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Review

A Review of the Adverse Effects of Neonicotinoids on the Environment

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Abstract: Neonicotinoids are a group of insecticides developed in the 1980s, reaching extensive use in agriculture in the 1990s due to their effectiveness against pests in various types of crops. In 2014, their use reached 25% of the global market. In the last decade, studies on their possible effects have been conducted, leading to bans and regulations in several European Union countries. Their persistence in soil and water can result in chronic exposure in aquatic and terrestrial organisms, including pollinator species. The accumulation of these compounds in the environment can disrupt ecosystems and affect the health of humans, plants, and animals. This review presents current knowledge on neonicotinoids, their mechanisms of action, and their transport in ecological spheres. Their presence in water and soil is evidenced, with specific concentrations reported in various regions. Their effects on non-target organisms, including aquatic animals and humans, can be negative, causing direct and indirect neurological and renal problems after exposure. More research is needed on the long-term effects on health and non-target organisms to fully understand the implications of these insecticides.

Keywords: pollution; water; soil; insecticides; air; human health; resistance; non-target organism

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1. Introduction

Neonicotinoid insecticides (NNIs) are a group of nitroguanidine systemic compounds derived from nicotine, which were developed in the early 1990s for insect management and became a convenient application due to their adaptability and lower resistance. NNIs were frequently applied to crops as soil and seedling pest treatments [1,2]. Seven NNIs reached the worldwide market, namely imidacloprid (IMI), thiacloprid (THIAC), clothianidin (CLO), thiamethoxam (THIAM), acetamiprid (ACE), nitenpyram (NIT), and dinotefuran (DIN); these NNIs constituted the best-selling class of insecticides and seed treatments [3,4]. However, the excessive use of NNIs not only in the agricultural industry but also in lawns and gardens, as well as among livestock and pets, led to an increasing risk of pest resistance and environmental pollution [4,5]. In 2014, the use of NNIs reached 25% of the global insecticide market. The three main NNIs used for crop protection—IMI, THX, and CLO—accounted for 85% of the total global market [6]. The primary areas where NNIs were extensively used included Latin America, Asia, and North America, constituting approximately 75% of their use, while Europe represented around 11% [7].

The mechanism of action of these compounds acts against nicotinic acetylcholine receptors (nAChRs) in the central nervous system of insects, causing a stimulation of the nervous system by blocking the transmission of cholinergic signals, which can result in altered behaviors, such as excessively exciting behaviors or paralysis and death [2].

In the last decade, worldwide organizations have expressed their concerns regarding the use of NNIs and passed legislation in this regard. In 2013, the European Union reported the potential neurodevelopmental toxicity of ACE and IMI [8]. France was the first country

in the world to prohibit the use of NNIs for crop protection [9]. In 2018, the European Food Safety Authority (EFSA) published a report declaring the risks of IMI, THIAM, and CLO and prohibited their outdoor use. This decision was based on scientific evidence highlighting the threats posed to bees and the environment [10,11]. The United States Environmental Protection Agency (EPA) declared a human health risk assessment of ACE, IMI, CLO, THIAM, and DIN [12]. However, despite all these regulations, NNIs are still authorized in over 120 countries and used on around 140 crops [13].

Only 5% of the active ingredients applied to crops are absorbed, while the rest may end up in soil, dust, wetlands, groundwater, non-target plants and insects, food, cultured marine species, urine, and human placenta, among others [14–17]. As compounds that are soluble in water, NNIs are mobile and have been detected in rivers and streams. In the United States, at least one type of neonicotinoid was present in 63% of all the streams analyzed [14]. These compounds are not effectively removed by wastewater treatment plants and become a source of contamination in surface water and groundwater [18].

Soil serves as a primary recipient and storage site for NNIs. Residues present in soil can potentially migrate to other environmental compartments. While earlier investigations into NNI residues in soil had predominantly focused on agricultural lands, a recent study reported the detection of six to seven NNIs in soil within greenhouse cultivation [19]. In a recent study, the average concentration of five NNIs across various land types was investigated. The highest concentration was observed in greenhouses, followed by orchards, parks, residential areas, and farms in a specific region of China [20]. The detection of NNIs requires sensitive, highly selective, and expensive analytical methods due to their low concentrations in the environment; however, such low concentrations do not mean that they are not dangerous [21].

Additionally, their low affinity for soil minerals contributes to leaching via bulk flow in certain conditions, depending on the type of NNIs and soil, which determine the force of sorption in the environment. Diverse studies have been conducted in many countries on the sorption and leaching of neonicotinoids, such as China, US, Spain, and Austria [22].

To date, the presence of NNIs in the environment is known to be extensive, and efforts have been made to prohibit their use, although their long-term adverse effects on organisms remain unknown as there are different species in each ecosystem, whose study requires comprehensive toxicology work. However, there are several studies about the potential risk of NNIs on humans, bees, ants, ladybugs, mammals, birds, amphibians, and reptiles, among others, in whom the presence of NNIs results in developmental neurodevelopmental damage [23–26].

NNI compounds have been found in drinking water and food chains, including in vegetables, honey, and fruit such as apples. This indirect exposure to NNIs is alarming because it means that humans may be exposed to compounds harmful to health without needing to be in direct contact with them [27].

Thus, the aim of this review was to examine the adverse effects on soil, water, atmosphere, humans, and non-target organisms from the use of NNIs in recent years, and to illustrate the consequences of the excessive use of novel insecticides without studies on their immediate and long-term negative effects.

2. Application of Neonicotinoids

NNIs are the most widely used class of insecticides globally due to their long-lasting systemic action and high pest control effectiveness. They can be applied through various methods, such as foliar sprays, trunk injection, or root drenching [27], allowing them to be absorbed throughout the plant's vascular tissue to confer systemic protection against some insect pests [23,28]. Since the introduction of the first NNI—IMI—in 1991, several others have been developed, including ACE, CLO, THIAM, THIAC, DIN, and NIT [29–31]. Each of these NNIs has specific structure (Figure 1).

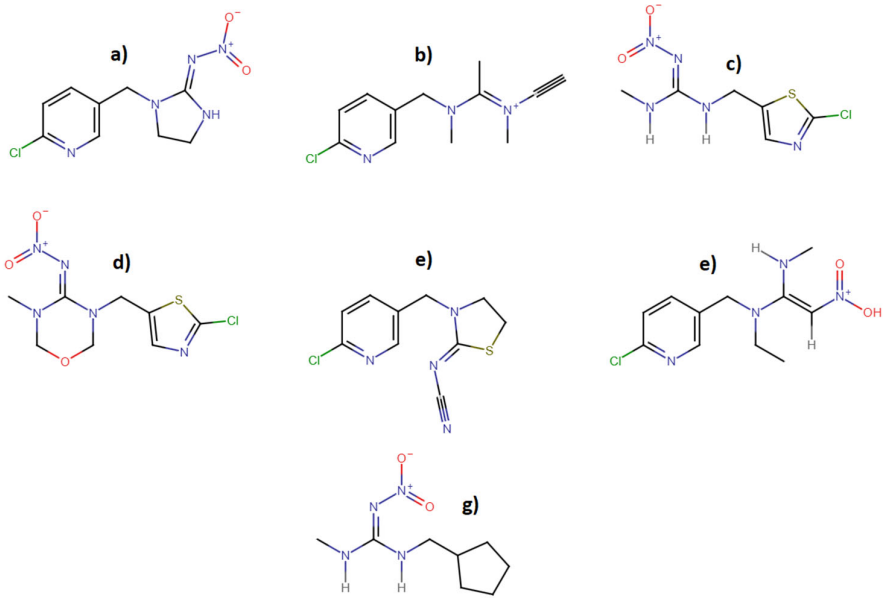

Figure 1. Chemical structures of the most popular groups of neonicotinoids. (**a**) Imidacloprid; (**b**) acetamiprid; (**c**) clothianidin; (**d**) thiamethoxam; (**e**) thiacloprid; (**f**) nitenpyram; (**g**) dinotefuran.

2.1. Imidacloprid (IMI)

Imidacloprid, 1-(6-chloro-3-pyridylmethyl)-*N*-nitroimidazolidin-2-ylidenoamine (Figure 1a), is a first-generation chlorinated nicotinic insecticide developed in the 1980s by Bayer Corporation [31]. It is widely used in agriculture, especially as a seed coating, and is sold under the trade names Confidor, Admire, Gaucho, Hachikusan, Premise, and Prothor, among others [32]. It is recommended as an insecticide to control pests such as whiteflies, thrips, and other insects with piercing/sucking mouthparts [33]. The mechanism of action of IMI is the simulation of acetylcholine; a malfunction of this neurotransmitter affects the nervous system of insects, causing their death [34].

2.2. Acetamiprid (ACE)

N-[(6-chloropyridin-3-yl)methyl]-*N′*-cyano-*N*-methylethanimidamide (Figure 1b) is a first-generation NNI introduced to the Japanese market in 1995 and belongs to the chloropyridinyl subclass [35,36]. ACE is used for the control of sucking-type insects, mainly aphids that feed on the sap of leaves and stems of plants [37]. It is usually applied via foliar spraying on crops [38] and is also used for seed protection [39]. ACE acts as a nicotinic acetylcholine receptor agonist, which, upon binding to these receptors, causes the accumulation of acetylcholine at synapse sites in the nervous system and leads to the paralysis and death of insects [38,40].

2.3. Clothianidin (CLO)

1-[(2-chloro-1,3-thiazol-5-yl)methyl]-3-methyl-2-nitroguanidine (Figure 1c) is a second-generation NNI jointly developed by Takeda Chemical Industries and Sumitomo Chemical with Bayer. Since 2002, it has become one of the most applied insecticides due to its broad insecticidal spectrum, high activity at low concentrations, and long-term control effects [41,42]. It has found extensive application in crops such as tomato, rice, tea, maize, rape fruit, and citrus [43,44]. Its basic mode of action is to target nicotinic acetylcholine receptors in the nervous system of insects [45]. It is often utilized as a seed treatment [46] or applied as a foliar spray and soil drenches [47]. CLO is effective in small amounts against insect pests of the Hemiptera, Thysanoptera, Diptera, Coleoptera, Lepidoptera, Orthoptera, and Isoptera orders [42].

2.4. Thiamethoxam (THIAM)

[3-[(2-chloro-1,3-thiazol-5-yl)methyl]-5-methyl-1,3,5-oxadiazinan-4-ylidene]nitramide (Figure 1d) is a second-generation NNI developed by Novartis in 1991 and was first marketed in 2013 [48]. It has been extensively applied for the protection of over 115 crops, such as rice, maize, cotton, and mango, in at least 64 countries. THIAM is effective against a variety of chewing and sucking pests, such as aphids, whiteflies, plant hoppers, thrips, and beetles [43,49]. It is widely applied as a foliar, soil, or seed treatment, with seed treatment being the largest agricultural use of THIAM [50,51].

2.5. Thiacloprid (THIAC)

[3-[(6-chloropyridin-3-yl)methyl]-1,3-thiazolidin-2-ylidene]cyanamide (Figure 1e) is a second-generation NNI introduced by Bayer Crop Science [52]. Considered a novel member of the NNI family, it acts on neurotransmitter receptors and causes interference with the normal nerve conduction of insects. As a result, it overexcites the insects and causes them to die through body spasm and paralysis [53]. THIAC is also used as a seed coating for maize [54]. It can be applied to protect crops such as oilseed rape, wheat, orchard fruits, and cotton [55]. It is used as both an acaricide and an insecticide against many mites and insect pests of crops and ornamentals [56].

2.6. Nitenpyram (NIT)

(*E*)-1-*N*′-[(6-chloropyridin-3-yl)methyl]-1-*N*′-ethyl-1-*N*-methyl-2-nitroethene-1,1-diamine (Figure 1f) is a second-generation NNI developed in 1995 by Sumitomo Chemical Takeda Agro Company [57]. It is widely used in agriculture for the control of sucking-type insects, such as aphids, whiteflies, thrips, and leafhoppers [58]. As it is less toxic than IMI, it is often used in veterinary medicine as an antiparasitic to exterminate fleas in dogs and cats [59,60]. Its mechanism of action involves the inhibition of nicotinic acetylcholine receptors to prevent the flux of sodium ions from the nervous system of insects [61].

2.7. Dinotefuran (DIN)

1-methyl-2-nitro-3-(oxolan-3-ylmethyl) guanidine (Figure 1g), a third-generation NNI, is a nitroguanidine compound developed by Mitsui Chemicals in Japan in 2002 and registered by the US EPA in 2004 to control insect pests [62]. It acts as an agonist of nicotinic acetylcholine receptors in the nervous system of insects [63]. DIN has been used to improve the protection of numerous plant species, such as *Citrus sinensis* (Rutaceae), berries (Ericaceae), and *Brassica pekinensis* (Brassicaceae) [64,65]. It can be applied on foliage and soil via spraying and drenching and has a broad spectrum of activity against a wide range of sucking and biting insects, including Coleoptera, Diptera, and certain Lepidoptera species [62,66].

In Table 1, as mentioned previously, the first neonicotinoid to be commercialized was IMI, followed by ACE, THIA and NIT. With the development of IMI, the history of NNIs began. The first-generation neonicotinoids are IMI and ACE. The second generation are THIAM, CLO, THIA and NIT. Finally, the third generation is DINO. The major difference between them is their structure. Also, some other applications of NNIs, mode of application and target are mentioned in Table 2.

Table 1. Neonicotinoid generations and some of their characteristics.

Generation	Characteristics	Neonicotinoid	References
First	- Developed in the 1980s - Chloropyridylmethy compounds (6-chloropyridin-3-ylmethyl as a substituent). - Partial agonist of acetylcholine receptor	Imidacloprid Acetamiprid	[31]

Table 1. *Cont.*

Generation	Characteristics	Neonicotinoid	References
Second	- Developed in the 1990s - Chlorothiazolylmethyl compounds (2-chlorothiazol-5-ylmethyl) - Target nicotinic acetylcholine receptors in nervous system	Thiamethoxam Clothianidin Thiacloprid * Nitenpyram *	[41,48,52,57]
Third	- Developed in 2002 - Tetrahydro-3-furylmethyl group as substituents - Act as agonist of nicotinic acetylcholine receptors in the nervous system	Dinotefuran	[64]

* Some authors consider these NNIs first-generation NNIs [67–70].

Table 2. Applications of the most popular groups of NNIs.

Neonicotinoid	Crop	Mode of Application	Target Insect	References
Imidacloprid	*Vitis vinifera* L. (Vitaceae)	Soil spraying	*Erythroneura variabilis* (Hemiptera: Cicadellidae)	[71]
	Solanum melongena L. (Solanaceae)	Soil spraying	*Aphis gossypii* (Hemiptera: Aphididae) *Myzus persicae* (Hemiptera: Aphididae)	[72]
	Nicotiana tabacum L. (Solanaceae)	Foliar spraying	*Myzus* spp. (Hemiptera) *Bemisia tabaci* (Hemiptera: Aleyrodidae)	[73]
	Solanum tuberoso L. (Solanaceae)	Soil spraying	*M. persicae* *Paratrioza cockerelli* (Hemiptera: Triozidae)	
	Solanum lycopersicum L. (Solanaceae)	Spraying	*A. gossypii* *Frankliniella occidentalis* (Thysanoptera: Thripidae)	
Acetamiprid	*Gossypium hirsutum* L. (Malvaceae)	Spraying	*A. gossypii*	[40]
	Capsicum frutescens L. (Solanaceae)	Foliar spraying	*F. occidentalis* *Bemisia argentifolii* (Hemiptera: Aleyrodidae) *Bactericera cockerell* (Hemiptera: Triozidae)	[74]
	Rosa spp. (Rosaceae)	Foliar spraying	*Macrosiphum rosae* (Hemiptera: Aphididae)	[75]
Clothianidin	*Oryza sativa* L. (Poaceae)	Spraying	*B. tabaci* *Nilaparvata lugens* (Hemiptera: Delphacidae)	[76]
	Saccharum officinarum (Poaceae)	Soil drench	*Odontotermes obesus* (Balttodea: Termitidae) *Microtermes obesi* (Isoptera: Termitidae)	[77]
Thiamethoxam	*S. lycopersicum* L.	Spraying	*A. gossypii* *B. tabaci* *Thrips tabaci* (Thysanoptera: Thripidae)	[78]
	Glycine max L. (Fabaceae)	Seed treatment	*Ceratoma trifurcata* (Coleoptera: Chrysomelidae)	[79]

Table 2. *Cont.*

Neonicotinoid	Crop	Mode of Application	Target Insect	References
Thiacloprid	*Brassica napus* L. (Brassicaceae)	Foliar spraying	*Meligethes aeneus* (Coleoptera: Nitidulidae)	[80]
	Camelia sinensis L. (Theaceae)	Spraying	Aphidoidea *Aleurocanthus spiniferus* (Hemiptera: Aleyrodidae)	[81]
	G. hirsutum L. (Malvaceae)	Seed treatment	*A. gossypii* *B. tabaci*	[82]
Nitenpyram	*O. sativa* L.	Spraying	*Sogatella furcifera* (Hemiptera: Delphacidae)	[57]
	Malus spp. (Rosaceae)	Spraying	*Apolygus lucorum* (Hemiptera: Miridae)	[83]
	Other uses: (*Felis catus* L. and *Canis familiaris* L.)	Oral	*Ctenocephalides felis* (Siphonaptera: Pulicidae)	[59,84]
Dinotefuran	*Lycium barbarum* L. (Solanaceae)	Spraying	Eriophyidae *Psylla* spp. (Hemiptera: Psyllidae) Aphidoidea	[85]
	Apium graveolens L. (Apiaceae)	Drenching	Agromyzidae	[62]

3. Effect on the Environment

As mentioned above, NNIs have been applied for plant protection in multitude of ways, and it is estimated that around 90% or more of the active compounds applied do not reach their target and diffuse through the environment [86]. NNIs can persist in the environment for a single day up to as long as 19 years in soil and sediment. Thus, they are capable of disseminating in soil, water, and biota [87]. Once in the environment, they affect organisms in every ecosystem (mainly insects, but also organisms such as birds [88], fishes [89], and amphibians [90,91]). Some of the effects of NNIs on the environment are mentioned in more detail below.

3.1. NNI Transport Mechanisms and Analysis Techniques

NNIs may diffuse through their environment to reach other ecosystems and pollute resources such as surface and underground water as well as soil, leading to undesirable effects on non-target organisms.

NNIs are primarily used as a treatment to protect the seeds of several crops by acting as a coat. This practice is so common that in some crops, it is hard to find seeds that have not been treated with NNIs [92]. Seed coating is a method of promoting plant growth and thus improving seed quality. The protective coating provides different kinds of substances such as fungicides, acaricides, herbicides, and insecticides [93]. However, this practice may result in NNIs diffusing through the environment. For example, vacuum-type planters can displace the insecticide coating from the seed into the atmosphere [94]. The airflow used for the vacuum enters the equipment to reach the sowing elements and exits through a fan. During this process, pesticide-laden dust particles detach from the coating and get expelled from the planter, resulting in dust drift with these particles [95]. Seed coating is not the only mechanism; some other agricultural practices may also promote the distribution of neonicotinoids. NNIs can easily mix with irrigation water and soil when applied via foliar spraying [96]. Additionally, foliar spraying results in their release into the atmosphere where they are more likely to be distributed in their particulate phase [97].

Some of the properties of NNIs may also help in their distribution. Low sorption coefficients as well as solubility in water enhance their distribution in bodies of water as

they can be easily transferred through agricultural runoff, leaching, and drainage. Soil erosion caused by raindrops and water runoff is a great example of this as runoff detaches, transports, and finally deposits the soil material elsewhere. Thus, runoff transport is one of the main pathways for surface water contamination, and the risk increases if NNIs are applied just before a rainfall event. IMI and CLO are the main NNIs that distribute through this method due to their water-soluble properties [98].

Insects can also contribute to the distribution of NNIs, causing adverse effects on themselves and thus, on the ecosystem. Pollinators such as bumblebees and honeybees visit crops to collect pollen and nectar, but if these crops have been treated with NNIs, then these pollinators become contaminated. When they return to the hive, the colony becomes contaminated, increasing worker mortality and resulting in queenlessness over time [99].

There are some techniques for determining the concentration of NNIs in the environment, depending on the compound and the matrix in which they are found. Casillas et al. (2022) implemented a high-performance liquid chromatography system (HPLC 212) coupled with a quadruple mass spectrometer (320-MS-TQ) to identify the presence of NNIs in the Tajo River basin [100]. Wan et al. (2020) quantified IMI and its degradation byproducts such as desnitro-imidacloprid (DN-IMI), imidacoprid-urea (IMI-urea), and desnitro-imidacloprid-olefin (DN-IMI-olefin) in surface water, treated water, and tap water in Wuhan, central China, using ultra-high-resolution liquid chromatography by isotope dilution (ExionLC) coupled with a triple quadrupole mass spectrometer by electrospray ionization (AB SCIEX QTRAP 6500+) [101]. A study conducted by Hladik and Kolpin (2016) identified neonicotinoids in stream samples from the United States using a liquid chromatograph (LC) coupled with a tandem mass spectrometer (MS-MS) [102]. Similarly, Yi et al. (2019) detected high concentrations of IMI and ACE in surface waters in the Pearl River of Guangzhou through liquid chromatography–mass spectrometry (LC-MS/MS) analysis [103].

3.2. Effect on Water

The effectiveness of the treatment of wastewater contaminated by NNIs depends on their physicochemical properties because they are very soluble in water. They have been applied in different sectors, including in urban and veterinary settings and for agricultural pest control [104]. They usually reach aquatic ecosystems via runoff after being applied to crops; in addition, they are hardly biodegradable and slowly hydrolyze at acidic or neutral pH [105].

The solubility of NNIs is a key property that allows them to function effectively as systemic pesticides to be absorbed by crops, depending on the conditions of water pH, room temperature, and the form of application (either in granules or as a seed treatment) [12]. Due to their high solubility in water and low octanol–water partition coefficient (logKow), NNIs have a low tendency to be adsorbed on soil particles [106] and have been frequently found in water [107,108]. Table 3 shows that NIT is the most soluble neonicotinoid (570,000 mg L^{-1}) with a low logKow (−0.66) and a non-volatilization value of 3.54×10^{-13} Pa m^3 mol^{-1}. These properties influence the distribution of NNIs and their effect on the environment, which triggers a negative impact and leads to their persistence [109,110].

In a study on national streams in the United States, Hladik et al. (2014) determined that at least one neonicotinoid compound was present in 63% of the 48 streams studied, with maximum concentrations of 260, 43, and 190 ng L^{-1} being detected for CLO, IMI, and THIAM, respectively, which represented the most commonly used compounds [111].

Kim et al. identified the concentrations of ACE, CLO, IMI, NIT, THIAC, THIAM, and IDN in samples from drinkable water treatment plants (DWTPs); DIN was detected to be the NNI with a higher concentration (23.5 ng L^{-1}) due to its extensive use for treating pests. In addition, DIN has a higher solubility and a lower logKow, which result in its lower elimination rate in granular activated carbon (GAC) filtration processes [27].

Table 3. Chemical properties (water solubility, Henry's law constant, octanol–water partition coefficient-logKow) and environmental persistence (aqueous hydrolysis D)$_{50}$ of neonicotinoids [a].

Neonicotinoid	Molecular Formula	Solubility in Water at 20 °C (mg L^{-1})	Henry's Law Constant at 25 °C (Pa m^3 mol^{-1}) [b]	Aqueous Hydrolysis DT$_{50}$ (Days) at 20 °C and pH 7 [c]		LogKow at pH 7, 20 °C [d]
				Stable pH	Note	
Imidacloprid	$C_9H_{10}ClN_5O_2$	610 (High)	1.7×10^{-10}	5–7	DT$_{50}$ approx. 1 year—pH 9	0.57
Acetamiprid	$C_{10}H_{11}ClN_4$	2950 (High)	5.30×10^{-08}	4–7	DT$_{50}$ 420—pH 9	0.8
Clothianidin	$C_6H_8ClN_5O_2S$	327 (Moderate)	2.9×10^{-11}	4–9	DT$_{50}$ 14.4—pH 9, 50 °C	0.90
Thiamethoxam	$C_8H_{10}ClN_5O_3S$	4100 (High)	4.70×10^{-10}	1–7	DT$_{50}$ 11.5—pH 9	−0.13
Nitenpyram	$C_{11}H_{15}ClN_4O_2$	570,000 (High)	3.54×10^{-13}	3–7	DT$_{50}$ 2.9—pH 9	−0.66
Dinotefuran	$C_7H_{14}N_4O_3$	39,830 (High)	8.7×10^{-09}	4–9	-	−0.549

[a] Pesticide Properties Database (PPDB), available at: https://sitem.herts.ac.uk/aeru/ppdb/en/index.htm (accessed on 10 March 2024). [b] All values of Henry's law are non-volatile. [c] Stable hydrolysis at acidic or neutral pH values; however, under alkaline conditions (pH 9) hydrolysis may occur. [d] All values of logKow are low.

Tsegay et al. (2024) evaluated the concentrations of NNIs in the Yangzen River basin region. They determined that the high concentrations of NNIs in this region are due to their widespread use; the increased use of formulations containing active ingredients such as IMI, ACE, and THIAM, particularly in China; and their dispersion and incorporation into surface waters through adhesion to airborne particles. It was determined that the NNIs with the highest concentrations were NIT and DIN, and it was observed that infants had a higher exposure to NNIs, with a maximum daily intake of 40.84 ng kg^{-1} bwd^{-1}, which was seven times higher compared to that for adolescents (7.3 ng kg^{-1} bwd^{-1}). The highest exposure was associated with DIN in infants [112]. Likewise, snowmelt was found to be an important mechanism in the transport of NNIs that influenced the contamination of surface waters [50].

According to a study conducted by Casillas et al. (2022), IMI is the most significant NNI as it has the greatest sales worldwide; in their study, the presence of ACE, CLO, IMI, THIAM, and THIAC was evaluated in 19 water samples from the Tagus River basin, and it was concluded that there was the presence of at least one NNI in 17 of the 19 water samples, with a mean value of 2.75 ng L^{-1} for IMI and a value of 0.47 ng L^{-1} for ACE, as they were the most predominant insecticides used in agricultural practices [100]. Similarly, in a nationwide study on NNI transport in US streams, Hladik and Kolpin (2015) detected mostly IMI (140 ng L^{-1}), followed by CLO (66 ng L^{-1}) and THIAM (190 ng L^{-1}) [102]. Table 4 show a summary of the maximum concentrations of NNIs found in a series of different matrices in urban areas around the world is presented.

Table 4. Maximum concentration of neonicotinoids in different water matrices among several urban areas of the world.

Country	Neonicotinoid	Region	Type of Water	Transport Mechanism	Concentration (ng L^{-1})	Reference
Korea	DIN	Nakdong River in South Korea	Drinking water	Precipitation leaching	23.5	[27]
China	NIT DIN	Yangtzen River Basin	Surface water	Agricultural runoff and atmospheric deposition	90.7 63.2	[112]
Canada	CLO	Alvena, Saskatchewan	Surface water Melwater	Meltwater runoff	137 487	[50]
China	IMI	Northeast, north, northwest, east, south and southwest	Tap water Drinking water Well water	Runoff and infiltration	4.18 1.76 1.48	[113]

Table 4. *Cont.*

Country	Neonicotinoid	Region	Type of Water	Transport Mechanism	Concentration (ng L^{-1})	Reference
USA	CLO IMI	University of Iowa and Iowa City	Tap water	Runoff and infiltration	3.89–57.3 1.22–39.5	[114]
Switzerland	THIAM THIAC	Swiss plateau	Surface water	Atmospheric deposition and runoff	65 47	[115]
China	IMI THIAM	Paerl River, Guangdong	Surface water and effluents from WWTPs	Runoff	24.0–322 (in total)	[116]
China	ACE CLO	Guanzhou	Surface water	Adhered to sediments and runoffs	73.1 375	[117]

3.3. Negative Effects on Aquatic Organisms

According to the research work by Merga and Van den Brink, these chemicals can affect organisms in waterbodies, such as aquatic insects, crustaceans, and fish, altering their behavior, development, and reproduction. Concerns about the effects of NNIs on aquatic ecosystems have led to increasing research efforts to better understand their impact and to take measures to mitigate their negative effects. A study in 2021 demonstrated that macroinvertebrate and zooplankton community structures were significantly changed by IMI contamination in mesocosms that were administered repeated doses of $\geq$0.1 and $\geq$0.01 μg L^{-1}, respectively [118].

NNIs are recognized for their adverse effects on aquatic ecosystems, particularly on non-target communities of aquatic invertebrates, with insects being the most sensitive [119]. In general, NNIs can have harmful effects on the survival, growth, mobility, and behavior of various sensitive aquatic invertebrate species at concentrations equal to or less than 1 μg L^{-1} under acute exposure and 0.1 μg L^{-1} under chronic exposure [120].

In a study by Huang et al. (2021), the adverse effects of IMI metabolization, as well as the toxicokinetic and toxicity of its metabolites, were examined in two aquatic arthropod species: the mayfly *Cloen dipterum* (Ephemeroptera: Baetidae) and the amphipod *Gammarus pulex* (Amphipoda: Gammaridae). Both species showed comparable toxicity, and the findings regarding the internal kinetics of IMI revealed that both IMI and its metabolites were toxic and persistent within the body tissues in a concentration range between 5 and 15 μg L^{-1} [121].

In general, environmental concentrations are below lethal levels for almost all organisms, but there is still concern about the effects of NNIs on aquatic insects exposed to sublethal concentrations. Mayflies are aquatic insects that are highly sensitive to NNIs, and sublethal exposure can reduce their mobility, thus indirectly increasing their mortality. In one study, *Stenacron* and *Stenonema* mayfly nymphs were exposed to CLO concentrations below the 96 h EC_{50} (7.5 μg L^{-1}) to examine their risk of predation by the predator salamanders *Eurycea cirrigera* or *Corydalus cornutus* nymphs. The results showed that while exposure to CLO only had no impact on mortality, it increased the mortality of mayflies that were exposed to these predators [122].

Aquatic invertebrates can exhibit negative effects from exposure to NNIs. Many studies have focused on the individual exposure to a single type of insecticide, and a comprehensive study of exposure to mixtures of insecticides in aquatic community systems has not been performed. Duchet and colleagues conducted a study in 2023, where they examined a mixture of three NNIs (IMI, CLO, and THIAC) in an invertebrate community using a mesocosm over 50 d. A cascade effect was observed from the top to the bottom of the system, affecting all the present species, including zooplankton and predators such as

crustaceans and insects, with a concentration of 0.25 μg L^{-1} of IMI, 3.11 μg L^{-1} of CLO, and 1.49 μg L^{-1} of THA. Additionally, complex toxicity within the system was noted [123].

Another species that has been found to exhibit sensitivity to NNIs in recent studies is *Asellus aquaticus* (Isopoda: Asellidae). A toxicokinetic and toxicodynamic study was conducted to understand this species' sensitivity regarding the size and sex of individuals. After 4 d, the internal concentration of IMI and its metabolite IMI-olefin was measured. There was no difference between males and juveniles of both sexes; they exhibited an internal concentration of 400 μg kg^{-1}, with an initial concentration of IMI of 1000 μg L^{-1} and a concentration of IMI-olefin of 75 μg kg^{-1}. Females showed a lower internal concentration of IMI and IMI-olefin at 100 μg kg^{-1} and 25 μg kg^{-1}, respectively, which might be due to the low internal biotransformation of IMI. Additionally, IMI-olefin proved to be more toxic than IMI in females than in males [124].

Amphibians are also affected by NNIs, as shown in a study by Fonseca-Peña et al. (2022) in which tadpoles of three species (*Rhinella arenarum*, *Rhinella fernandezae*, and *Scinax granulatus*) were exposed to IMI and THIAM. The LC_{50} was calculated for all three species at different development stages and was found to range between 11.28 and >71.2 mg L^{-1} for both NNIs. The tests showed that exposure to THIAM at the lowest concentration (80 mg L^{-1}) caused a lower metamorphic success rate in tadpoles of *Rhinella arenarum*, as well as a smaller size. These results revealed the effects of THIAM on the metamorphosis of amphibians, thus affecting their survival [90]. Another study, carried out by Shinya et al. (2023), exposed *Silurana tropicalis* frogs to CLO in water to determine the distribution of NNIs in this species. The results showed that after 24 h, the pollutant was detected in the skin and intestines at a concentration of 0.25 mg kg^{-1} and 0.15 mg kg^{-1}, respectively, after exposure to the highest concentrations (0.5 mg kg^{-1}), indicating the absorption of CLO. Additionally, the results of the brain analysis showed a decrease in the level of serotonin when exposed to the highest concentrations, suggesting a negative effect on brain functions [91].

Fish are also among the non-target species affected by NNIs. Multiple studies have documented alterations in the behavior of two particular species: The freshwater fish Rohu *Labeo rohita* (Cypriniformes: Cyprinidae) showed changes in their swimming patterns, both fast and slow in various directions, when exposed to IMI at a concentration of 120 mg L^{-1}, and the determined value of LC_{50} over a period of 96 h was 550 mg L^{-1} [125]. Similarly, the Nile tilapia *Oreochromis niloticus* (Percomorphi: Cichlidae) displayed changes, presenting discoloration after exposure to a concentration of 120 mg L^{-1}, while a state of lethargy started at a concentration of 140 mg L^{-1}. The value of LC_{50} over a period of 96 h was 183 mg L^{-1} [126]. El-Garawani et al. (2022) examined the effects of ACE and IMI in *O. niloticus* juveniles when exposed to 1/10 of the LC_{50} value, which was 195,810 mg kg^{-1} at 96 h for ACE and 150,760 mg kg^{-1} at 72 h for IMI. Both ACE and IMI caused a significant increase in erythrocytic micronucleus by 2.2- and 10-folds, respectively. There were also nuclear abnormalities, as well as histopathological changes in the gills, liver, and muscles, with greater severity in the ones exposed to IMI [89].

Another species affected by NNIs is *Gambusia affinis* (Cyprinodontiformes: Poeciliidae). In recent studies, the chronic effect of commercial THIAM on adult females of this species during the reproductive period was investigated. These individuals were exposed to the pollutant at concentrations of 10, 20, and 40 mg L^{-1} for a period of 28 d. The results showed that the compound significantly affected the condition of the individuals after 21 d of exposure, causing oxidative stress in their body tissues, as well as affecting the reproductive cycles [127].

In the previous sections, studies aiming to determine the concentrations of NNIs in bodies of water are presented, in which concentrations in the magnitude of ng L^{-1} have been found. The majority of the acute and chronic exposure tests described earlier were conducted over short periods of time. In these studies, concentrations in the range of mg L^{-1} were used to observe the effect on individuals over a short period and with greater intensity in order to determine the possible chronic effects that aquatic organisms may

present. Further studies focusing on the long-term effects that aquatic organisms may present are needed to approach reality more closely and reach an accurate conclusion regarding the effects of NNIs on the environment.

3.4. Effect on Soil

As mentioned earlier in this review, NNIs are a subject of interest due to their use in different types of crops as seed coatings or sprays, so they can be found in different geochemical fractions of the soil [128].

ACE is an insecticide of interest because it has been classified by the EFSA (European Food Safety Authority) as a category 2 carcinogen (a substance that has been shown to be capable of inducing mutations in human germ cells). It is a chemical that has been found in various crops and/or agricultural products [129]. In the case of *Pisum sativum* (Fabaceae) in the Food Code issued by the Food and Agriculture Organization of the United Nations (FAO) and the European National Commission (EU), the value reported as residue in the soil is minimal compared to the maximum permissible limits of both associations (0.3 mg kg^{-1} and 0.6 mg kg^{-1}); thus, ACE does not represent a risk to the products obtained from this crop. For *Capsicum annuum* var. *Jalapeño* (Solanaceae), the value reported in México is in compliance with the maximum permissible limits of both associations (the FAO limit is 2 mg kg^{-1} and the EU limit is 0.3 mg kg^{-1}), as is the case for *Solanum lycopersicum* (Solanaceae) in China (0.5 mg kg^{-1} for the EU limit). However, the value is close to the maximum permissible limit for *Malus pumila* Mill. Gala (Rosaceae) in China (FAO limit of 0.7 mg kg^{-1} and EU limit of 0.8 mg kg^{-1}), and it is recorded that the residual ACE in the soil of *Brassica oleracea* var. *cabitata* (Brassicaceae) exceeds by more than double the maximum permissible limits in both legislations for this vegetable. The value recorded for *Chrysanthemums morifolium* (Brassicaceae) cultivated in the region of Hyanshan, China, is 13.73 mg kg^{-1}, which exceeds the limit set by the European Union (3 mg kg^{-1}) by almost five times [20,130–136].

CLO plays an important role in vector control for malaria prevention in several African countries, although the FAO has reported that it is a non-bio-accumulative pesticide [137]. As shown in Table 5, most of the samples exceed the maximum permitted levels set by the EU and, in some cases, by the FAO for the use of this NNI in soil and agricultural products, such as *P. sativum* soil (EU limit of 0.01 mg kg^{-1}), *Musa paradisiaca* (Musaceae) soil (EU limit of 0.01 mg kg^{-1} and FAO limit of 0.01 mg kg^{-1}), *Oryza sativa* (Poaceae) crop (EU limit of 0.01 mg kg^{-1} and FAO limit of 0.05 mg kg^{-1}), and *Zea mays* (Poaceae) subsoil (EU limit of 0.01 mg kg^{-1} and FAO limit of 0.02 mg kg^{-1}); even *C. morifolium* crop soil exceeds the limit (0.02 mg kg^{-1}). Thus, the only crop that falls within the international standards is *Saccharum officinarum* (Poaceae) (EU limit of 0.01 mg kg^{-1}). It could be important to review the ecological conditions that have meant that CLO has not represented a danger to the human population until now [132,133,138–142].

IMI is the most widely used NNI. This insecticide has been restricted by the EU as a seed treatment for *Z. mays*, *Helianthus annuus* (Asteraceae), and Brassica vegetables. In previous reports regarding different soils or agricultural products, a value of 39.56 mg kg^{-1} has been reported for *P. sativum* in the Philippines, which exceeds both international standards by almost twenty times (maximum limit of 2 mg kg^{-1} for both the FAO and EU). In the same country (Philippines), the minimum value reported for *O. sativa* exceeds the EU limit (0.001 mg kg^{-1}) by almost thirteen times, and for *M. paradisiaca*, the value is 1.048 mg kg^{-1} (versus the maximum limit of 0.05 mg kg^{-1} set by the FAO and 0.001 mg kg^{-1} by the EU), which is just over a thousand times the limit set by the EU. By far the highest value reported is for *Z. mays* in Mongolia, at 2897.5 mg kg^{-1} (versus the FAO limit of 0.02 mg kg^{-1} and EU limit of 0.01 mg kg^{-1}), which, if we take the EU standard as a reference, exceeds the limit by almost three hundred thousand times; however, these standards do not apply directly to soil, and further studies are required. The minimum value reported for *C. morifolium* also exceeds the international standard (limit of 0.05 mg kg^{-1} set by the EU) by twenty times, and those reported for *C. annuum* var. *Jalapeño* (FAO limit of 1 mg kg^{-1} and EU limit

of 0.09 mg kg^{-1}) and *M. pumila* Mill. Gala (EU limit of 0.01 mg kg^{-1} by EU) exceeds the EU standard by fifty times. The only value that does not exceed the international standard is that reported for *B. oleracea* var. *Italica* in Mexico, with a value lower than the limit of 0.01 mg kg^{-1} set by the EU [20,132,133,135,137,142–145].

In the case of THIAM, the limits set by the international standards are not exceeded in soils cultivated with *P. sativum* (FAO limit of 0.3 mg kg^{-1} and EU limit of 0.01 mg kg^{-1}), *B. oleracea* var. Italics (FAO limit of 5 mg kg^{-1} and EU limit of 0.01 mg kg^{-1}), and *S. lycopersicum* (EU limit of 0.01 mg kg^{-1}); thus, despite contamination by other NNIs, the residue of THIAM is minimal. For the particular case of *O. sativa*, the value exceeds the EU regulation by five times (limit of 0.01 mg kg^{-1}) but not that of the FAO (limit of 3 mg kg^{-1}). The same is true of *C. annuum* var. *Jalapeño*, since its value exceeds the limit set by the EU (0.01 mg kg^{-1}) by about 90 times but not that of the FAO (7 mg kg^{-1}), although the value refers to residues in soil and is not specific to grain analysis. In *C. morifolium* cultivation soil, the value reported exceeds the maximum limit allowed by the EU (0.05 mg kg^{-1}) by almost nine times. In the case of *M. pumila* Mill. Gala, the value also exceeds the limit (0.01 mg kg^{-1} EU) by 90 times. In the case of *Z. mays* in Mongolia, the reported value exceeds its limits (FAO limit of 0.05 mg kg^{-1} and EU limit of 0.01 mg kg^{-1}) by more than 1000 times. In the same way, the highest reported value for *M. paradisiaca* in the Philippines is 30,000 times the limits permitted by the international standards (FAO limit of 0.02 mg kg^{-1} and EU limit of 0.01 mg kg^{-1}); even though the values are reported in soil in the last two cases, it remains possible that the consumption of these foods is risky because the concentrations of THIAM in them are unknown [20,132,133,135,137,142,145–147].

Some cases of THIAC in soils where *Solanum melongena* var. *China* is cultivated have been reported; however, its value does not exceed the limits set by regulations (EU limit of 0.7 mg kg^{-1}). For the case of *C. annuum* var. *Jalapeño*, the FAO permits a higher value, as shown in Table 5 (1 mg kg^{-1}), while the EU limit is 100 times lower (0.01 mg kg^{-1}). Likewise, for sub-surface soil of *Z. mays*, the reported value exceeds the permitted value (0.01 mg kg^{-1}) [148–152].

In the case of DIN, the reported values were compared with only the EU limits for *O. sativa* (8 mg kg^{-1}), *M. pumila* Mill. Gala (0.8 mg kg^{-1}), *Lactuca sativa* (Asteraceae) (4 mg kg^{-1}), *Apium graveolens* (Umbelliferae) (0.6 mg kg^{-1}), and *S. lycopersicum* (4 mg kg^{-1}); in no case did the reported value exceed the institution's permitted limit. The value reported in China for *Actinidia deliciosa* (Actinidiaceae) was due to artificial contamination with other NNIs applied in soil. For NIT, there is no regulation issued by either institution; however, since this is a specific type of pesticide and it may induce global contamination, bioaccumulation, and subsequent damage to health, it is important to mention this pesticide, which remains a precedented case for future research [62,151–154]. Table 5 shows the different levels of NNIs reported in several types of crops or agricultural products.

Table 5. Neonicotinoids in soils or products.

Neonicotinoid	Mean Concentration (mg kg^{-1})	Agricultural Soil or Product	Insolation Country	Reference
Acetamiprid	0.000002	Soil of *Pisum sativum* (Fabaceae)	Luzon, Philippines	[132]
	1.00–13.73	Leaves of *Chrysanthemums morifolium* (Asteraceae)	Huangshan, China	[133]
	17.43	Soil of *Brassica oleracea* var. *cabitata* (Brassicaceae)	Karbala, Iraq	[134]
	0.059	*Capsicum annuum* var. *Jalapeño* (Solanaceae)	Sinaloa, Mexico	[135]

Table 5. *Cont.*

Neonicotinoid	Mean Concentration (mg kg^{-1})	Agricultural Soil or Product	Insolation Country	Reference
Acetamiprid	0.000414	*Solanum lycopersicum* (Solanaceae)	Tianjin, China	[136]
	0.585	*Malus pumila* Mill. Gala (Rosaceae)	Jiangsu, China	[20]
	0.000000414	Soil of Parks	Beijing, China	[20]
Clothianidin	0.022–0.236	Soil of *Pisum sativum* (Fabaceae)	Luzon, Philippines	[132]
	1.430–126.31	Soil of *Musa paradisiaca*. (Musaceae)	Mindanao, Philippines	[132]
	1.73	*Chrysanthemum morifolium* growing soil (Asteráceas)	Huangshan, China	[133]
	0.00000016	Soil of Parks	Beijing, China	[20]
	0.01	Growing of *Saccharum officinarum* (Poaceae)	Guangxi, China	[142]
	0.09	Growing of *Oryza sativa* (Poaceae)	Inner, Mongolia	[141]
	2.7	Sub-surface soil of *Zea mays* (Poaceae)	Zongganqu, Mongolia	[142]
Imidacloprid	0.758–39.56	Soil of *Pisum sativum* (Fabaceae)	Luzon, Philippines	[132]
	0.013–0.028	Soil of *Oryza sativa* (Poaceae)	Marinduque, Philippines	[132]
	1.048–903.31	Soil of *Musa paradisiaca*. (Musaceae)	Mindanao, Philippines	[132]
	0.99–8.64	*Chrysanthemum morifolium* growing soil (Asteraceae)	Huangshan, China	[133]
	0.847	*Malus pumila* Mill. Gala (Rosaceae)	Jiangsu, China	[20]
	0.00952	Soil of Parks	Beijing, China	[20]
	2897.5	Sub-surface soil of *Zea mays* (Gramíneas)	Zongganqu, Mongolia	[142]
	4.509	*Capsicum annuum* var. *Jalapeño* (Solanaceae)	Sinaloa, Mexico	[135]
	0.0087	*Brassica oleracea* var. *Itálica* (Brassicaceae)	Puebla and Guanajuato, Mexico	[145]
Thiamethoxam	0.005–0.050	Soil of *Pisum sativum* (Fabaceae)	Luzon, Philippines	[140]
	0.05–0.011	Soil of *Oryza sativa* (Poaceae)	Marinduque, Philippines	[140]
	0.278–267.87	Soil of *Musa paradisiaca* (Musaceae)	Mindanao, Philippines	[140]
	0.18–0.43	*Chrysanthemum morifolium* growing soil (Asteraceae)	Huangshan, China	[133]
	0.890	*Malus pumila* Mill. Gala (Rosaceae)	Jiangsu, China	[20]
	0.00000058	Soil of Parks	Beijing, China	[137]
	62.4	Sub-surface soil of *Zea mays* (Poaceae)	Zongganqu, Mongolia	[142]
	0.896	*Capsicum annuum* var. *Jalapeño* (Solanaceae)	Sinaloa, Mexico	[135]
	0.0045	*Brassica oleracea* var. *Itálica* (Brassicaceae)	Puebla and Guanajuato, Mexico	[145]
	0.00401	*Solanum lycopersicum* (Solanaceae)	Tianjin, China	[147]

Table 5. *Cont.*

Neonicotinoid	Mean Concentration (mg kg^{-1})	Agricultural Soil or Product	Insolation Country	Reference
Thiacloprid	3988.7	*Zea mays* (Poaceae)	Zongganqu, Mongolia	[142]
	0.059	*Capsicum annuum* var. *Jalapeño* (Solanaceae)	Sinaloa, Mexico	[135]
	0.01	*Solanum melongena* var. *China* (Solanaceae)	La Vega, República Dominicana	[150]
Dinotefuran	0.01	*Oryza sativa* (Poaceae)	Tamil Nadu, India	[152]
	0.384	*Malus pumila* Mill. Gala (Rosaceae)	Jiangsu, China	[20]
	0.300	*Lactuca sativa* (Asteráceas)	Pyeongtaek, Korea	[62]
	0.580	*Apium graveolens* (Apiaceae)	Pyeongtaek, Korea	[62]
	0.00000027	Soil of Parks	Beijing, China	[138]
	0.00502	*Solanum lycopersicum* (Solanaceae)	Tianjin, China	[147]
Nitenpyram *	0.01–0.54	*Actinidia deliciosa* (Actinidiaceae)	Sichuan, China	[153]
	0.01–0.45	*Actinidia deliciosa* (Actinidiaceae)	Zhejiang, China	[153]
	0.01–033	*Actinidia deliciosa* (Actinidiaceae)	Jiangsu, China	[153]

* This work used artificial pollution.

From Table 5, it can be seen that the most worrying values are presented for the use of IMI in Mongolia on *Z. mays*, which is not surprising, since it is the most used NNI worldwide. However, as this analysis was carried out in soil, it is necessary to carry out more studies to know if the use of this insecticide is harmful for consumers. The establishment of the soil values in Table 5 provides us a view of the situation in Mexico, since one of the two values reported exceeds the limits permitted by the EU and FAO [135,142,145,155].

3.5. Negative Effects on Terrestrial Organisms and Insect Pollinators

Reptiles also display negative effects from exposure to neonicotinoids. Studies have examined how their endocrine system is impacted and how this affects their growth and development. A study was carried out on the lizard species *Eremias argus* (Squamata: Lacertidae) by subjecting them to continuous exposure to NNIs for 28 d at a dose of 20 mg kg^{-1}, and the observed effects included inadequate thyroid function and alterations in the endocrine system [156].

Birds can be used as subjects to assess the presence of NNIs as they inhabit various spheres and feed at different trophic levels; coated seeds, contaminated prey, and polluted water can be ingested by these animals. Additionally, preening their feathers may result in contamination if NNIs have been deposited. The concentrations of five NNIs (IMI, THIAC, CLO, THIAM, and ACE) were evaluated in two species: the barn owl, *Tyto alba* (Strigiformes: Tytonidae), and the Alpine swift, *Tachymarptis melba* (Apodiformes: Apodidae). NNIs were quantified in the feathers of nestlings and adults in the case of the barn owl over two time periods in 2012 and 2016. In the Alpine swift, NNIs were quantified in nestlings' feathers, adult plasma samples, and food samples over a period of ten years. It was found that in the Barn owl, 69% of nestling feathers and 56.9% of adult feathers contained at least one detectable NNI. The total concentrations of NNIs were 0.00066 mg kg^{-1} in nestlings and 0.00017 mg kg^{-1} in adults. As for the Alpine swift, NNIs were detected in 75% of food samples and 20% of plasma samples, with concentrations of 0.00024 mg kg^{-1} and 0.00006 mg kg^{-1}, respectively [157].

Humann-Guilleminot et al. (2023) studied CLO deposition in *Passer domesticus* (Passeriformes: Passeridae) feathers and blood after being fed with organic seeds treated with CLO at a concentration of 0.25 mg kg^{-1} each day. Samples were taken before and after exposure. All bird samples contained CLO, showing that the ingested CLO transited through plasma

and was deposited into newly grown feathers, thus suggesting a possible use of feathers as a biomonitor of exposure [88].

Hsiao et al. conducted a study in 2019 examining the effects of prolonged IMI treatment on the echolocation system of bats. This intricate system enables bats to navigate through intricate environments and detect objects even in complete darkness. Their study revealed that bats exposed to IMI insecticide at a concentration of 20 mg kg^{-1} exhibited signs of disorientation and displayed erratic flight patterns. Furthermore, exposure to IMI correlated with a significant increase in neural apoptosis within the hippocampal CA1 region and the medial entorhinal cortex of bats [158].

Fetal and lactational exposure to CLO in male mice, even at a no-observed-adverse-effect level (NOAEL) of 65.1 mg kg^{-1} day^{-1}, may inhibit neurogenesis and cause different behavioral abnormalities at different developmental stages. The findings indicate that during the juvenile period, CLO suppresses neurogenesis, interferes with signaling pathways, and heightens anxiety-like behaviors. Moreover, in adulthood, it leads to increased locomotor activity [159].

Pollinators have also been affected by NNIs, with adverse effects being observed in their populations after exposure to these pesticides in the environment. According to the EPA, NNIs are classified among the most toxic chemicals to bees. In a study conducted using a non-honeybee species, *Osmia lignaria* (Hymenoptera: Megachilidae), known as mason bee, contact toxicity tests were performed over 96 h using three different NNIs (IMI, CLO, and THIAM). It was observed that this pollinator species was highly sensitive to these insecticides. The LD_{50} values ranged from 5.51 to 32.86 ng bee^{-1}, with slight variations between females and males. For CLO, the LD_{50} was 4.9 ng bee^{-1} for females and 2.9 ng bee^{-1} for males. In the case of THIAM, the LD_{50} was 9.7 ng bee^{-1} for females and 5.1 ng bee^{-1} for males. Finally, for IMI, the LD_{50} value was 25.5 ng bee^{-1} for females and 26.4 ng bee^{-1} for males [160].

Bumblebees are another species of significant value as pollinators. Recent studies have examined the relationship between the presence of NNIs in the environment and their metabolism under conditions of nutritional stress. The worker species *Bombus impatiens* (Hymenoptera: Apidae) was exposed to an IMI concentration of 5 µg L^{-1} under acute and chronic exposures, combined with nutritional stress of food deprivation, over periods of 24 h and 7 d. Greater stress was observed in this species when IMI exposure was combined with food deprivation, showing that NNIs can affect the carbon mechanisms of bumblebees [161].

The honeybee *Apis mellifera* (Hymenoptera: Apidae) plays an important role in food production and pollination systems. The effect of the brain lipidome in adult bees after their exposure to CLO was evaluated to examine the impact on their neurological system, gene expression, and self-grooming behavior. The exposure lasted for 7 d with sublethal oral doses of CLO ranging from 0 to 0.035 ng L^{-1}, based on real concentrations found in the environment. Neuropathology was observed in the honeybees, which was associated with a reduction in self-grooming behavior, making them more prone to parasites and affecting their social behavior [162].

One of the species that shows negative effects from NNIs and has been widely studied is the honeybee *A. mellifera*. Behavioral and genetic expression dysfunctions have been observed in these bees. In one study, 2-day-old bee larvae were fed with sugar water containing ACE at concentrations ranging from 0 to 25 mg L^{-1} to analyze the effects of this NNI on their metabolism. It was observed that at concentrations of 5 mg L^{-1}, the metabolism of the larvae was negatively affected, hindering their proper development [163]. Table 6 show a summary of different species and their reported LD_{50} and LC_{50}.

Table 6. Summary of some species and their reported LD_{50} and LC_{50} values.

Organism	Neonicotinoid	LC_{50}	LD_{50}	Reference
Rattus norvegicus (Rodentia: Muridae)	IMI ACE THIAC	No data No data No data	Oral 450 mg kg^{-1} Oral 182 mg kg^{-1} Oral 640 mg kg^{-1}	[164]
Mus musculus (Rodentia: Muridae)	IMI DIN	No data No data	130–170 mg kg^{-1} >2000 mg kg^{-1}	[165]
Lepomis macrochirus (Perciformes: Centrarchidae)	IMI CLO	No data No data	241 mg L^{-1} >93.6 mg L^{-1}	[166]
Osmia lignaria (Hymenoptera: Megachilidae)	IMI, CLO, and THIAM	No data	5.51 to 32.86 ng bee^{-1}	[160]
Rhinella arenarum (Anura: Bufonidae)	IMI and THIAM	11.28 and >71.2 mg L^{-1}	No data	[90]
Labeo rohita (Cypriniformes: Cyprinidae)	IMI	550 mg L^{-1}	No data	[125]
Apis mellifera (Hymenoptera: Apidae)	IMI	No data	118.74 ng bee^{-1}	[167]
Perdix perdix (Galliformes: Phasianidae)	IMI CLO	283 mg kg^{-1} >752 mg kg^{-1}	15–41 mg kg^{-1} 430 mg kg^{-1}	[166]

4. Some Effects on Humans

To be able to deduce the possible effects that NINs could have on humans, tests are conducted on organisms that are sensitive to small changes in their environment and the widespread damage that can occur in the organisms' internal systems. The neurotoxic impacts of NNIs seem to vary across different brain regions, with the hippocampus being particularly susceptible. Upon exposure, mammals exhibit irregularities in motor functions, mood regulation, anxiety levels, and social behavior, along with significant deficits in cognitive abilities such as orientation, learning, and memory. These disturbances pose a significant threat to mammalian survival and human health [168].

While studies on the direct effects of NNIs on humans are limited, some evidence about their impact on human health through indirect exposure has been documented. One of the main routes of human exposure is through food ingestion. These compounds can remain in treated fruits, vegetables, and other products, raising concerns about food safety and the ingestion of pesticide residues. Prolonged exposure to ACE can result in the sustained activation of certain nAChRs possessing high permeability to Ca^{+2} ions. Elevated levels of Ca^{+2} can trigger or inhibit various intracellular signaling pathways within neurons and glial cells, inducing changes in neurotransmission, oxidative stress, or inflammation, thereby exacerbating neurotoxic conditions within the cells and provoking the activation of diverse apoptotic pathways that culminates in neuronal cell death [169].

Although residue levels in foods are generally considered low and within safe limits established by regulatory agencies, there is concern about chronic exposure to low levels of NNIs and their potential long-term effects on human health [170]. In this sense, a study carried out in 2022 shed light on the prevalence of neonicotinoids in honey, a topic of growing concern in the scientific community. In this study, 57 honey samples from different regions of China and 37 from other Asian countries were analyzed, and NNIs or their metabolites were detected in 97.9% of the samples. ACE, THIAM, and IMI emerged as the main neonicotinoids detected in honey, with respective detection frequencies of 92.6%, 90.4%, and 73.4% [171].

Ponce-Vejar et al. conducted a study to detect the concentration of neonicotinoids in honey from bee colonies located in different regions of Jalisco, Mexico, that differed in their type of agriculture. Fourteen pesticides in variable concentrations were detected in 63% of the samples analyzed. Neonicotinoids were the most frequent insecticides and were

found in higher concentrations in honey. The number, frequency, and concentration of pesticides were higher in samples collected from hives located in areas where intensive and highly technical agriculture is practiced. Furthermore, 87.5% of those samples had concentrations of IMI that exceeded the sublethal doses for bees (>0.00025 mg kg^{-1}) but are not considered dangerous for human health according to the European Commission. The results suggest that honey can be used as a bioindicator of environmental contamination by pesticides, highlighting the need to continue monitoring contaminants in this product to determine the risks of pesticide impacts on the health of pollinators and ecosystems and possible implications for human health [172].

Despite the initial belief in the low toxicity of neonicotinoids to mammals, recent evidence suggests a variety of adverse effects in animals and humans, such as neurotoxicity, immunotoxicity, and organ damage [173]. Agonistic activity and binding affinity to α4β2 acetylcholine receptors in vertebrates correlate with their toxicity [174]. Chronic exposure to neonicotinoids can increase the levels of these receptors without affecting the sensitivity of the binding site. Furthermore, nicotinic acetylcholine receptor dysfunction is related to various diseases [175]. Activation of α7 receptors during development can result in neuronal death.

In addition, neonicotinoids are agents that damage the CNS as they have been shown to be neurotoxic and affect neuronal transmission by acting as agonists of nAChRs, thereby interfering with the normal function of these receptors in the brain's central and peripheral nervous systems. By binding to postsynaptic nAChRs, neonicotinoids trigger continuous stimulation of these receptors, causing an exacerbated release of neurotransmitters, such as dopamine, serotonin, glutamate, and GABA. This neuronal overstimulation results in symptoms of neurotoxicity [174].

In vitro studies have shown that exposure to the neonicotinoid pesticide CLO in the human neuroblastoma cell line SH-SY5Y at a concentration of 249.67 mg L^{-1} significantly increased cell growth and neurite outgrowth and downregulated the genes involved in neuronal function and morphology, providing information on potential risks to the human nervous system and suggesting potential effects on human neuronal function and development [176]. The same concentration of ACE and IMI was used to explore the mechanisms of toxicity in a human embryonic stem cell-based differentiation model that simulates early embryonic development. Transcriptomic analysis revealed significant NNI-induced alterations in the expression of numerous genes, disruption of approximately 100 biological processes, and modulation of two signaling pathways. In particular, the BMP4 signaling pathway emerged as critical in the perturbations induced by these pollutants, which could influence early embryonic development. Treatment with an S9 fraction of human liver, which mimics hepatic metabolism, showed promise in mitigating the toxic effects of these pollutants [177].

Preclinical studies have been conducted to identify adverse effects on human health using a mouse model exposed to NNIs. Some studies have demonstrated the neurotoxicity of NNIs to nAChRs, although the specific mechanism is still a matter of debate [178–180]. It has been observed that exposure to IMI (45 and 90 mg kg^{-1} body weight; oral route) for 28 d can cause a significant decrease in the pain threshold and spontaneous locomotor activity in rats [181]. Rats receiving high doses of THIAM (50 or 100 mg kg^{-1}) for 7 consecutive days showed an increase in anxiety behavior by 8 and 14%, respectively, which could be correlated with a decrease in acetylcholinesterase activity [182].

Renal toxicity has also been observed in in vivo models. In a study conducted by Ozsahin et al., both adult male rats and offspring received daily oral gavage doses of IMI (4 mg kg^{-1} body weight) or CLO (20 mg kg^{-1} body weight) dissolved in distilled water for a period of 90 days. The results revealed an increase in the levels of fatty acids, cholesterol, and vitamins in kidney tissues in both young individuals and adult males [183].

Growing concern about the effects of neonicotinoids on public health has driven the need to evaluate population exposure to these insecticides. In a study carried out by Nimako et al. (2021), the presence of NNIs in the non-farmer population of Ghana was

evaluated by analyzing urine samples from 75 healthy volunteers. The results revealed the presence of seven NNIs and three of their metabolites, with a median concentration of 0.00015 mg L^{-1} for N-dm-acetamiprid IMI, 0.00045 mg L^{-1} for CLO, 0.00014 mg L^{-1} for NIT, 0.00021 mg L^{-1} for THIAM, 0.00101 mg L^{-1} for DIN, 0.00008 mg L^{-1} for ACE, and 0.00014 mg L^{-1} for THIAC, all identified with detectable levels in the majority of the samples. Of particular concern is that approximately 92% of the participants were simultaneously exposed to multiple NNIs, suggesting widespread exposure in the population. Additionally, significant differences were observed in estimated daily intakes between men and women, with the medians ranging between 0.47 and 1.27 μg kg^{-1} day^{-1} for women, and between 0.66 and 0.91 μg kg^{-1} day^{-1} for men [173].

Another study evaluated exposure to NNIs in a representative sample of the US population. The findings revealed that approximately 49.1% of the general US population, between ages from 3 to 11 years, showed detectable concentrations of at least one of the six NNIs biomarkers analyzed. Furthermore, the weighted detection frequencies were observed to be 35% for N-desmethyl-ACE, 19.7% for 5-hydroxy-imidacloprid, 7.7% for CLO, 4.3% for IMI, and less than 0.5% for ACE and THIAM. These results suggest widespread exposure to NNIs in the US population. Furthermore, children aged 3–5 years who fasted less than 8 h were found to be more likely to have N-desmethyl-ACE concentrations above the 95th percentile than adolescents and adults. Additionally, people of Asian descent were more likely than non-Asian individuals to have concentrations of N-desmethyl-acetamiprid and 5-hydroxy-imidacloprid above the 95th percentile [183]. However, more studies are required to understand the sources of exposure to NNIs in this population.

It has been observed that the mechanism of action of NNIs at the cellular level is to induce oxidative stress, which can result in damage to cellular macromolecules such as DNA, lipids, and proteins. This oxidative stress can cause cell death through apoptotic or necrotic mechanisms, with the consequent possibility of DNA damage, increased lipid peroxidation, and protein damage [173]. For example, lipid peroxidation, as measured by changes in the levels of malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARSs), increases significantly with exposure to NNIs. Increases in MDA levels in liver and plasma tissues have been observed in rats exposed to IMI, suggesting oxidative damage to the liver. Furthermore, oral administration of IMI to male mice significantly increases MDA levels [184]. IMI exposure has also been associated with an increase in lipid peroxidation in the ovaries of female rats and testes and kidneys of male rats, as well as a significant increase in TBARSs in the kidneys of male rats [185]. Other studies have shown that exposure to other neonicotinoids, such as NIT and THIAM, can also increase lipid peroxidation.

Additionally, neonicotinoids can cause DNA damage, as demonstrated by studies showing an increase in micronucleus frequency and comet score in human lymphocytes and in germ cell DNA in the testes of rats exposed to neonicotinoids [173]. Although less researched, NNIs can also cause protein damage, as indicated by studies showing the formation of protein peroxidation products in freshwater mussels exposed to ACE [173]. These findings highlight the importance of neonicotinoid-mediated oxidative stress and its potential health effects.

5. Conclusions

Since the introduction of the first neonicotinoid insecticide, ACE, to the agricultural market in the 1980s, six other NNIs have been developed and used mainly via spraying on a wide variety of crops belonging to the families of Vitaceae, Solanaceae, Malvaceae, Rosaceae, Poaceae, and Fabaceae, among others, and as an efficient control method for insects of the order Hemiptera (Aphididae, Triozidae, Aleyrodidae, Delphacidae, Miridae, Psyllidae, etc.), Tizanoptera (Thripidae), Coleoptera (Chrysomelidae and Nitidulidae), Isoptera (Termitidae), and Siphonaptera (Pulicidae).

The extensive use of NNIs in agriculture has revolutionized pest control, providing long-lasting systemic protection. From the first-generation IMI to the third-generation DIN, each NNI offers specific advantages in targeting pests, contributing to their popularity globally.

Due to their convenient use, NNIs have been widely used throughout the market. However, recent studies have affirmed that exposure to their compounds generates a variety of adverse effects. It is essential to conduct more studies in target and non-target organisms to understand each of the complications that NNIs bring with them and continue research into alternative pest management strategies for sustainable agricultural practices. Furthermore, through such studies, authorities can reach conclusions regarding more rigorous restrictions.

Studies have shown the presence of NNIs in honey and other foods, raising questions about chronic exposure at low levels. Research has demonstrated the neurotoxicity of NNI and their potential to cause neurodevelopmental problems, as well as kidney toxicity and oxidative stress, which can lead to DNA and protein damage. As such, stricter standards must be applied within global and national regulations where the application of these pesticides is common, and regulatory agencies must verify compliance.

The widespread detection of NNI in human biological samples underscores the need for continued surveillance and research to fully understand their long-term health implications and mitigate potential risks to human health. As a perspective, consideration should be given to banning the use of NINIS once there is scientific support for humans and the environment, but for the time being, the best approach for the agricultural sector is to continue research into alternative pest management strategies for sustainable agricultural practices.

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