021).

Pawłocik and Sokołowska et al. reported that swimming speed and thoracic movement of crustacean large fleas were inhibited after exposure to acetamiprid for 2 h, and this inhibition was concentration-dependent; after 24 h of exposure, low and medium concentrations (25 and 50 mg L^{-1}, respectively) of acetamiprid stimulated the heart rates of the large fleas causing them to increase, while high concentrations (100 mg L^{-1}) reduced their heart rates, which shows that neonicotinoid insecticides can change the behavior and physiological parameters of large fleas and increase the sensitivity of these animals to predator pressure (Pawłocik and Sokołowska, 2017).

In a previous study, freshwater prawns served as novel aquatic invertebrate model for assessing negative impacts of NEOs on non-target organisms, and it was found that freshwater prawns had a reduced heart rate, reduced gill ventilation, and death (Siregar et al., 2021). Interestingly, Barbee and Stout, have reported the acute toxicity of three NEOs (thiamethoxam, dinotefuran, and clothianidin) to *Girard larvae* was measured and compared with two pyrethroids (etofenprox and lambda-cyhalothrin), and it was found that NEOs were comparatively less harmful alternative than pyrethroids in the crop rotation of rice–crayfish. Of course, this also required on-site chronic and acute neonicotinoid toxicity tests on crayfish (Barbee and Stout, 2009).

The sublethal toxicity of neonicotinoids to fish showed oxidative stress and DNA damage. As a model organism, zebrafish has been used for studying NEOs affects on aquatic organisms (vertebrates) and to fill in the gaps concerning other vertebrates (such as humans) that are more difficult to study (Hicken et al., 2011). In a survey study, when the acetamiprid concentration was more than 263 mg L^{-1}, zebrafish embryos exhibited significant teratogenic and mortality effects (Ma et al., 2019b). In addition, the sublethal (deformity, hatch rate, body length, heart rate, and changes in touch response and spontaneous movement) and lethality was observed from 6 h to 120 h after fertilization. Acetamiprid at 760 mg/L and 974 mg/L can also stop the development of the zebrafish motor neuron system, which may be related to the lack of butyryl cholinesterase in zebrafish (Ma et al., 2019a). Moreover, Yan and Ge's research found that thiamethoxam and imidacloprid could cause DNA damage and oxidative stress in zebrafish, respectively, and that DNA damage has an obvious dose-effect relationship (Ge et al., 2015; Yan et al., 2016a). Besides these adverse effects, NEOs can also affect the metallic balance of fish. Zhang et al. demonstrated that a sublethal acetamiprid dose induces oxidative stress in zebrafish and suppresses the synthesis of protein, which results in the accumulation of most amino acids (Zhang and Zhao, 2017). At the same time, sublethal doses of acetamiprid can also cause DNA and RNA damage, leading to the accumulation of uridine and adenosine. The sublethal impacts of NEOs on non-target organisms are shown in Table 3.

3.4. Toxicity in mammals

Neonicotinoid structure is similar to the natural insecticide nicotine, and they target nAChRs (nicotinic acetylcholine receptors) in the insect's CNS. Mammalian nAChRs are widely found in the CNS, and neonicotinoid insecticides were previously considered to be less toxic to mammals, but increasingly more studies have shown that NEOs effects on mammals cannot be ignored. To date, studies of the effects of neonicotinoid insecticides on mammals have mainly involved neurotoxicity, genetic toxicity, reproductive toxicity, and organ toxicity.

3.4.1. Neurotoxicity

In a previous study, imidacloprid (337 mg L^{-1}) was injected in intraperitoneal area in rats on the ninth day of pregnancy. All offspring were measured and evaluated 30 days after birth. It was found that AChE activity in the cortex, midbrain, plasma, and brainstem (125–145%) increased, accompanied by obvious movement disorders. However, the expressions of the GFAP (glial fibrillary acidic protein) in the motor cortex and hippocampal dentate gyrus of the offspring of the imidacloprid-treated female mice increased. These alterations could cause long-term negative impacts on the health of the offspring (Abou-Donia et al., 2008). In a study conducted by Rodrigues KJ et al., exposure to medium and high doses (50 or 100 mg/kg/d) of thiamethoxam for 7 consecutive days increased the anxiety behavior in rats, and both HACU (high-affinity choline uptake) and acetylcholinesterase activity in the hippocampal synaptosomes of the rats significantly decreased (Rodrigues et al., 2010). It is speculated that thiamethoxam and its metabolites acts on rats' central nAChRs. There has also been researching that found that ACE exposure in utero and lactation may interfere neural circuits' development, which are required for male mice to perform social behaviors and anxiety-related behavior (Sano et al., 2016).

In 2016, a review was conducted on in vivo, in vitro, and epidemiological studies of neonicotinoid insecticides registered at the time (Sheets et al., 2016a). Developmental neurotoxicity in response to nicotine exposure was not observed. However, the study found that higher doses commonly caused systemic toxicityindicating that NEOs do not pose selective affects during the nervous system development.

3.4.2. Reproductive toxicity

The negative effects of NEO exposure on mammalian reproduction and development have been reported in several studies (Abou-Donia et al., 2008; Gu et al., 2013; Terayama et al., 2018; Berheim et al., 2019), including higher embryonic mortality, premature birth, decreased pregnancy rates, decreased sperm production and function, decreased

Table 3
Sublethal effects of neonicotinoid insecticides on fish, bees, and birds.

Taxon	Research object	Concentrations	Sublethal effects	References
Aquatic invertebrates	Fish	TMX, IMI, NIT (0.3–20 mg L^{-1})	Oxidative stress	(Ge et al., 2015; Tian et al., 2018; Topal et al., 2017; Yan et al., 2015; Yan et al., 2016b)
		ACE (760, 974 mg L^{-1})	Stopped development of the nervous system	Ma et al. (2019a)
		ACE (760, 974 mg L^{-1})	Disturbed metabolic balance	(Alam et al., 2014; Zhang and Zhao, 2017)
Aquatic invertebrates	Saccostrea glomerata	IMI (0.01, 0.1, and 1 mg L^{-1}; 4 days)	Imidacloprid causes stress at <0.1 mg L^{-1}	Ewere et al. (2020)
Non-targets insects	Bees	IMI (0.7 μg kg^{-1}; 6 μg kg^{-1}; 30 ng·bee^{-1}; 300 ng·bee^{-1})	Reduced fecundity and growth rate	(Abbott et al., 2008; Whitehorn et al., 2012a)
		IMI (2.5–20 ng·bee^{-1})	Influenced activity	Lambin et al. (2001)
		CLO (40 ng·bee^{-1})	Influenced immune system	(DiPrisco et al., 2013)
Birds	Male quails	CLO (1 mg kg^{-1}) IMI (1, 10 mg kg^{-1})	DNA damage	(Hoshi et al., 2014; Tokumoto et al., 2013)
		IMI (0.7–1.4 mg g^{-1}, 10 mg kg^{-1})	Oxidative stress	(Hoshi et al., 2014; Lopez-Antia et al., 2015)
	Red Munia	IMI (0.155 mg kg^{-1})	Affected the thyroid homeostasis	(Pandey and Mohanty, 2017)

Note: IMI, imidacloprid; ACE, acetamiprid; TMX, thiamethoxam; CLO, clothianidin; THC, thiacloprid; NIT, nitenpyram.

offspring weights, and stillbirths.

Kapoor U et al. studied the effects of imidacloprid on female rats after 90 days of oral administration (Kapoor et al., 2011). At a high dose (20 mg g^{-1}·d^{-1}), a decreased ovarian weight was found, accompanied by pathomorphological changes in the atretic follicles, follicles, and antral follicles. Similarly, significant changes in catalase, superoxide dismutase, glutathione peroxidase, lipid peroxidation, and glutathione were also observed at a 20 mg kg^{-1}·d^{-1} dose level. In addition, an in vitro study conducted by Janka Babeľová et al. showed that, when prokaryotic-stage mouse embryos were exposed to neonicotinoid insecticides (thiacloprid, acetamiprid, thiamethoxam, and clothianidin) and related product solutions, all neonicotinoid insecticides at 100 μmol/L) negatively affected mouse embryo development. Thiamethoxam and acetamiprid reduced blastocysts quality at a concentration of 10 μmol L^{-1} (Babeľová et al., 2017). It was also found that dead cells percentage in blastocysts increased at the concentrations of 10 μmol/L and 100 μmol/L in rabbit embryo experiments.

3.4.3. Organ toxicity

Because the main function of the liver is metabolism and the elimination of toxicity, the liver is the main target organ of neonicotinoid pesticide injury. However, usually, only exposure to high doses of neonicotinoids will cause obvious liver toxicity, and this will be accompanied by a reduced food intake and weight loss (Thompson et al., 2020).

Bhardwaj S et al. conducted a 90-day oral toxicity study in female rats with imidacloprid. Imidacloprid did not have any obvious toxic effects on female rats at 5 and 10 mg/kg/d concentrations (Bhardwaj et al., 2010). However, at 20 mg/kg/d, the kidney, brain, and liverof the rats showed pathological changes, and serum GPT (glutamate pyruvate transaminase) activity, GOT (glutamate oxaloacetate transaminase), glucose, and BUN (blood urea nitrogen) content significantly increased. The hepatotoxic effect of thiamethoxam (TMX) is reflected in the attenuation of liver enzyme activity; an increase in bilirubin levels; and changes in liver structure, including hepatocyte necrosis and apoptosis, lymphocyte infiltration, and fibrosis caused by liver cell death (El Okle et al., 2018). When rabbits were administered thiamethoxam (250 mg kg^{-1}) for 90 consecutive days, TMX inhibited apoptosis and activated cell survival pathways by modulating the rabbits' oxidation/antioxidant status and the production of pro-inflammatory cytokines, and it had potential hepatotoxicity and cancer-promoting effects (El Okle et al., 2018).

3.4.4. Genotoxicity

Some classic experimental methods (comet test, micronucleus test, chromosome aberration test, etc.) have been developed for genetic toxicity testing. Most researchers use human peripheral blood lymphocytes as experimental material, and some researchers use somatic cells and germ cells from mice and rabbits as experimental material. Most test results are significant (Zhang et al., 2020).

After the intragastric administration of thiacloprid (112.5 mg/kg for 24 h or 112.5 mg/kg/d up to 30 days) to rats, it was found that the mitotic index (MI) and the number of binucleated (BN) cells significantly reduced, and chromosomal aberrations (CAs) significantly increased (Şekeroğlu et al., 2013). There have been studies that used a combination of the micronucleus test (MNT) and chromosome aberrations (CAs) to evaluate the genotoxic effect of acetamiprid on the bone marrow of Swiss albino male mice (Bagri and Jain, 2019). Acetamiprid treatment led to a dose-dependent rise in the frequency of chromosomal aberrations and micronuclei in each bone marrow cell. Thus, daily exposure to 4.6 mg kg^{-1}·d^{-1} of ACE for 60 and 90 days caused genotoxicity and cytotoxicity to the Swiss albino male mice somatic cells (Bagri et al. 2019). Table 4 lists the toxic effects of neonicotinoid insecticides on mammals.

3.5. Influence of neonicotinoids on humans

There have been many studies showing the existence of residual NEOs in the environment; the negative impact of NEOs on several species, including mammals; and the possible ways for humans to be exposed to neonicotinoids (Fig. 3). However, human data on the exposure and toxicity of neonicotinoids are limited.

Cimino et al. summarized eight pieces of literature that investigated the impact of neonicotinoid pesticide toxicity on the human health (Cimino et al., 2017). Four of these examined acute exposure (no adverse effects were observed in one item, and adverse effects were observed in three items), and the other four reported an association between chronic neonatal exposure and adverse development or neurological prognosis (both show a good correlation between exposure to neonicotinoid insecticides and adverse health effects in humans). Some studies have taken human peripheral blood lymphocytes (PBLs) as the research object and exposed neonicotinoids in vitro. All insecticides (thiacloprid, clothianidin, and imidacloprid) have genotoxic and cytotoxic effects on human PBLs, and at high concentrations, they significantly reduce the viability of human lymphocytes and cause cell death (Calderon-Segura et al., 2012). Forrester MB compiled 1142 exposure cases reported by the Texas Poison Control Center in the United States (Forrester, 2014) and found that most of the products contained dinotefuran (17%) and imidacloprid (77%). The main exposure routes are ingestion (51%), the skin (44%), and the eyes (11%), and common clinical adverse reactions are eye irritation (6%), skin irritation (5%), vomiting (2%), nausea (3%), oral irritation (2%), red eye (2%), and

Table 4
Toxic effects of neonicotinoid insecticides on mammals.

Type	Object	Neonicotinoid concentrations	Toxic effects	References
Neurotoxicity	Embryos of mice and rabbits	THC, ACE, TMX, CLO (10, 100 μmol L^{-1})	Influence the developmental ability of the embryo	Babeľová et al. (2017)
	Mice	ACE (1, 10 mg kg^{-1})	Interfered With the development of neural circuits	Sano et al. (2016)
	Rats	IMI (1–100 μmol L^{-1}) ACE (1–100 μmol L^{-1})	Induces excitatory Ca^{2+} influx and changes the transcriptome	(Kimura-Kuroda et al. 2012, 2016)
Genotoxicity	Rats	THC (112.5 mg kg^{-1}, 24 h or 112.5 mg kg^{-1}, 30 d)	The mitotic index and the binucleated cells numbers were significantly reduced; Chromosomal aberrations.	Şekeroğlu et al. (2013)
Organ toxicity	Kidney (Infant and adult rats)	IMI (4, 15, 20 mg kg^{-1}) TMX (12 mg kg^{-1})	Changes in physiological and biochemical indexes accompanied by pathological changes	(Arfat et al., 2014; Bhardwaj et al., 2010; Ozsahin et al., 2014)
Reproductive Toxicity	Rats	IMI (0.5, 2, 8 mg kg^{-1})	Apoptosis and fragmentation of seminal DNA was higher	(Bal et al. 2012a, 2012b)

Note: IMI, imidacloprid; ACE, acetamiprid; TMX, thiamethoxam; CLO, clothianidin; THC, thiacloprid.

erythema (2%). In addition, chronic toxicity studies have also reported an association between neonicotinoid exposure and some diseases, mainly congenital heart defects, anencephaly, and autism spectrum disorders (Yang et al., 2014; Keil et al., 2014; Carmichael et al., 2014). Notably, with the increased use of neonicotinoids, there has been an increasing trend of NEOs being found in the urine of Japanese women (Simon-Delso et al., 2015). Additionally, the levels of some NEOs increased in children and adults after pesticides were sprayed, and urinary thiacloprid detection rates were significantly higher in those with typical nicotinic symptoms (Ikenaka et al., 2019; Marfo et al., 2015).

Although it has been observed that humans are exposed to neonicotinoids through some channels, there is not enough data to find a direct link between neonicotinoids and human health. The current research on neonicotinoid pesticide exposure is mainly conducted through urine analysis. To better understand the relationship between neonicotinoid exposure and human health, more samples, including human blood, hair, and semen, are needed. In addition, attention should be paid to the health risks of specific groups such as farmers.

4. Biodegradation of neonicotinoids

Neonicotinoids are widely used in crops and have many advantages that traditional pesticides do not have. However, if used excessively, they will remain in the environment and be difficult to degrade, which will bring great pressure to environmental governance. At the same time, pesticide residues in the environment can also cause harm to non-target species including insects, aquatic organisms and pollinators (Bhatt et al., 2021a,b; Mishra et al., 2021; Liu et al., 2022). Recognizing this issue, investigations have been conducted to minimize environmental neonicotinoid residues. Among them, the use of biological control strategies was found to be a risk-free and economically viable approach (Bilal et al., 2021; Govarthanan et al., 2022; Mishra et al., 2022). To date, the bioremediation of neonicotinoid pesticides mostly uses isolated bacteria as catalytic microorganisms, which catalyze the degradation of pesticides through various enzymes produced by bacteria, convert the pesticides into less toxic products, and release them into the environment (Ahmad et al., 2021; Anjos et al., 2021).

4.1. Degradation of neonicotinoid by microorganisms

To date, isolated bacteria have been mostly used to catalyze the biodegradation process (Table 7), and the degradation efficiency depends on multiple factors, such as pesticide type, soil microorganisms, and soil moisture content (Bhatt et al., 2020, 2022; Pang et al., 2020b). Based on the pesticide structure and catabolic activity of biodegrading microorganisms, pesticides could produce varying metabolic compounds (Huang et al., 2022; Li et al., 2022; Zhang et al., 2022b).

Recently, a study reported that *Ensifer adhaerens* TMX-23 has the ability to degrade neonicotinoids that remain in soil (Sun et al., 2021). *E. adhaerens* TMX-23 degrades thiacloprid to thiacloprid amide by nitrile hydratase (NhpA and NhcA), and in the presence of copper NhpA expression of is up-regulated, accelerating the elimination of THI residues by *E. adhaerens* TMX-23 in the soils. *Rhodococcus ruber* (CGMCC 17550) has been established to effectively degrade neonicotinoid (nitenpyram) through hydroxylation pathway (Dai et al., 2021). In direct correlation to rise in quiescent *R. ruber* CGMCC 17550 cell biomass, the degradation rate of nitenpyram increased, and after 72 h of culture, in the transformation solution consisting of 100 mg/L nitenpyram, the degradation rate of nitenpyram reached 98.37% when the OD600 was 9. In addition to bacteria, white-rot fungi have showed excellent potential to degrade neonicotinoids and convert them to low-toxicity metabolites (Chen et al., 2021; Wang et al., 2019). Nitenpyram was completely degraded under ligninolytic conditions by the white-rot fungus *Phanerochaete sordida* YK-624whereas only 20% reduction was noted under nonligninolytic conditions. A novel and non-neurotoxic nitenpyram metabolite (E)-*N*-((6-chloropyridin-3-yl) methyl)-*N*-ethyl-*N′*-hydroxy acetimidamide was identified in this study. At the same time, this article also demonstrates the importance of

Table 5
Chemical properties (solubility, logK_{OC}) and environment persistence (DT_{50} for soil and hydrolysis) of neonicotinoid insecticides.

Neonicotinoids[a]	Solubility in water at 20 °C ($mg{\cdot}L^{-1}$)	Water photolysis (DT50 in days)	Water hydrolysis[b] (DT_{50} in days)	Soil persistence[c] (DT_{50} in days)	Soil affinity (log K_{OC})
Acetamiprid	2950	34	Stable; 420 (pH 9)	2–20	2.3
Thiacloprid	184	10–63	Stable	9–27	3.67
Nitenpyram	590,000	NA	Stable; 2.9 (pH 9)	1–15	1.78
Imidacloprid	610	<1	Stable; >1 year (pH 9)	104–228	2.19–2.29
Clothianidin	340	<1	Stable; 14.4 (pH 9)	13–1386	2.08
Thiamethoxam	4100	2.7–39.5	Stable; 11.5 (pH 9)	7–72	1.75
Dinotefuran	39,380	<2	Stable	50–100	2.08

Note: aData sources: Pesticide Products Database (PPDB) and Hazardous Substances Data Bank (HSDB). Information is from the following website: https://www.nlm.nih.gov/toxnet/index.html. bThe compound is more stable in water and soil under anaerobic conditions. cUnder acidic or neutral pH conditions, compounds are stable to hydrolysis, whereas under alkaline conditions (pH 9), hydrolysis can occur.

Table 6
Detection frequencies and concentration ranges of neonicotinoid insecticides in vegetables and fruits.

			Acetamiprid	Thiacloprid	Nitenpyram	Imidacloprid	Clothianidin	Thiamethoxam	Dinotefuran
Vegetables	n = 47 (Ying et al., 2016)	Detection frequency/%	100.00	11.00	0.13	100.00	49.00	1.00	0.04
		Concentration range/ ($ng \cdot g^{-1}$)	0.2–140.0	0.01–0.1	2.8–44.0	<DL-148.0	<DL-181.0	<DL-529.0	<DL-1.06
	n = 12 (Chen et al., 2014)	Detection frequency/%	–	–	–	58.00	25.00	33.00	8.00
		Concentration range/ ($ng \cdot g^{-1}$)	–	–	–	0.4–7.2	0.6–0.7	0.3–13.2	0.10
Fruits	n = 24 (Ying et al., 2016)	Detection frequency/%	1.00	0.04	0.00	1.00	0.12	0.52	0.00
		Concentration range/ ($ng \cdot g^{-1}$)	0.23–37.7	0.01	N.D.	<DL-1.95	<DL-0.3	<DL-21.8	N.D.
	n = 17 (Chen et al., 2014)	Detection frequency/%	24.00	18.00	–	82.00	18.00	18.00	6.00
		Concentration range/ ($ng \cdot g^{-1}$)	0.3–100.7	0.4–18.3	–	0.1–4.2	0.1–1.9	0.2–2.4	34.80

Table 7
Degradation studies of neonicotinoid insecticides by isolated microorganisms.

S. No.	Microorganisms	Neonicotinoids	Metabolites	References
1	*Variovorax boronicumulans* CGMCC 4969	Acetamiprid	(E)-*N*′-carbamoyl-N-[(6-chloro-3-pyridyl)methyl]-*N*-methylacetamidine	Sun et al. (2017)
2	*Fusarium* sp. CS-3	Acetamiprid	*N*-((6-chloropyridin-3-yl)methyl)-N-methylacetamide), (6-chloropyridin-3-yl)methanol, 6-chloronicotinic acid	Shi et al. (2018)
3	*Bacillus thuringiensis*	Imidacloprid	Nitroso imidacloprid, guanidine imidacloprid, 6-cloronicotinic acid	Ferreira et al. (2016)
4	*Pseudomonas* sp. RPT 52	Imidacloprid	Imidacloprid urea, 1-(pyridine-3-ylmethyl)imidazolidin-2-one	Gupta et al. (2016)
5	*Stenotrophomonas maltophilia* CGMCC 1.1788	Imidaclothiz	5-Hydroxy imidaclothiz, olefin imidaclothiz	Dai et al. (2010a)
6	Black soils	Clothianidin	Thiazolmethylurea, dechlorinated clothianidin	Zhang et al. (2018)
7	*V. boronicumulans* J1	Thiacloprid	Thiacloprid amide	Zhang et al. (2012)
8	*Ensifer meliloti* CGMCC 7333	Thiacloprid	Amide thiacloprid	Sun et al. (2016)
9	*E. adhaerens* TMX-23	Thiamethoxan	Nitrosoimino, urea	Zhou et al. (2013)
10	*Phanerochaete sordida* YK-624	Dinotefuram	*N*-((4aS,7aS,E)-1-methylhexahydrofuro [2,3-d]pyrimidin-2(1H)- ylidene) nitramide	Wang et al. (2019)
11	*P. chrysosporium*	Thiamethoxam	(Z)-*N*-(3-methyl-1,3,5-oxadiazinan-4-ylidene)nitramide, 3-methyl-1,3,5-oxadiazinan-4-imine	Chen et al. (2021)
12	*Pseudomonas* sp. 1G	Imidacloprid	Nitrosoguanidine, desnitro, urea	Pandey et al. (2009)
13	*Hymenobacter latericoloratus* CGMCC 16346	Imidacloprid	6-Chloronicotinic acid	Guo et al. (2020)
15	*Sphingobacterium*sp., *Agrobacterium*sp.	Imidacloprid	Imidacloprid-guanidine	Gautam et al. (2022)
16	*Pseudomonas stutzeri* smk	Clothianidin	2-Chloro-5-methyl thiazole, methyl nitroguanidine, methyl 3-[thiazole-yl], methyl guanidine	(Parte and Kharat, 2019)
17	*Streptomyces canus* CGMCC 13662	Acetamiprid	IM-1-2 ((E)-1-(1-(((6-chloropyridin-3-yl)methyl) (methyl) amino)ethylidene) urea)	Guo et al. (2019)

cytochrome P450 in the degradation process of white-rot fungi. After the addition of the P450 inhibitor aminobenzotriazole (ABT), the degradation activity of nitenpyram was significantly reduced, and the results indicated that cytochrome P450 participated in nitenpyram degradation (Wang et al., 2019). Similarly, neonicotinoid degradation by white-rot fungi was also demonstrated in another study (Chen et al., 2021). For the first time, Chen et al. discovered the excellent degradation potential of *Phanerochaete chrysosporium* toward thiamethoxam and converted it into metabolites with less biotoxicity, namely, 3-methyl-1,3,5-oxadiazinan-4-imine and (*Z*)-*N*-(3-methyl-1,3,5-oxadiazinan-4-ylidene) nitramide. Cytochrome P450 is crucial for the degradation process. The addition of the cytochrome inhibitor 1-ABT significantly reduced the degradation rate of thiamethoxam, and the degradation rate of thiamethoxam was only about 30% after the addition of 1-ABT in comparison to 98% without 1-ABT in the medium.

Imidacloprid is the most comprehensively studied neonicotinoid insecticide, and the imidacloprid biodegradation by various strains was first described in 2007 (Anhalt et al., 2007). Imidacloprid is mainly adsorbed in the soil by organic matter where microorganisms efficiently degrade imidacloprid. The degradation efficiency of imidacloprid under different conditions varies from 46% to 97% (Anhalt et al., 2007; Gupta et al., 2016; Wu et al., 2020). *Pseudomonas* sp. PRT 52 was isolated through soil enrichment, which could metabolize three pesticides (coragen, imidacloprid, and endosulfan). Imidacloprid has been used as the sole energy and carbon source was and was found to degrade 46.5% imidacloprid (0.5 mM) in 40 h (Gupta et al., 2016). Ferreira et al. isolated a novel pesticide-degrading bacterium from contaminated marine sediments. After identification, it was found that it had the highest similarity to *Bacillus thuringiensis*, and it degraded about 78% of acetamiprid within 11 days. This is the first reported case of the biodegradation of acetamiprid by *B. thuringiensis* (Ferreira et al., 2016). A strain of BCL-1 obtained from a soil enrichment culture degraded about 67% of acetamiprid within 48 h at 30 °C and degraded 92.44% of imidacloprid in 20 days, and metabolites including 6-chloronicotinic acid, imidacloprid guanidine, and nitroguanidine could be obtained (Hu et al., 2013). In imidacloprid resistance studies, three enzymes, namely, glutathione synthase (GSS), cytochrome P450 mono-oxygenase (P450), and epidermal protein (CP) were found to encode imidacloprid resistance (Naqqash et al., 2020).

4.2. Biodegradation pathways of neonicotinoids

At present, research on the biodegradation pathways of imidacloprid is relatively mature, as shown in Fig. 4. A similar aldehyde oxidase converts the ‘magic notro’ group to a nitrosoguanidine metabolite under microaerophilic conditions, and the parent molecule and/or nitrosoguanidine passes through the more toxic nitroguanidine intermediate body and is further converted into non-toxic urea metabolites (Pandey et al., 2009). Imidacloprid is cleaved to 6-chloronicotinic acid by the formation of nitrosoguanidine and the oxidative cleavage of the

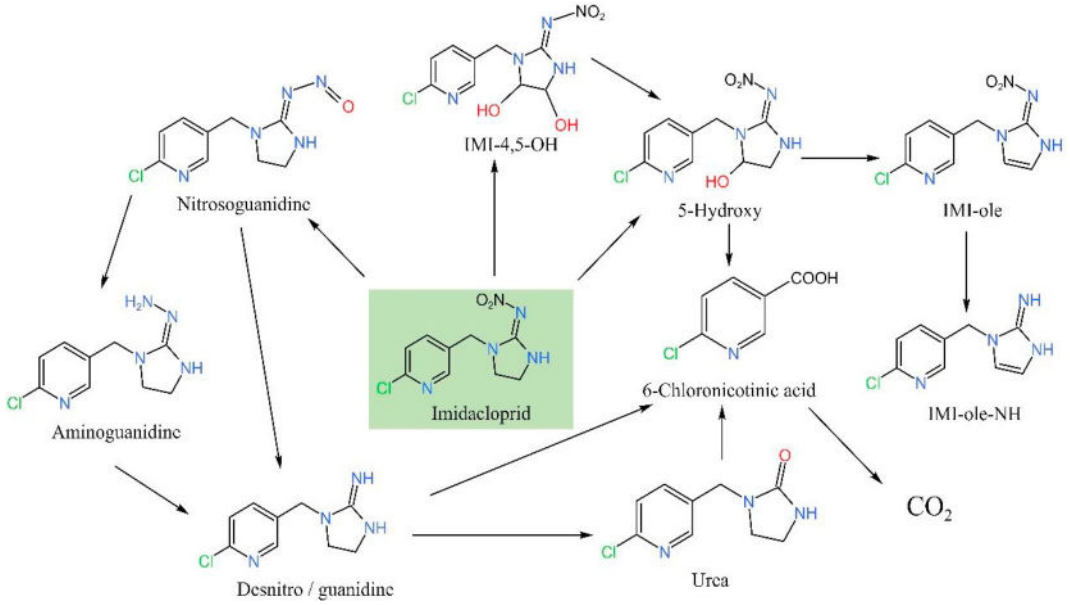

Fig. 4. The biodegradation pathways of imidacloprid. The parent molecule and/or nitrosoguanidine are first further converted to nontoxic urea metabolites via more toxic nitroguanidine intermediates, which can also be generated by oxidative cleavage to 6-chloronicotinic acid (Pandey et al., 2009; Phugare et al., 2013; Wang et al., 2018). Note: IMI, imidacloprid.

imidacloprid guanidine residue (Phugare et al., 2013), and 6-chloronicotinic acid is eventually converted to carbon dioxide (Sharma et al., 2014).

In recent years, the degradation pathways of acetamiprid have gradually improved (Fig. 5). Multiple studies have demonstrated the production of compound 1, which can be produced by the oxidative cleavage of imidacloprid by the microbial consortium ACE-3 (Xu et al., 2020). In addition, *Rhodotorula mucilaginosa* IM-2 could also change acetamiprid into compound 1 (Dai et al., 2010b). Subsequently, compound 1 can be *N*-deacetylated to compound 2 that has been established in *Stenotrophomonas* sp. as well (Tang et al., 2012). Cyanoimine (= N–CN) provides high affinity to acetamiprid gives it a higher affinity for insect's nAChR (nicotinic acetylcholine receptor), resulting in the paralysis and death of the pest (Tang et al., 2012). Metabolic compound 3 has been revealed in various studies. *S. maltophilia* CGMCC 1.1788 could perform acetamiprid demethylation into IM2-1, which is compound 3 here (Chen et al., 2008).

5. Conclusions and outlook

Neonicotinoids are the fastest-growing insecticide class since pyrethroid commercialization. In the past ten years, due to the advantages of neonicotinoids over traditional pesticides, they have been considered as ideal substitutes for some pesticides. However, more studies are showing that neonicotinoids also have toxic effects on non-target organisms. Neonicotinoids have been partially banned in Europe, but the use rate of neonicotinoids is still high worldwide, which means that many non-target organisms are still exposed to insecticides.

The residues of neonicotinoids in the environment increase the possibility of non-target organism exposure. The current research on

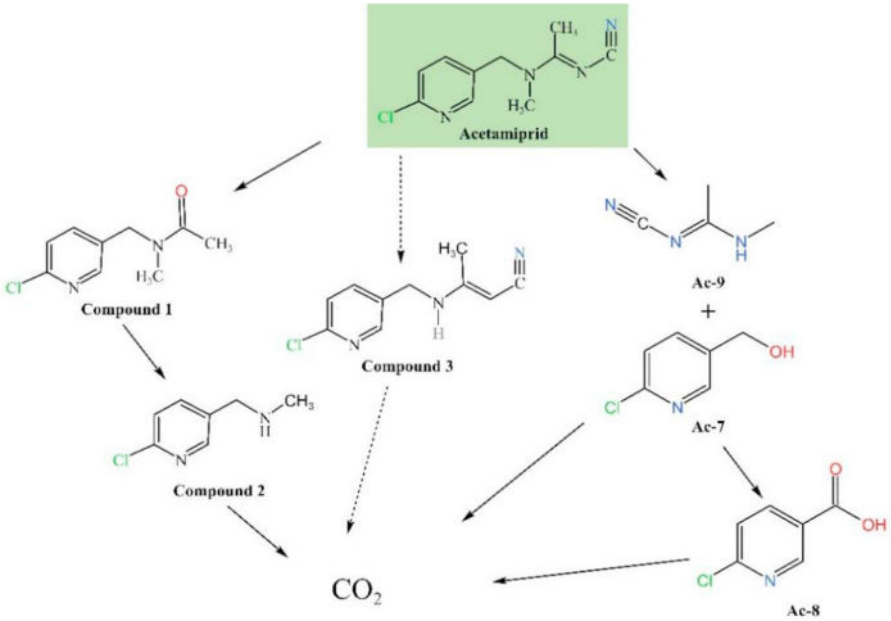

Fig. 5. The biodegradation pathways of acetamiprid. Acetamiprid undergoes oxidative cleavage and *N*-deacetylation to generate intermediate metabolites, and it finally enters the tricarboxylic acid cycle to generate non-toxic carbon dioxide (Chen et al., 2008; Xu et al., 2020; Pang et al., 2020b; Anjos et al., 2021). Note: Ac, acetamiprid; Compound 1, *N*′-[(6-chloropyridin-3-yl) methyl]-*N*-methylacetamide; Compound 2, *N*-methyl-(6-chloro-3-pyridyl)-methylamine; Compound 3, *N*1-(6-chloro-3-pyridyl)methyl-*N*2- cyanoacetamidine; AC-7, (6-chloropyridin-3-yl)methanol; AC-8, 6-hydroxynicotinicacid; AC-9, (E)-*N*-cyano-N-methylaceamidamide.

neonicotinoids shows that their toxic effects on non-target organisms vary between species. Among them, imidacloprid has the highest toxicity, and both dinotefuran and nitenpyram have lower toxicity. It needs to be pointed out that the current experiments on neonicotinoids are mostly carried out in laboratories, and there are few studies carried out under real outdoor environmental conditions. In the laboratory environment, experimental conditions and human factors affect the results. Therefore, more research is needed to verify these toxic effects. Future research can consider the following aspects: (1) observing the toxic effects and mechanisms of a variety of neonicotinoid insecticides or combined exposure with other pesticides on different species of organisms, which are more in line with the exposure of organisms in the real environment; (2) combining a variety of analytical methods to study the toxic mechanism of neonicotinoid insecticides in different species to provide a standard for the future use of pesticides on the market; and (3) intensifying the research on vertebrates and model organisms to infer the effect on humans.

While studying the toxicity of neonicotinoid pesticides, the removal of these residues from the environment is a topic of increasing interest. At present, there are various methods for pesticide residual removal from the environment, including physical, chemical, and biological means. Among them, biological means, especially microbial degradation technology, have become the most effective remediation strategy for the removal of neonicotinoid residues from the environment. Biodegradation does not cause secondary pollution; the degradation process is fast; the cost is low; and the degradation process is low-carbon and energy-saving, which is in line with the current environmental protection concept of energy conservation and emission reduction. Biodegradation is comparatively a better method than physicochemical methods. Microorganisms can convert neonicotinoids into nontoxic or less toxic metabolites through various metabolisms. The metabolic pathways of some neonicotinoids including thiacloprid, thiamethoxam, imidacloprid, clothianidin, and acetamiprid, are well known; however, studies on nitenpyram and dinotefuran are still scarce. In addition, the synergistic effect of microbial communities on neonicotinoid degradation requires further investigation. Finally, the study of functional genes and enzymes for microbial degradation is important to better understand the degradation mechanisms in polluted environments. Several neonicotinoid-degrading strains have been isolated, there are few studies on their functional genes and enzymes. In the future, advanced technologies such as proteomics, metabonomics, and transcriptomics are needed to explore the missing links and molecular mechanisms and catalytic pathways involved in the process of biodegradation. The recent advancements in high-throughput molecular and next-generation sequencing tools might ease the field applicability of neonicotinoid-degrading microbes from different contaminated areas.

Author contributions

Shaohua Chen & Pankaj Bhatt: conceived of the presented idea. **Xidong Zhang**: contributed to the writing and prepared the figures and tables. **Xidong Zhang, Yaohua Huang, Wen-Juan Chen, Siyi Wu, Qiqi Lei, Zhe Zhou, Wenping Zhang, Sandhya Mishra, Pankaj Bhatt, and Shaohua Chen**: participated in revising and editing the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

This work was supported by grants from the Key Realm R&D Program of Guangdong Province, China (2020B0202090001), the Natural Science Foundation of Guangdong Province, China (2022A1515010422), the Science and Technology Planning Project of Guangdong Province, China (2021B1212040008, 20210205), and China Postdoctoral Science Foundation (2020M672655).

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