Exposure Level of Neonicotinoid Insecticides in the Food Chain and the Evaluation of Their Human Health Impact and Environmental Risk: An Overview

Yuanyuan Zhao [1], Jiawen Yang [1], Jinbo Ren [2], Yilin Hou [1] , Zhenzhen Han [1], Jiapeng Xiao [1] and Yu Li [1,*]

[1] MOE Key Laboratory of Resources and Environmental System Optimization, North China Electric Power University, Beijing 102206, China; zyy0210@ncepu.edu.cn (Y.Z.); 1182102075@ncepu.edu.cn (J.Y.); 1182229053@ncepu.edu.cn (Y.H.); 120192232411@ncepu.edu.cn (Z.H.); 120192232431@ncepu.edu.cn (J.X.)

[2] Jilin Branch of China Kunlun Contracting Engineering Corporation, No. 888 Binjiangxi Road, Jilin 132013, China; rjb0124-jl@cnpc.com.cn

* Correspondence: liyuxx@ncepu.edu.cn; Tel.: +86-10-6177-2836

check for updates

Abstract: Neonicotinoid insecticides (neonics) were the most rapidly growing class of insecticides over the past few decades, and are used mainly for vegetables, fruits, and grains. Although neonics exhibit lower toxicity in mammals and humans compared to traditional insecticides, increasing numbers of studies are demonstrating that neonics may accumulate in the food chain and environmental media. Long-term exposure to neonics may raise potential risks to animals and even to humans. The present report reviews the development, application, and prohibition of neonics in the farmland ecosystem, and summarizes the exposure level and harmful effects of these insecticides in the food chain. In addition, the present review analyzes and summarizes the evaluation of the human health impact and environmental risk of the neonics, and overviews the unresolved problems and future research directions in this field. The aim of the present report was to review the exposure level, potential toxicity, human health impact, and environmental risk assessment of neonics in various media in order to provide reliable technical support for strengthening the environmental and food safety supervision and green pesticide designing.

1. Introduction

Neonicotinoid insecticides (neonics) are a novel class of insecticides that act selectively on the nicotinic acetylcholine receptors (nAChRs) in the central nervous system of insects [1]. Since the introduction of the first neonic, named imidacloprid, by the Bayer Corporation in the 1980s, seven major neonics have reached markets worldwide: imidacloprid, thiacloprid, clothianidin, thiamethoxam, acetamiprid, nitenpyram, and dinotefuran [2]. Representing the fourth kind of insecticide, neonics are gradually replacing several conventional insecticides currently in the market, such as the chlorinated hydrocarbons, organophosphorus insecticides, carbamates, and synthetic pyrethroids; owing to their advantages, such as low dosage requirements, rapid effects, and high activity, the neonics have become widely used insecticides throughout the world [3].

Neonics are commonly used for foliage spraying in field systems and for soil and seed treatment during crop planting to protect seedlings from early-season root and leaf pests [4]. Neonics have been registered in 120 countries and are used for over 140 crops, such as rice, wheat, corn, cotton, peanut, and soybean. In addition, neonics exert good control of sucking pests in the atmosphere, e.g., aphids and

leaf-hoppers, and pests in the soil, such as grubs, termites, and nematodes [5]. Neonics belong to the group of neuro-active insecticides, which are capable of inducing toxicity by controlling insect behavior and by excessively exciting or paralyzing the insects by blocking the transmission of cholinergic signals [6]. nAChRs, which are the main target of the neonics, are used widely in the control of crop diseases and insect pests. In 2008, Barbara et al. studied radioligand binding of nAChR, and observed that neonics interacted mainly with [3H]-α-bungarotoxin and [3H]-imidacloprid in the nAChR. Meanwhile, the precise binding site interactions, providing implications for understanding the ligand-binding interactions between the nAChRs in insects and neonics, were identified using membranes from the whole body as well as from specific tissues of insects [7]. In 2015, Simon-Delso et al. demonstrated that imidacloprid, the forerunner of neonicotioid insecticides, is a partial agonist of insect nAChRs, while clothianidin and acetamiprid appear to be full agonists using the patch clamp method [8]. In 2018, Taillebois et al. reported a discussion on the number of binding sites between nAChR and neonics, stating that the binding sites of neonics were from radioligand binding on the native tissues. In addition, the authors compared the binding properties of the most commonly used neonics in several insect species, and reported that the neonic–nAChR binding sites were linked to the biological samples used and the insect species under consideration [9].

Although neonics exhibit certain selectivity compared to other insecticides, with the increase in the number of neonics and the gradual expansion of their usage, the adverse effects of neonics on the food chain in the ecosystem are becoming apparent—for example, damage to the leaves of crops, harm to non-target organisms and human health, and pollution of the environment [10]. In 2016, Zhang et al. conducted spinach planting experiments, in which they observed that neonics could cause leaf lesions. Subsequently, the authors conducted a detailed investigation of the impact of neonics on a series of crops, the results of which revealed that soybeans exhibited a continuous reaction and were more sensitive compared to spinach. In addition, the authors observed that the leaf lesions were caused via the production of active oxygen and peroxidation damage, and, more importantly, the leaf lesions could affect the yield of the agricultural products and cause food safety problems [11]. In addition to their influence on crops, neonics are reported to exert certain lethal and sub-lethal effects on non-target organisms, such as bees and earthworms, according to a large number of studies conducted in the field or in the laboratory [12]. Bees are of high economic value as pollinators. In the process of collecting nectar and pollen, bees may be exposed to residual insecticides in the air or on the surface of plants, which may affect their behavior, nutrient metabolism, and immune system [13]. The health of other pollinators in the same niche as bees may also encounter the threat of neonics [14]. Neonics are also detected widely in environmental reservoirs, such as soil and water, due to their high bioaccumulation ability [15]. In 2013, a study conducted by the U.S. Geological Survey revealed that 53% of the surface water was contaminated with at least one neonic, and the residues of neonics were higher compared to the residues of organophosphorus insecticides and carbamates [16]. In 2016, the Ministry of Agriculture and Rural Affairs of the People's Republic of China specified that the maximum residues in food were of neonics (GB 2763-2016). In this context, several regions formulated and issued relevant policies. For instance, in 2013, the European Union (EU) issued relevant prohibitions in regard to the application of clothianidin, imidacloprid, and thiamethoxam to certain crops. Until 2018, the scope of such relevant prohibitions had been expanded further, and the three above-stated neonics have been banned for outdoor use [17]. Through the comparative analysis of the above results, we can see that, although researchers have analyzed the action principle and binding site of neonics, their research results are more in-depth than previous studies. In addition, many scholars have studied the lethal effects of neonics on a variety of non-target organisms and their residues in different media. These results provide more comprehensive and reliable information for the future research of neonics from different perspectives.

Several researchers have evaluated the impact of neonics on the food chain in the ecosystem using samples collected through a combination of in vitro and in vivo methods [18]. However, considering that all previous studies are based on investigations conducted on parts of neonics in

certain areas, the overall research works are relatively scattered and incapable of providing a complete and multi-directional recognition of the impact of neonics on the whole society. Therefore, in the present work, key research results were collected and arranged, and the progress of research on neonics was summarized. First, the development process, the application, and the prohibition of neonics were sorted and analyzed, and then the advantages and disadvantages of each generation of neonics and other insecticides were evaluated. Next, the exposure level and the potential risk of neonics in the whole food chain, including producers and consumers, were analyzed on the basis of the application, scope, and target organisms of neonics. Finally, the detection amount and the potential risks of neonics in various environmental media, such as water, soil, atmosphere, and the human body, were evaluated and summarized. The present report seeks, through an overview, to identify more research perspectives on the insect behavior control caused by neonics.

2. Development and Application of Neonics in Farmland Systems

2.1. History of the Development of Neonics

Neonics originated from the nicotine in plant pesticides, which may be traced back to the 1790s. At that time, tobacco extract was utilized as an insecticide to control pests in fruit trees, rice, and vegetables. In 1828, researchers determined that the effective component of tobacco extract was S-nicotine, following which nicotine was successfully synthesized in 1904 [19]. Since then, researchers have successively optimized the structure of nicotine, and were able to finally develop the first generation of neonics, represented by imidacloprid [20]. The synthesis and biological evaluation of a large number of derivatives led to the exploration of the structure and activity of neonics. In this context, in 1996, Bayer (Germany) and Takeda (Japan) jointly commenced the development of the second generation of neonics, finally presenting these in the market in 2002. This generation of neonics exhibited contact killing, stomach toxicity, and inhalation activity, and demonstrated higher safety, wider insecticidal spectrum, faster action, and longer duration compared to the first generation of neonics [21]. Subsequently, researchers in Japan combined the properties of excellent insecticidal performance and long duration of the previous two generations of neonics, and considering the economy, effectiveness, and safety, commenced research and development of the third generation of neonics, culminating in the development of dinotefuran, which was successfully listed in 2002. As a representative of the third generation of neonics, dinotefuran had chemical structures different from the first and second generations of neonics. In dinotefuran, the characteristic structure, furfuryl, replaces the chloropyridinyl and the chlorothiazolyl of the first and second generations of neonics, respectively, and does not contain halogen. Therefore, the third generation of neonics is also referred to as the "nicotine furan" (although none of the structures are similar to pyridine), and it also exhibits a wider insecticidal spectrum and longer duration, similarly to all neonics [22].

Even after the development of the three afore-stated generations of traditional neonics, the development of neonics continues to progress. The first of the novel neonics, sulfoxaflor, was developed and registered in 2012, 2013, 2015, and 2016 in South Korea, the United States, Canada, the EU, and China, respectively. Sulfoxaflor is used mainly for the control of pests in fruits and vegetables [23]. With the aim of resolving the problem of high toxicity to bees exhibited by certain neonics, the Bayer Corporation launched the second of the novel neonics, flupyradifurone, in 2014. Flupyradifurone is used to control sucking pests of tomatoes, cucumbers, potatoes, peppers, watermelons, and citrus crops [24]. In 2017, researchers in the United States successfully developed a novel type of mesoionic or zwitterion insecticide named triflumezopyrim, which was used mainly to control rice planthoppers, leaf-hoppers, and other highly resistant pests, and exhibited no adverse effects on pollinating insects [25].

The three above-stated novel neonics exhibit good inhaling activity and high toxicity to sucking pests, while their toxicity to mammals, fish, birds, and other non-target organisms is relatively low [26]. Even though the toxic effect of neonics on non-target insects has been recognized and novel neonics to

resolve these problems have been developed, researchers have not yet considered the adverse effects of neonics on other organisms in the ecosystem and the environment, and, as such, the pollution problem caused by neonics has not been resolved so far, which is the limitation and disadvantage of the use of neonics in several regions.

2.2. Application and Prohibition of Neonics in Farmland Systems of Different Regions

Currently, there are four generations of neonics for application in farmland systems in markets in over 120 countries, including the United States, Canada, and other developed countries [25–30]. In China, over 2076 neonics are registered, accounting for 7% of the total number of registered pesticides, among which five neonics are mainly used, with imidacloprid presenting the largest number of registered products, followed by acetamiprid, thiamethoxam, nitenpyram, and thiacloprid. In the United States, over four neonics are registered, including imidacloprid, acetamiprid, thiacloprid, and thiamethoxam, which are used to control pests in agricultural and non-agricultural crops. In Canada, imidacloprid, thiacloprid, thiamethoxam, clothianidin, dinotefuran, acetamiprid, sulfoxaflor, and flonicamid are registered for use. In Australia, the use of neonics such as imidacloprid, acetamiprid, thiacloprid, thiamethoxam, clothianidin, and sulfoxaflor as agrochemicals for food crops is allowed. The EU allows the use of imidacloprid, acetamiprid, thiacloprid, thiamethoxam, clothianidin, and flonicamid for plant protection as the effective components for achieving the objective of pest control [31] (Figure 1).
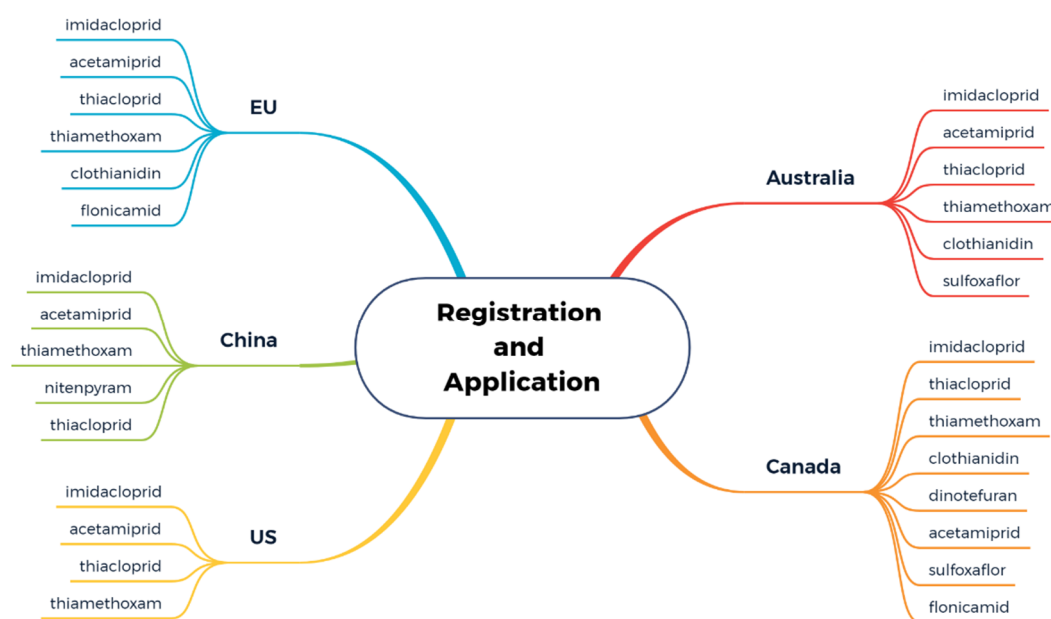

Figure 1. Registration and application of neonics in various countries.

However, with the widespread application of neonics worldwide, these are often detected in foods, wildflowers, and certain crops without even applying pesticides. Studies have demonstrated that neonics may have strong diffusivity and may, therefore, have spread throughout the ecosystem, threatening the safety of several non-target organisms, such as bees [32]. In consideration of the negative impacts of neonics on non-target organisms (particularly on bees) and human health, at the end of April 2018, the EU voted to ban the use of neonics. The ban, which came into force at the end of 2018, included a complete ban on imidacloprid, clothianidin, and thiamethoxam [33]. In September 2018, France became the first country among the EU nations to ban neonics for the protection of bee populations; according to national regulations, five neonics (clothianidin, imidacloprid, thiamethoxam, thiacloprid, and acetamiprid) were banned from sale and use [34]. Subsequently, the pesticide regulatory agencies in the United States, Canada, and other countries expressed their concern regarding

the impact of the existing neonics on pollinators, and stated that a comprehensive risk assessment of these insecticides would continue to be conducted [35].

In view of the above-stated problems, our research group has designed a few green substitutes for neonics in previous studies with the objective of screening out the neonics with multi-directional selective toxicity effects, i.e., to ensure the insecticidal effect while also maintaining low toxicity to non-target organisms, crops, and humans [1,36–38]. However, the current studies have certain limitations, such as that these studies designed neonics only from the perspective of source treatment, and did not provide a way to effectively block the adverse conduction effect of the registered neonics in the food chain or for the treatment of the contaminated soil and other media. It is expected that future studies would deepen the understanding of the transmission of neonics in the food chain, and would fundamentally achieve reasonable prediction and control of the source, process, and end-behavior of these insecticides as well as effective remediation of the contaminated soil.

2.3. Analysis of the Similarities and Differences in Toxicity Mechanisms among Traditional Neonics, Novel Neonics, and Other Insecticides

Since the 1980s, three generations of traditional neonics and three novel neonics have been developed. Comparative studies have revealed that the action mechanism of each generation of neonics is similar—serving as the activator of nAChRs, thereby affecting the central nervous system of insects, causing their death [20]. In addition, no cross-resistance was reported between any of the generations of neonics, although the insecticidal effects and the target pests were different. The first-generation neonics are used mainly to control sucking pests, such as aphids and leaf-hoppers, and exhibit high efficiency and low toxicity. The second-generation neonics are superior to the first generation in terms of activity, safety, and insecticidal spectrum. Owing to their unique structure, the third-generation neonics exhibit excellent performance in terms of high efficiency and harmlessness to crops. In addition, they exhibit a higher insecticidal effect on sanitary pests such as houseflies, cockroaches, and termites [39]. On the other hand, the novel neonics, in addition to the above-stated advantages, exhibit high solubility in water, the reason for their widespread use, as well as high efficacy and functionality for arthropod pests. Therefore, the novel neonics were commercialized and are now gradually replacing the traditional neonics [23].

Neonics are the fourth major group of synthetic insecticides after the organophosphorus insecticides, carbamates, and synthetic pyrethroids. In comparison to traditional organic insecticides, neonics exhibit better environmental safety, lower toxicity to mammals, milder odor, non-irritant quality, lower vapor pressure of the effective components, lower air pollution index, lower toxicity, and lesser impact on aquatic organisms [40]. Besides, owing to their unique mechanism of action, neonics are capable of demonstrating better efficacy in crop treatment compared to conventional highly toxic insecticides; in addition, there is no cross-resistance, which allows effective control of pests that are resistant to the previous generations of insecticides [41]. Although neonics have certain advantages over other insecticides, their widespread use in recent years has made neonics, particularly the ones with broad-spectrum and high residues, a potential factor endangering the ecological security [42].

3. Exposure Level and Potential Hazards of Neonics in the Food Chain

3.1. Exposure Level and Potential Hazards of Neonics in Producers

Owing to the good inhaling ability of neonics, approximately 2–20% may be absorbed by plants and may accumulate in the roots, stems, leaves, flowers, and fruits of the plants [42,43]. It was reported that neonics have been distributed and accumulated widely in the global environment [44], contaminating various environmental substrates, such as drinking water, vegetables, fruits, and even milk [27], and exerting toxic effects on humans and other species [45,46].

In 2012, Hu et al. reported imidacloprid and acetamiprid as the neonics with high detection rates in tea, with concentrations ranging from 10 to 212 µg/kg and 10 to 808 µg/kg, respectively [47],

which was consistent with the neonic detection in tea reported by Liu et al. in 2010 [48], although the enrichment degree in the former study was higher than that in the latter (imidacloprid 2.8–6.3 μg/kg and acetamiprid 0.2–10 μg/kg). These results confirmed the above-stated view that with the increasing use of neonics, their residues in various products are also increasing [16]. In 2014, Chen et al. analyzed the common fruits, vegetables, and honey in the market, and demonstrated that over 90% of the samples had at least one neonic, while over half of the samples contained two or more novel nicotine insecticides [49]. In 2016, Tan et al. reported detecting seven neonics in 49 types of vegetables and 24 types of fruits collected from the Beijing market, with concentrations ranging from 0.01 to 126 ng/g, and with imidacloprid, acetamiprid, and thiamethoxam being the ones with the highest detection rates [50]. In 2017, Wood and Goulson reported that the concentrations of imidacloprid in two rape nectar samples were 52 and 70 ng/mL, respectively, which was more than five times the expected maximum concentration in imidacloprid-treated rape nectar [51]. In 2020, Wintermantel et al. investigated the crops grown in those regions of western France that had banned neonics for five years, and reported detecting three restricted neonics in rape nectar, while imidacloprid was detected in all study years. In particular, in 2014 and 2016, the detection rate of imidacloprid in nectar samples was greater than 60%, with certain samples exhibiting concentrations as high as 70 ng/mL [52]. Furthermore, studies have revealed that wild flowers close to fields were polluted with neonics [52,53], with their concentration distribution exceeding even that of the crops treated with neonics [54].

According to the above-stated survey results, although certain regions, such as China, the EU, and France, have explicitly banned the use of neonics such as imidacloprid and thiamethoxam [55–57], the persistence of neonics in the environment has not allowed complete elimination of the adverse effects of neonics in the ecosystem even after the implementation of the ban [32,58,59]. Neonics may be detected in various products even after several years of cessation of application [60,61]. Therefore, the studies of neonics also have some limitations and disadvantages. It is necessary to explore the transmission process of neonics in the food chain, the area on which future research should focus in order to further understand the mechanism of migration and transformation and to block the adverse transmission.

3.2. Exposure Level and Potential Hazards of Neonics in Primary Consumers

3.2.1. Exposure Level and Potential Hazards of Neonics in Bees

Although neonics are capable of effectively controlling pests in farmland systems, the application of these insecticides may cause harm to beneficial arthropods, including bees [62]. According to a global report on neonic content in honey published by *Science*, at least one neonic was detected in 75% of the honey samples, and a combination of at least two neonics was detected in 45% of the honey samples [63]. Bees, as the most important pollinators, play an important role in the pollination of crops, urban horticulture, and protection of endangered plants [64]. When bees forage in a flowering zone, buffer zone, cover crops, or catch crops, they may come into contact with pesticides floating from the treated land and may directly eat the polluted nectar and pollen, which ultimately affects the foraging, learning, and memory ability of the worker bees [54,65]. In addition, neonics may increase mortality in bees through the reduction of their homing ability and the reproduction success rate of bumblebees and solitary bees [66]. Therefore, it is crucial to control the enrichment of neonics in non-target organisms such as bees and to prevent the "accidental injury" they cause to the non-target organisms and crops.

In 2005, Decourtye et al. utilized the proboscis extension response (PER) method to train bees to become capable of associating odor stimulation with sucrose, and observed that after consuming $LD_{50/20}$ (48 h) sugar water of dinotefuran, there was a decrease in the western bees' ability of tongue extension response, as well as in their learning ability [67]. In 2008, Hassani et al. studied the effects of sub-lethal doses of neonics on bee behavior under laboratory conditions. The results demonstrated that when the bees were fed with 1 μg acetamiprid, each bee's sensitivity to the sucrose solution increased. If there was greater than 0.1 μg acetamiprid in the body of the bee for a long time, its olfactory memory

would be damaged [68]. In 2012, Henry et al. developed a colony simulation model to monitor the bees' collection behavior for one month and observed that the normal collection time of western bees was 300 s, while after the ingestion of sub-lethal doses of imidacloprid and thiamethoxam, there was a loss of localization ability, the homing time was increased, and the number of round trips per day was also reduced [69]. In the same year, Yang et al. processed bees in the hive, recorded their pupa, pupate, emergence rate, and other parameters, and observed that when the western bee larvae ingested 24–8000 ng of imidacloprid, the number covering the larva would be reduced. After the ingestion of 0.4 ng of imidacloprid, the emergence rate of bees remained unaltered, although damage to their olfactory organs in adulthood was caused [70]. In 2014, Tan et al. experimentally observed that the number of bees collected by Chinese bees decreased by 23%, and the collection quality decreased by 46% after the ingestion of sugar water containing 34 ng/μL of imidacloprid [71]. In 2015, Rundlöf et al. demonstrated through field experiments that the content of neonics in rape plants caused serious damage to reproduction in bumblebees and monophones [72]. In 2017, McArt et al. reported that neonics could induce chronic sub-lethal effects in various plant pollinators (including bees) [73], such as a reduction in the adaptability of single bees [74], "colony collapse disorder", damage to bees' pollination service, foraging ability [75], and growth rate [76], damage to bees' health [54], and gene damage [77]. In 2020, Wintermantel et al. reported the evaluation of the risk of neonics in eight fields, stating that the mortality rate in pollen pickers due to acute toxicity was 50% [32].

It may be inferred from the above-stated research results that although the adverse effects of neonics on non-target organisms, such as bees, were recognized long ago, these problems have not been effectively resolved to date. Moreover, several scholars have reported that neonics, in addition to their highly toxic effect on bees, exert negative effects on mice at the same nutritional level as bees [78].

3.2.2. Exposure Level and Potential Hazards of Neonics in Rats

Several studies have reported that neonics, such as thiacloprid and acetamiprid, are able to reduce embryo quality in mice and also exert negative effects on the reproductive health, metabolism, and genes in rats [78].

In regard to reproductive toxicity, a study conducted in 2011 on female rats observed significant pathomorphological changes in the follicles, antral follicles, and atretic follicles along with ovarian weight decrease in the group treated with imidacloprid at a dietary concentration of 20 mg/kg/day. However, no significant changes were observed in the groups receiving dietary concentrations of 5 and 10 mg/kg/day [79]. In 2012, Bal et al. treated developing and adult male rats with low doses (0.5, 2, and 8 mg/kg/day) of imidacloprid via oral gavage for three months. The results revealed that the weights of the epididymis, the sperm parameters, and testosterone levels were lower in all the imidacloprid-treated developing rats, while apoptosis and fragmentation of seminal DNA were observed to occur mainly in the two higher-dose groups. In addition, the authors observed a dose-dependent relationship between the seminiferous tubule apoptosis and imidacloprid consumption [80–83]. Although the two above-stated studies had different research perspectives, the results of both of these studies presented similar findings, suggesting that even though low doses of imidacloprid did not exert a significant adverse effect on the pathological morphology of the follicles, in general, such insecticides nonetheless damaged the reproductive tissues in rats. In 2013, similar methods were utilized by Bal, who treated developing and adult rats with clothianidin (90 days of oral exposure) at the doses of 2, 8, and 32 mg/kg/day. The results demonstrated that clothianidin exerted detrimental effects on the reproductive organ systems, and that further severe effects are likely to be observed at higher dose levels in developing rats [81]. In 2015, Hirano et al. once again demonstrated that the effect of clothianidin on the reproductive organs of rats was more severe under environmental pressure [84]. In 2018, Han et al. conducted a study on female rats exposed to neonics, and reported that in the experimental group treated with imidacloprid at a dietary concentration of 20 mg/kg/day, there were visible pathomorphological changes in the follicles, anal follicles, and atretic follicles, and the ovarian weight was reduced, which was in complete agreement with the findings reported by Kapoor [27].

In hepatotoxicity, toxin metabolism and elimination occur in the liver. The liver is also a principal target organ for damage caused by neonics. Currently, the researchers are focused mainly on the hepatotoxicity and hepatocarcinogenesis of imidacloprid, thiamethoxam, and their metabolites in rats. In 2010, Bhardwaj et al. reported detecting imidacloprid in female rats with three oral concentrations (5, 10, and 20 mg/kg/day) during a longer exposure time (90 days), and also that the mild pathological changes in the liver were observed only in the high-dose imidacloprid treatment (20 mg/kg/day) group [85]. Toor et al. evaluated the hepatotoxicity of neonics by measuring liver histological changes and enzyme activity in female albino rats exposed to imidacloprid at concentrations of 45 and 9 mg/kg/day for four weeks. In the higher-dose group, the observed histological changes included degeneration of hepatocytes, dilations of the central vein, and an increase in levels of liver enzymes. However, no significant changes were observed in the rats treated with low doses of imidacloprid [86]. In 2014, Vohra et al. treated female albino rats with imidacloprid at the doses of 10 and 20 mg/kg/day for 60 days, and observed that the liver histopathology in the high-dose group was altered, exhibiting dilation and congestion of the central vein and degeneration of hepatocytes, while the transaminases were not greatly elevated [87]. However, in the same year, Kapoor et al. reported that the level of serum transaminases in adult female rats was increased at the dose of 20 mg/kg/day [88]. Furthermore, Arfat et al. conducted an in vivo study in mice. Upon injecting imidacloprid at the concentrations of 5, 10, and 15 mg/kg/day into adult male albino mice for 15 days, it was observed that the levels of serum glutamate oxaloacetic transaminase, glutamic pyruvate kinase, alkaline phosphatase, and total bilirubin, as well as damage to liver tissue, had increased at the dose of 15 mg/kg/day [89].

In regard to genotoxicity, several studies assessing the genotoxicity of neonics were conducted by measuring chromosome aberrations (CAs) and sister chromatid exchanges (SCEs), and by performing the comet assay and the micronucleus test (MN). For instance, in 2012, Calderon et al. compared the genotoxic effects of thiacloprid, clothianidin, and imidacloprid on human peripheral blood lymphocytes using alkaline comet and trypan blue dye exclusion assays, the results of which revealed that imidacloprid exhibited the strongest genotoxicity [90]. In 2014, Kocaman et al. confirmed the genotoxicity of thiacloprid in human peripheral blood lymphocytes, including decreased nuclear division index, proliferation index, and mitotic index at all concentrations (75, 150, and 300 mg/L), using SCE, CAs, and MN tests [91]. In 2015, Galdikova et al. treated bovine peripheral lymphocytes with thiacloprid at the concentrations of 30, 60, 120, 240, and 480 mg/mL, and reported that the frequency of DNA damage and unstable chromosome aberrations significantly increased at the concentrations ranging from 120 to 480 mg/mL [92]. In 2016, Kataria et al. treated female mice with imidacloprid at the doses of 37.5, 75.0, and 112.5 mg/kg for 24 h, and observed that female mice in the middle- and high-dose groups exhibited significant mitotic inhibition, while micronucleus formation was detected only in the high-dose group (Figure 2) [93].

A comparison of the degree of damage caused to different organs of rats by different doses of neonics reveals that both high and low doses of neonics could cause damage to the reproductive system of rats. On the other hand, in the genetic system of rats, high doses of neonics would cause more obvious damage, while the low doses of neonics cause lesser damage. In the liver system, only high doses of neonics would cause damage. Therefore, it is speculated that the reproductive system of rats is the most sensitive to neonics, followed by the genetic system and the liver system, respectively.
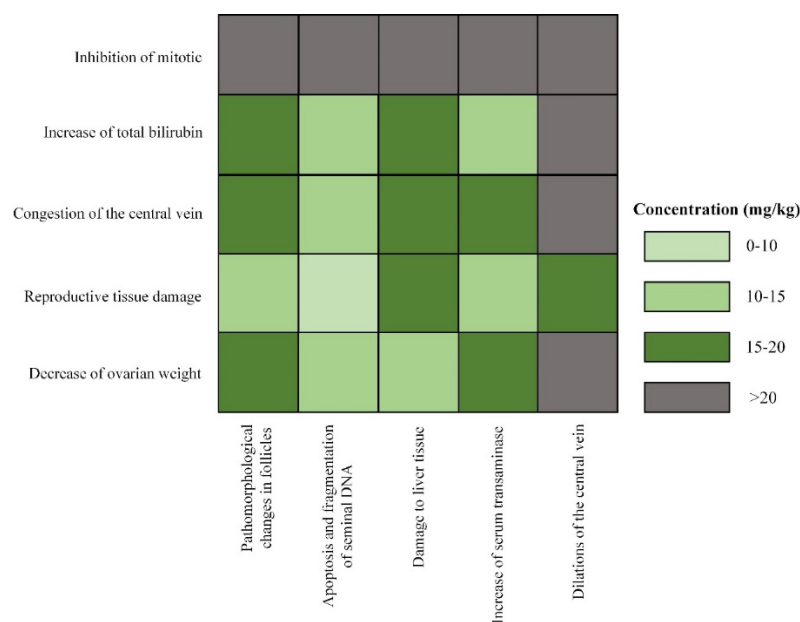
Figure 2. Harmful effects of neonics on rat organs.

3.3. Exposure Level and Potential Hazards of Neonics in Secondary Consumers

In addition to toxic effects on lower animals, neonics possess characteristics of difficult volatilization, high water solubility, and long degradation period in the soil, which enable contact with reptiles through a variety of ways, such as inhalation, food intake, and skin contact [94]. Therefore, neonics are a great threat to the reptiles living in the soil [30]. In 2010, the International Union for Conservation of Nature (IUCN) classified 28% of the reptiles as critically endangered (CR), endangered (EN), or vulnerable (VU) species [95]. As the largest family of reptiles, lizards account for 70% of the reptile species, and are highly sensitive to pollutants. Therefore, application of neonics is considered one of the important reasons for the decline in the numbers of lizards [96].

In 2013, Bicho et al. conducted field studies and observed that the thyroid system of lizards living in agricultural areas could be disrupted, which ultimately affected their reproductive function [97]. In 2014, Park et al. developed nine novel Argus microsatellites in the Korean Peninsula using biotin enrichment technology in order to understand the population's genetic structure and define the protection unit of Mongolian racerunner (a small lizard). Using Bayesian structure analysis, the authors observed that the habitat of lizards highly overlapped with the pesticide application area, and their population size was severely decreasing [98]. In 2017, Zhu et al. reported that long-term exposure to endocrine disruptors may affect the growth and development of animals. Lizards grow and develop with the process of molting and regeneration, and are exposed to endocrine disruptors for a long duration. Therefore, growth inhibition may affect the molting process of lizards, leading to a decline in the motor function and an increase in the infection rate, thereby affecting individual survival [99]. In 2020, Wang et al. evaluated the damage caused to the thyroid system of lizards upon exposure to furandione, thiamethoxam, and imidacloprid for 28 days, and confirmed that continuous exposure to neonics directly affected the thyroid system of lizards. In particular, exposure to furandione affected the intake and utilization of thyroid iodine in lizards, resulting in thyroid insufficiency, and subsequently in thyroid epithelial hyperplasia and increase in follicular volume. Thiamethoxam could activate thyroid function in lizards, significantly increase plasma T3 and T4 concentrations, and promote the binding of T3 and thyroid hormone receptor, while imidacloprid could inhibit the secretion of thyroid hormone in lizards, resulting in the down-regulation of thyroid hormone receptor and the related phase II metabolizing enzyme genes [35].

The above-stated research results confirm that the neonics have adverse effects on the thyroid and endocrine systems of the reptiles. When lizards and other reptiles ingest or absorb these insecticides, they affect the balance of normal hormone function, ultimately affecting the growth and development of these animals. This is a limitation and disadvantage of neonics. Therefore, in future research related to this field, in addition to the toxic effect exerted by neonics on bees and other beneficial insects, their effect on hormones should be included in the research scope, with the objective of minimizing the harm caused by the neonics to non-target animals.

3.4. Exposure Level and Potential Hazards of Neonics in Top-Level Consumers

Certain scholars believe that, in addition to the impact on non-target insects and reptiles, neonics affect other non-target invertebrate taxa, as well as the wild animals that rely on these invertebrate taxa for food [100–102]. The health and sustainability of aquatic invertebrate communities depend, to a large extent, on the abiotic and biological characteristics of the aquatic system, particularly in wetlands [103].

To date, only a few studies have evaluated the relationship between the response of aquatic communities and exposure to neonics [104]. For instance, in 2016, Anderson and Sánchez-Bayo evaluated the potential threat of neonics to aquatic invertebrates in laboratory and meso research, and observed that acute, chronic, and sub-lethal toxicity in various taxa were widespread [105,106]. In 2018, Evelsizer and Skopec constructed a model that could simultaneously monitor the community of aquatic invertebrates, the concentration of neonics, and other relevant environmental attributes. The authors reported that the attenuation of the community correlated positively with the concentration of neonics [107]. The above-stated studies determined the impact of neonics on aquatic invertebrates in the laboratory and meso research only, and did not evaluate the relationship between the neonics and the invertebrate community under field conditions [108]. In 2020, Schepker et al. evaluated the levels of six neonics, nutrients, and physical properties of water in the samples of aquatic invertebrates and surface water collected from 26 wetlands in Nebraska. It was observed that although the concentration of neonics was lower than the benchmark concentration recommended as per government regulations, there was a significant negative correlation between the concentration of neonics and the biomass of the aquatic invertebrates [109].

The above-stated research results strongly suggest damage caused by neonics to fruits, vegetables, crops, and certain animals. It may be inferred that most of the organisms at each trophic level of the food chain are likely to be affected by these insecticides, which would lead to the instability of the food chain and even of the whole ecosystem. Although these results have established a good foundation for future research on neonics, the research and development of green pesticides, the blocking of pollutant transmission, and the remediation of contaminated soil continue to be in the initial stages, which have some limitations.

4. Assessment of the Human Health Impact and Environmental Risk of Neonics

In recent years, neonics have been continuously detected in the environment. Neonics enter the food chain through drinking water and food intake, causing great safety risks to human health [110]. In the present report, exposure of the human body and multi-environment media (water, soil, and atmosphere) to neonics was reviewed, and their impact on the human health and the environmental risks of these insecticides were comprehensively evaluated.

4.1. Distribution Characteristics and Assessment of the Health Impact of Neonics on the Human Body

4.1.1. Distribution Characteristics of Neonics in the Human Body

In comparison to traditional insecticides, neonics exhibit lower toxicity to mammals and humans. However, an increasing number of studies demonstrate that exposure to neonics causes a potential risk to mammals, including humans. In recent years, certain scientists have begun exploring different

methods for the determination of neonics and their metabolites in human urine, serum, hair, and other biological samples.

In 2014, Ueyama et al. successfully detected seven neonics in 52 Japanese urine samples without a history of occupational spraying, among which thiamethoxam, dinotefuran, imidacloprid, and clothianidin exhibited the detection rates of 100%, 100%, 96%, and 96%, respectively, while the detection levels of furandione and imidacloprid were 2.27 and 1.54 mg/L, respectively [111]. The next year, Ueyama et al. also reported detecting seven neonics in urine samples of 95 adult Japanese women aged 45–75 in the period between 1994 and 2011. The authors observed that during this period, the detection rate and the total concentration of neonics in the urine of Japanese women had increased significantly. For instance, imidacloprid was detected in urine only in the year 1994, while the detection results for 2011 revealed that the detection rate of thiamethoxam and dinotefuran were greater than 70%. At the same time, the geometric mean concentration of neonics in the urine maintained a steady increase, which indicated that the number of neonics consumed by the human body had increased during this period [112]. In 2016, Osaka et al. studied the exposure characteristics of seven neonics in urine of 223 three-year-old children (118 boys and 105 girls) in Japan, and observed that the average and maximum concentrations of these neonics were 4.7 and 370.2 nmol/g creatinine, respectively, while the concentrations of certain neonics in urine of the children were generally higher in summer than in winter [113]. In 2019, Tao et al., using imidacloprid as an example, studied and compared the detection levels of neonics in urine of rural and urban residents, and observed that the detection rate of neonics in urine of both rural and urban residents was 100%, with the detection concentration of imidacloprid in urine of urban residents determined to be 0.91–2.68 ng/mL; the imidacloprid detection concentration in rural residents was 0.02–8.91 ng/mL, which was approximately 1.47 times the content of imidacloprid in urine of the urban residents [114].

Moreover, several studies have reported the detection of a variety of neonics in human samples other than human urine. For instance, in 2013, Kavvalakis et al. compared the exposure levels of imidacloprid in the hair of urban and rural populations, and observed that the detection rate of imidacloprid in the hair of the rural residents engaged in agricultural processing was higher than that in the hair of the urban residents. The median concentration and the highest concentration were 0.03 and 27 ng/mg, respectively [115]. In 2014, Tadashi et al. were the first ones to propose and establish an analytical method for the simultaneous determination of eight neonics and three acetamiprid-specific metabolites; the detection limit and the quantitative limit of these 11 compounds in serum were measured using liquid chromatography-tandem mass spectrometry. The results demonstrated that the detection limit and the quantitative limit of these 11 compounds in human serum were 0.1–0.2 and 0.5–10 ng/mL, respectively, while the recovery was 80.9–101.8% [116].

The above-stated research results suggest that the levels of neonics are generally higher in the human body samples of rural residents compared to urban residents, which is mainly due to the extensive use of neonics in agricultural production, combined with a long period of validity, slow degradation, and widespread presence of neonics in the agricultural environment. As a consequence, the populations residing close to agricultural areas are generally more exposed to pesticides compared to those residing far away from agricultural areas [117]. More importantly, increased attention should be paid to the health risks caused due to pesticide exposure [118].

4.1.2. Assessment of the Impact of Neonics on Human Health

In the last 20 years, the number of people exposed to neonics in daily life has been increasing steadily, and long-term exposure to neonics is expected to have an adverse effect on the human body [119]. Therefore, there should be awareness regarding the increased human exposure to neonics and the associated potential health impacts.

Recent studies have demonstrated that exposure to neonics, such as imidacloprid, exerts adverse effects on human health. In 2014, Wei et al. investigated whether exposure to neonics during early pregnancy would cause anencephaly, spina bifida, and cleft lip and palate in pregnant women.

The subjects belonged to San Joaquin Valley, California, and included 73 anencephalic children, 123 children with spina bifida, and 394 those with cleft lip and palate. The results of the correlation analysis conducted in that study revealed that the use of agricultural pesticides such as imidacloprid close to the residences of pregnant women during pregnancy was positively correlated with the probability of occurrence of fetal teratogenic mutation [120]. In the same year, Keil et al. used the Bayesian logic model to evaluate the relationship between autism spectrum disorders and the use of imidacloprid. The analysis dataset contained complete information regarding 262 normal development controls and 407 autistic children. Sensitivity window analysis conducted in that study revealed that, in comparison to normal development controls, the autistic children exhibited higher levels of imidacloprid exposure during pregnancy. Therefore, a certain correlation existed between imidacloprid exposure and autism spectrum disorders [121]. Furthermore, Koureas et al. investigated the oxidative damage to DNA in different populations in Greece, and studied its correlation with pesticides and other potential risk factors; the study included 80 insecticide sprayers, 85 rural residents, and 121 residents of the city of La SAR. It was observed that the frequency of neonics was associated with the 80 pesticide sprayers in terms of the oxidative damage to whole blood DNA [122]. In 2015, Marfo et al. studied 35 symptomatic patients with unknown causes and 50 asymptomatic patients, and proposed that a correlation existed between the concentration of neonics in the urine and the increased prevalence of neurological symptoms, including amnesia, finger tremor, headache, etc. [123]. In 2017, Seltenrich et al. indicated that long-term exposure to neonics would result in adverse development or neurological outcomes, including tetralogy of Fallot, congenital anencephaly, autism spectrum disorder, memory loss, and finger tremor [124]. In 2018, Mesnage et al. reported that neonics could cause adverse reproductive, developmental, and physiological effects, including decreased sperm production and function, reduced pregnancy rate, increased fetal mortality, still-birth rate, and preterm birth rate, as well as weight loss and lipid accumulation in the offspring [125].

Although it has been recognized that exposure of neonics exerts adverse effects on human health, there nonetheless exist certain limitations in the current research related to this field, and it is difficult to provide a comprehensive speculative conclusion. Therefore, for the neonics already developed and registered, further investigation is required to predict their impact on human health theoretically. In addition, future research and development related to neonics should focus on reducing their accumulation and transmission in agricultural products in order to reduce their exposure to humans via food intake.

4.2. Distribution Characteristics and Risk Assessment of Neonics in Environmental Media

4.2.1. Distribution Characteristics of Neonics in Environmental Media

Just ~5% of the active components of neonics are capable of being absorbed by crops, and most of these components are diffused into a wider range of environmental media and may even enter the water environment through migration and transformation [27]. Moreover, the low molecular weight and high water solubility of the neonics increase the problem of environmental pollution. Neonics exposed to the environment mainly originate from human activities, such as agricultural planting, and the neonics entering the environment complete the redistribution among the environmental media via complex migration and transformation paths.

Distribution Characteristics of Neonics in Water

Owing to the high solubility of neonics, they may conveniently pollute the water through surface runoff, drainage, and dry and wet deposition, thereby causing harm to aquatic organisms. In 2013, Morrissey et al. comprehensively summarized the pollution levels of neonics in global surface water during the period between 1998 and 2013. It was estimated that the geometric average concentration of neonics in surface water was 0.13 µg/L, while the peak geometric average value was 0.63 µg/L (n = 27) [44]. Since then, several studies have focused on investigating pollution levels of neonics in

the broader aquatic environment, including wetlands, farmland, rivers, and sediments. For instance, in 2014, the concentration of both thiamethoxam and clothianidin detected in the grassland wetland of Saskatchewan (central and eastern Canada) was 17.5 ng/g dw [126]. In 2015, Schepker et al. collected surface water samples from 26 wetlands (12 wetland buffer zones and 14 wetland non-buffer zones) in Nebraska, and evaluated the samples for six neonics. The results revealed that more than 73% of the water samples in the non-buffer zones of the wetland exhibited the presence of neonics, among which imidacloprid accounted for 15%. Although the content of the neonics in the water samples from the wetland buffer zones was significantly lower, the neonics were nonetheless prevalent [109]. In 2016, Sadaria et al. detected neonics in a sewage treatment plant, with a detection concentration of 0.002–0.11 μg/L, and observed that imidacloprid, acetamiprid, and clothianidin would exist in the sewage treatment plant for a long time and were difficult to remove, which might be due to the difficulty of the traditional sewage treatment methods in removing such pollutants, resulting in the pollution of surface water, drinking water sources, and underground water once again. In addition, the study reported detecting high concentrations of imidacloprid and acetamiprid in sediment, indicating that neonics in sediment may not be conveniently degraded and/or removed [127]. In 2019, Yi et al. reported detecting neonics in 14 sampling points of surface water and sediment in the Guangzhou section of Pearl River. The reported detection concentration of neonics in surface water samples was 92.6–321 ng/L, with imidacloprid, clothianidin, and acetamiprid, the most obvious ones, exhibiting the detection rate of 100% [30]. A comparative study detected an average neonic concentration of 12 ng/L in the rivers around Osaka in Japan [128] and 118 ng/L around Sydney in Australia [44]. It may be observed that compared to other regions, the Guangzhou section of the Pearl River exhibited relatively high levels of neonics, even higher than those detected in the agricultural area of a grassland wetland in Canada [129]. The main causes for the above-stated phenomena could be related to the runoff from the agricultural regions and grasslands containing neonics and the hydraulic transmission of effluents from sewage treatment plants [30]. In addition to surface water, the sediments of nine sampling points in the Guangzhou section of the Pearl River presented neonics content in the range of 0.40–2.59 ng/g dw. However, imidacloprid, which presented a high detection rate in the surface water, was not detected in any of the sediment samples, which might be related to its physical and chemical properties or its dissolution and dilution effects caused due to the frequent water exchange among tidal river networks [130].

In addition to the above-stated studies, Table 1 provides a detection summary of neonics in the water of certain other regions since 2013. It may be observed through a comparative analysis that the concentration of neonics has not decreased in recent years, and in certain countries (such as The Netherlands), the concentration of neonics in water has rather increased. Moreover, the concentrations of neonics in the samples from different sources were considerably different, which might be related to pesticide dosages, human activities, and environmental conditions. For instance, certain farmlands in Canada and wetlands in Texas in the United States presented high detection concentrations of neonics (the latter region presented a concentration as high as 225 μg/L), while the other surface water samples presented a relatively low detection content of neonics.

Table 1. Average concentration of neonics in the water samples from different regions.

Region	Sampling Point	Sample Type	Compound	Concentration μg/L	Reference
China	Beijing	sewage treatment plant	imidacloprid	0.045–0.11	[131]
	Fujian	sediment	imidacloprid	141	[132]
			acetamiprid	162	
US	-	surface water	imidacloprid	0.005–0.10	[133]
			clothianidin	0.003–0.07	
			dinotefuran	0.005–0.11	
			acetamiprid	0.03	
	Texas	wetland	thiamethoxam	225	[108]
			acetamiprid		
	Farmland	surface water	clothianidin	0.85	[134]
	River	surface water	imidacloprid	1.46	[135]
	-	sewage treatment plant	imidacloprid	0.059	[127]
			acetamiprid	0.0020	
			clothianidin	0.07	
	Wisconsin	groundwater	imidacloprid	0.26–3.34	[136]
			clothianidin	0.21–3.34	
			thiamethoxam	0.20–8.93	
Canada	Wetland	surface water	clothianidin	3.10	[126]
			thiamethoxam	1.50	
	Saskatchewan	surface water	clothianidin	0.27 ± 0.072	[137]
			thiamethoxam		
	Farmland	surface water	clothianidin	55.70	[138]
			thiamethoxam	63.40	
	Ontario, farmland	surface water	thiamethoxam	1.12	[139]
Holland	-	surface water	imidacloprid	320	[140]
Germany	-	surface water	imidacloprid	0.25	[141]
Vietnam	Farmland	surface water	imidacloprid	53	[63]
Brazil	Reservoir	surface water	imidacloprid	0.0021	[142]
Portugal	River	surface water	imidacloprid	0.0080	[143]
Hungary	River	surface water	clothianidin	0.017–0.040	[144]
			thiamethoxam	0.0040–0.030	
Spain	River	surface water	imidacloprid	0.0023–0.019	[145]
Australia	Sydney, river	surface water	clothianidin	0.42	[43]
			imidacloprid	4.56	
			thiamethoxam	1.37	

Distribution Characteristics of Neonics in Soil

In addition to causing water pollution, neonics also pollute the soil. One way that the neonics enter the soil is through the planted seeds that contain the neonics. The other way is when the neonics are applied to the plants in the farmland through absorption or stem injection, and these plants containing the pesticide residues decompose and release these residues into the soil [146]. Therefore,

for environmental risk assessment, it is necessary to understand the pollution status of neonics in the soil.

In 2014, Dankyi utilized liquid chromatography tandem mass spectrometry (LC-MS/MS) and electrospray ionization (ESI) techniques to assess the neonic content in 52 soil samples obtained from cocoa cropland, and reported that imidacloprid was detected in approximately 50% of the samples, with its concentration ranging from 4.3 to 251.4 µg/kg; in addition, clothianidin was detected in approximately 10% of the samples, with concentrations in the range of 9.8–23 µg/kg [147]. In 2015, Botías et al. analyzed soil planted with rape and wheat in the UK, and observed that imidacloprid, clothianidin, thiamethoxam, and thiacloprid were the main neonics distributed in the soil, with contents in the ranges 7–7.90, 4.10–28.60, 4–9.75, and 1–0.22 ng/g, respectively [52]. In the same year, in the United States, De et al. continuously planted soil samples with corn and soybean throughout the year, and finally reported that the main neonic in the soil was clothianidin, with a content of 2.00–12.20 ng/g [134]. In 2016, in Canada, Limayrios et al. detected clothianidin and thiamethoxam as the main neonics in the soil planted with corn, with contents of 3.45 and 0.91 ng/g, respectively [148]. In the same year, Xu et al. successively planted soil samples with rape and corn, and reported that the contents of clothianidin in these soil samples were 5.70 and 7.00 ng/g, respectively [149]. Furthermore, Abdel-Ghany et al. developed a novel high-performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS) method for the simultaneous determination of eight neonics and their two major metabolites in the soil of Qaluybiya, Egypt. According to the results, all eight neonics, as well as their two main metabolites, were detected in the soil samples of this area. The range of the detection concentration was 12.5–50 ng/mL for acetamiprid, 2.5–100 ng/mL for imidacloprid, 12.5–90 ng/mL for dinotefuran, 6.25–100 ng/mL for thiamethoxam, 3.5–100 ng/mL for clothianidin, 1.5–60 ng/mL for flonicamid, 1–30 ng/mL for furandione, 2.5–50 ng/mL for thiacloprid, 6–100 ng/mL for 6-chloronicotinic acid, and 25–100 ng/mL for 1-methyl-3-nitrguanidine [150]. In 2018, Zhou et al. determined the residues of nine neonics in the soil of parks (n = 35) and residential areas (n = 33) in Tianjin, China, using the rapid pre-treatment technology of LC-MS/MS. The total concentrations of the nine neonics detected in the parks and residential areas were 0.27–230.76 and 0.23–132.66 ng/g, respectively, with imidacloprid exhibiting the highest detection rate, followed by acetamiprid and thiamethoxam, respectively [151]
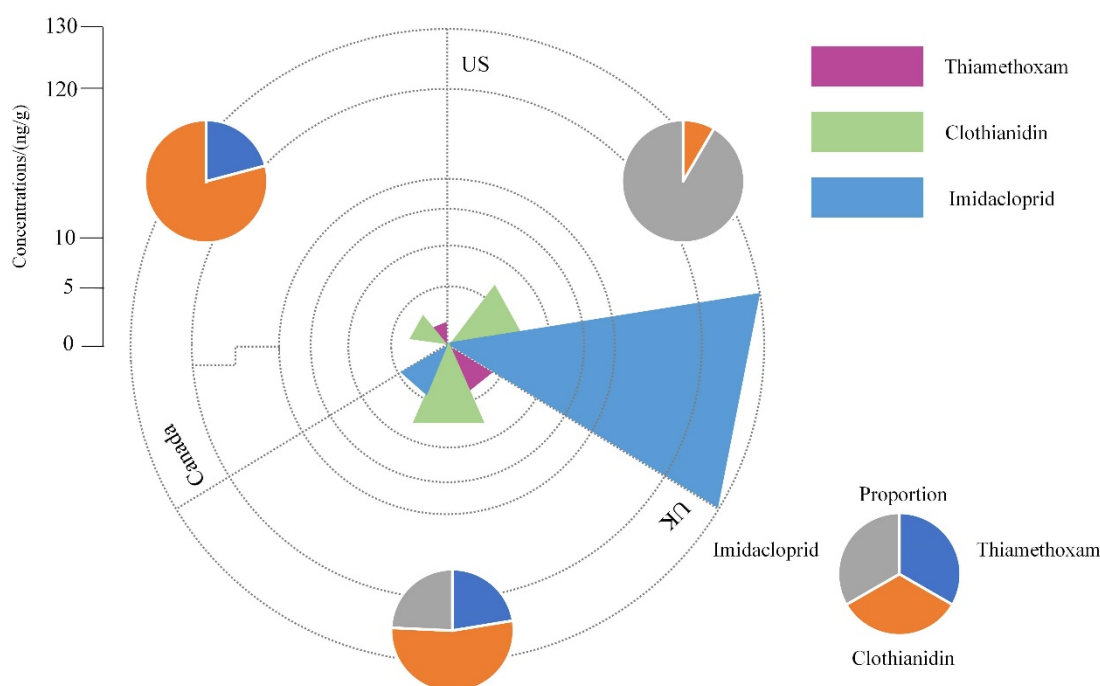
The above-stated results suggest that the types and residues of neonics in the soil were at a high level, which may eventually increase the possibility of human exposure to neonics.

Distribution Characteristics of Neonics in the Atmosphere

The atmosphere is an important medium for the spread and diffusion of neonics. Human activities during agricultural production, such as pesticide spraying and seed coating, discharge neonics into the atmosphere. These pollutants then enter the surrounding environment with the movement of the atmosphere, producing a far-reaching impact [152].

Since neonics are difficult to volatilize, they may exist in the atmosphere, mainly in the form of particles. Pneumatic seeders were used widely in 2003, resulting in the generation of numerous dust particles containing insecticides [153]. The release of these particles containing pesticides into the atmosphere would cause pollution of the field vegetation, which could ultimately lead to the exposure of non-target organisms to sub-lethal doses of pesticides [154]. In 2013, Girolami et al. demonstrated that abrasive particles could cause serious harm to the insects flying over the field during sowing, bees, and other pollinators in particular [155]. In 2015, Xue et al. reported that the residues of thiamethoxam and clothianidin in the dust accounted for 0.01–0.40% of the actual application amount, of which 92% originated from the coated seeds after the pesticide treatment, and the total concentration of neonics in the atmosphere was 0.10 µg·m^{-3} [156]. In 2016, Botías et al. demonstrated that the pollen and nectar of wild plants growing in the vicinity of seed-treated crops were critically polluted with neonics, which caused long-term exposure of pollinators to these substances [157]. Moreover, with the

transport and deposition of dust particles in the atmosphere, neonics would also pollute the soil and the water [158]. (Figure 3).

Figure 3. Distribution characteristics of neonics in soil.

The above-stated research results suggest that with the large-scale application of neonics, their detection concentration in the environment is continually increasing. Neonics are being detected in all media of the environment, and a large number of neonic residues in the environment would produce a greater adverse impact.

4.2.2. Environmental Risk Assessment of Neonics

As stated earlier, a large number of active pharmaceutical ingredients of neonics either remain in the soil and the atmosphere during the application process or enter the water environment through surface runoff, leaching, dry and wet deposition, or other ways, resulting in an extensive amount of residues in various media of the environment and critical pollution [23]. In addition, the residues of neonics in the environment serve as a threat to non-target organisms, including algae, zooplanktons [159], fish [160], earthworms [161], bees [162], insectivorous birds [72], and even humans [163].

In the previous studies conducted by our research group, certain green pesticide substitutes based on the bioconcentration factor (BCF), octanol-water partition coefficient (K_{ow}), and lethal concentration of 50% (LC_{50}) were designed in order to reduce the negative impacts of neonics on the environment. At the same time, multi-directional-selection toxic effect evaluation and human health risk assessment were also performed in those studies to ensure the efficacy of the insecticides while maintaining low toxicity to the non-target organisms, crops, and humans, so as to design a series of green substitutes of neonics for improving the ecological security and human health at the theoretical level [1,37,38]. However, the studies mentioned in the present report only discussed the bioaccumulation capacity of the neonics and did not consider the other characteristics, such as biodegradability [164].

Currently, the detection of neonics in various environmental media is becoming increasingly frequent, and their concentrations are also on the rise. However, the research works conducted on photodegradation, bioaccumulation, and persistence of neonics, which would result in critical adverse effects on the whole environment and the ecosystem, are scarce. Therefore, in order to achieve the

sustainable development of agriculture and for the benefit of society as a whole, it is of significance to pay attention to and study the environmental risks associated with neonics.

5. Conclusions

Neonics are used widely throughout the world, and the ecological problems caused by the application of neonics have attracted great attention globally. QuEChERS (Quick, Easy, Cheap, Efficient, Rugged and Safe), LC-MS/MS, and other detection methods have revealed the presence of a large number of neonics in the water, soil, atmosphere, and food chain, which is expected to have an adverse impact on the environment. The existing evidence provided by the epidemiological studies, both in vivo and in vitro, revealed that neonics have the potential to cause serious damage to non-target animals and humans within the ecosystem. Although these results have established a solid foundation for future studies to be conducted in relation to neonics, the research and development of green pesticides, the blocking of pollutant transmission, and the remediation of contaminated soil continue to be in the initial stages. In addition, even though the levels of pesticide residues in most foods are relatively low, the joint toxic effects produced as a result of the simultaneous presence of a number of residues of a variety of pesticides are not clearly understood so far. Therefore, it is important that the understanding of the transmission pathways of neonics in the food chain is deepened in order to fundamentally achieve reasonable prediction and control of the source, process, and end behavior of these insecticides in the future. Furthermore, effective remediation of contaminated soil and the problem of joint toxicity caused by the simultaneous presence of the residues of a variety of pesticides also deserve attention. The present report provides a large-scale theoretical reference for prospective research related to neonics, as well as reliable technical support for strengthening the environmental and food safety supervision and green pesticide design.

Author Contributions: Conceptualization, Y.Z. and Y.L.; formal analysis, J.R.; investigation, J.Y.; resources, Z.H. and Y.H.; data curation, J.X.; writing—original draft preparation, Y.Z.; writing—review and editing, Y.L.; visualization, Y.Z.; supervision, Y.L. All authors have read and agreed to the published version of the manuscript.

Abbreviations

Neonics	Neonicotinoid Insecticides
nAChRs	Nicotinic Acetylcholine Receptors
UN	European Union
CAs	Chromosome Aberrations
SCEs	Sister Chromatid Exchanges
MN	Micronucleus
IUCN	International Union for Conservation of Nature
CR	Critically Endangered
EN	Endangered
VU	Vulnerable
ESI	Electrospray Ionization
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry

References

1. Zhao, Y.Y.; Li, Y. Modified neonicotinoid insecticide with bi-directional selective toxicity and drug resistance. *Ecotoxicol. Environ. Saf.* **2018**, *164*, 467–473. [CrossRef] [PubMed]

2. Li, J.Y.; He, J.; Wu, W.Z. UPLC-MS/MS detection of 9 insecticides in honey. *Environ. Chem.* **2016**, *35*, 1921–1927.

3. Li, M.; Li, Z.G.; He, J.F.; Su, S.K. Advance in effect of neonicotinoid insecticides on behavior and physiology of honey bees. *J. Fujian Agric. For. Univ. (Nat. Sci. Ed.)* **2016**, *45*, 490–495.

4.   Jeschke, P.; Nauen, R.; Beck, M.E. Nicotinic acetylcholine receptor agonists: A milestone for modern crop protection. *Angew. Chem.* **2013**, *52*, 9464–9485. [CrossRef] [PubMed]

5.   Jeschke, P.; Nauen, R.; Schindler, M.; Elbert, A. Overview of the status and global strategy for neonicotinoids. *J. Agric. Food Chem.* **2011**, *59*, 2897–2908. [CrossRef] [PubMed]

6.   Millar, N.S.; Denholm, I. Nicotinic acetylcholine receptors: Targets for commercially important insecticides. *Invertebr. Neurosci.* **2007**, *7*, 53–66. [CrossRef]

7.   Barbara, G.S.; Grünewald, B.; Paute, S.; Gauthier, M.; Raymond-Delpech, V. Study of nicotinic acetylcholine receptors on cultured antennal lobe neurones from adult honeybee brains. *Invertebr. Neurosci.* **2008**, *8*, 19–29. [CrossRef]

8.   Simon-Delso, N.; Amaral-Rogers, V.; Belzunces, L.P.; Bonmatin, J.M.; Chagnon, M. Systemic insecticides (neonicotinoids and fipronil): Trends, uses, mode of action and metabolites. *Environ. Sci. Pollut. Res.* **2015**, *22*, 5–34. [CrossRef]

9.   Stivaktakis, P.D.; Kavvalakis, M.P.; Tzatzarakis, M.N.; Alegakis, A.K.; Panagiotakis, M.N.; Fragkiadaki, P.; Vakonaki, E.; Ozcagli, E.; Hayes, W.A.; Rakitskii, V.N.; et al. Long-term exposure of rabbits to imidacloprid as quantified in blood induces genotoxic effect. *Chemosphere* **2016**, *149*, 108–113. [CrossRef]

10.   Geoffrey, R.W.; Aline, T.; Gina, R.; Kaspar, R.; Orlando, Y.; Dave, S.; Peter, N.; Laurent, G. Neonicotinoid pesticides severely affect honey bee queens. *Sci. Rep.* **2015**, *5*, 14621.

11.   Zhang, X.; Liao, X.; Mao, K.; Zhang, K.X.; Li, J.H. Insecticide resistance monitoring and correlation analysis of insecticides in field populations of the brown planthopper Nilaparvata lugens (stål) in China 2012–2014. *Pestic. Biochem. Phys.* **2016**, *132*, 13–20. [CrossRef] [PubMed]

12.   Nagata, K.; Iwanaga, Y.; Shono, T.; Narahashi, T. Modulation of the Neuronal Nicotinic Acetylcholine Receptor Channel by Imidacloprid and Cartap. *Pestic. Biochem. Phys.* **1997**, *59*, 119–128. [CrossRef]

13.   Wang, K.; Pang, S.; Mu, X.Y.; Qi, S.Z.; Li, D.Z.; Cui, F.; Wang, C.J. Biological response of earthworm, Eisenia fetida, to five neonicotinoid insecticides. *Chemosphere* **2015**, *132*, 120–126. [CrossRef] [PubMed]

14.   Johnson, R.M. Honey Bee Toxicology. *Annu. Rev. Entomol.* **2015**, *60*, 415–434. [CrossRef] [PubMed]

15.   Stokstad, E. The case of the empty hives. *Science* **2007**, *316*, 970–972. [CrossRef] [PubMed]

16.   Tapparo, A.; Giorio, C.; Soldà, L. UHPLC-DAD method for the determination of neonicotinoid insecticides in single bees and its relevance in honeybee colony loss investigations. *Anal. Bioanal. Chem.* **2013**, *405*, 1007–1014. [CrossRef]

17.   Peng, J.H.; Liao, L.P.; Nie, S.Q.; Liang, J.; Fu, Q.M.; Wu, D.X.; Xu, W.J. Analysis of Triflumezopyrim Residues in Rice, Soil and Field Water. *Agrochemicals* **2018**, *57*, 50–53.

18.   Cao, L.D.; Zhu, P.; Zhao, Y.S.; Zhao, J.H. Using machine learning and quantum chemistry descriptors to predict the toxicity of ionic liquids. *J. Hazard. Mater.* **2018**, *352*, 17–26. [CrossRef]

19.   Cheng, X.; Yi, B. Development of thiamethoxam, a neonicotinoid of the second generation. *World Pestic.* **2001**, *23*, 17–25. (In Chinese)

20.   Taillebois, E.; Cartereau, A.; Jones, A.K.; Thany, S.H. Neonicotinoid insecticides mode of action on insect nicotinic acetylcholine receptors using binding studies. *Pestic. Biochem. Phys.* **2018**, *151*, 59–66. [CrossRef]

21.   Marlatt, V.L.; Leung, T.Y.G.; Calbick, S.; Metcalfe, C.; Kennedy, C. Sub-lethal effects of a neonicotinoid, clothianidin, on wild early life stage sockeye salmon (*Oncorhynchus nerka*). *Aquat. Toxicol.* **2019**, *217*, 105335. [CrossRef] [PubMed]

22.   Xu, L. The counter attack way of nicotinic insecticide furosemide. *Mark. Asp.* **2020**, *2*, 36–37. (In Chinese)

23.   Mathews, M.J.; Mead, R.N.; Galizio, M. Effects of N-Methyl-D-aspartate (NMDA) antagonists ketamine, methoxetamine, and phencyclidine on the odor span test of working memory in rats. *Exp. Clin. Psychopharmacol.* **2018**, *26*, 6–17. [CrossRef] [PubMed]

24.   Hesselbach, H.; Scheiner, R. The novel pesticide flupyradifurone (Sivanto) affects honeybee motor abilities. *Ecotoxicology* **2019**, *28*, 354–366. [CrossRef] [PubMed]

25.   Cordova, D.; Benner, E.A.; Schroeder, M.E. Mode of action of triflumezopyrim: A novel mesoionic insecticide which inhibits the nicotinic acetylcholine receptor. *Insect Biochem. Mol.* **2016**, *74*, 32–41. [CrossRef] [PubMed]

26.   Fu, L.F.; Fu, M.; Liu, Y.H. The European Union again tightened restrictions on the use of imidacloprid, thiamethoxam and thiamethoxam. *Pestic. Sci. Manag.* **2017**, *38*, 34–35.

27.   Han, W.; Tian, Y.; Shen, X. Human exposure to neonicotinoid insecticides and the evaluation of their potential toxicity: An overview. *Chemosphere* **2017**, *192*, 59–65. [CrossRef]

28. Tian, J. Molecular Modeling Study on the Interaction Mechanism between the Neonicotinoid Insecticides and nAChR. Master's Thesis, Lanzhou University, Lanzhou, China, May 2017.

29. Zhang, J.; Wei, Y.; Li, H.; Zeng, E.Y.; You, J. Application of Box-Behnken design to optimize multi-sorbent solid phase extraction for trace neonicotinoids in water containing high level of matrix substances. *Talanta* **2017**, *170*, 392–398. [CrossRef]

30. Yi, X.; Zhang, C.; Liu, H.; Wu, R.; Tian, D.; Ruan, J.; Zhang, T.; Huang, M.; Ying, G. Occurrence and distribution of neonicotinoid insecticides in surface water and sediment of the Guangzhou section of the Pearl River, South China. *Environ. Pollut.* **2019**, *251*, 892–900. [CrossRef]

31. Piao, X.; Ji, L.; Lin, R. Status analysis of neonicotinoid pesticide registration and management. *China Plant Prot.* **2015**, *35*, 70–74.

32. Wintermantel, D.; Odoux, J.F.; Decourtye, A.; Henry, M.; Allier, F.; Bretagnolle, V. Neonicotinoid-induced mortality risk for bees foraging on oilseed rape nectar persists despite EU moratorium. *Sci. Total Environ.* **2020**, *704*, 135–140. [CrossRef] [PubMed]

33. Li, R. Europe voted to ban neonicotinoids. *Bee Craft* **2018**, *69*, 9–13.

34. Yu, L. France has become the first country in the European Union to ban the sale of five neonicotinoids. *Pestic. Mark. Inf.* **2018**, *24*, 45–53.

35. Wang, Y.H.; Xu, P.; Chang, J.; Li, W.; Yang, L.; Tian, H.T. Unraveling the toxic effects of neonicotinoid insecticides on the thyroid endocrine system of lizards. *Environ. Pollut.* **2020**, *258*, 113–120. [CrossRef] [PubMed]

36. Zeng, X.L.; Qu, R.J.; Feng, M.B.; Chen, J.; Wang, L.S.; Wang, Z.Y. Photodegradation of Polyfluorinated Dibenzo-p-Dioxins (PFDDs) in Organic Solvents: Experimental and Theoretical Studies. *Environ. Sci. Technol.* **2016**, *50*, 8128–8134. [CrossRef] [PubMed]

37. Zhao, Y.Y.; Li, Y. Design of Environmentally Friendly Neonicotinoid Insecticides with Tuning of Bioconcentration and Bi-directional Selective Toxic Effects. *J. Clean. Prod.* **2019**, *22*, 113–121. [CrossRef]

38. Zhao, Y.Y.; Hou, Y.L.; Li, Y. Design of Green Substitutes for Neonicotinoid Insecticides and Multi-Directional Selective Toxicity Effects on Farmland Ecosystems. *J. Clean. Prod.* **2020**, accept. [CrossRef]

39. Chen, Y. Overview on 2014 World Insecticides Market. *Mod. Agrochem.* **2016**, *15*, 1–7.

40. Duan, C.Q. The Technical Study of Thiacloprid and Bupirimate and the Synthesis and Activity of Neonicotinoid Insectides Thiazoles Ramification Compound. Master's Thesis, Qingdao University of Science and Technology, Qingdao, China, October 2015.

41. Li, B.B.; Hou, C.S.; Diao, Q.Y. Neonicotinoid pesticides severely affect honey bee. *Apic. China* **2016**, *67*, 31–35.

42. Ge, J.; Cui, K.; Yan, H.Q.; Li, Y.; Chai, Y.Y.; Liu, X.J.; Cheng, J.F.; Yu, X.Y. Uptake, translocation and metabolism of imidacloprid in plants. *Bull. Insectol.* **2017**, *226*, 479–485.

43. Sánchez-Bayo, F. The trouble with neonicotinoids. *Science* **2014**, *346*, 806–807. [CrossRef]

44. Morrissey, C.A.; Mineau, P.; Devries, J.H.; Sanchez-Bayo, F.; Liess, M.; Cavallaro, M.C.; Liber, K. Neonicotinoid contamination of global surface waters and associated risk to aquatic invertebrates: A review. *Environ. Int.* **2015**, *74*, 291–303. [CrossRef] [PubMed]

45. Chagnon, M.; Kreutzweiser, D.; Mitchell, E.A.; Morrissey, C.A.; Noome, D.A.; Van der Sluijs, J.P. Risks of large-scale use of systemic insecticides to ecosystem functioning and services. *Environ. Sci. Pollut. Res. Int.* **2012**, *22*, 119–134. [CrossRef]

46. Pastor-Belda, M.; Garrido, I.; Campillo, N.; Viñas, P.; Hellín, P.; Flores, P.; Fenoll, J. Determination of spirocyclic tetronic/tetramic acid derivatives and neonicotinoid insecticides in fruits and vegetables by liquid chromatography and mass spectrometry after dispersive liquid−liquid microextraction. *Food Chem.* **2016**, *202*, 389–395. [CrossRef] [PubMed]

47. Hu, B.Z.; Cai, H.J.; Song, W.H. Determination of eight pesticide residues in tea by liquid chromatography-tandem mass spectrometry and its uncertainty evaluation. *Chin. J. Chromatogr.* **2012**, *30*, 889–895. (In Chinese) [CrossRef] [PubMed]

48. Liu, S.Y.; Zheng, Z.T.; Wei, F.L.; Ren, Y.P.; Gui, W.J.; Wu, H.M.; Zhu, G.N. Simultaneous Determination of Seven Neonicotinoid Pesticide Residues in Food by Ultraperformance Liquid Chromatography Tandem Mass Spectrometry. *J. Agric. Food Chem.* **2010**, *58*, 3271–3278. [CrossRef]

49. Chen, M.; Tao, L.; Mclean, J.; Lu, C.S. Quantitative analysis of neonicotinoid insecticide residues in foods: Implication for dietary exposures. *J. Agric. Food Chem.* **2014**, *62*, 6082–6090. [CrossRef]

50. Tan, Y.; Zhang, Q.; Zhao, C.; Wang, X.Y.; Li, J.R.; Wang, D.; Zhou, Y.; Lu, X.X. Residues of neonicotinoid pesticides in vegetables and fruit and health risk assessment of human exposure via food intake. *Asian J. Ecotoxicol.* **2016**, *11*, 67–81. (In Chinese)

51. Wood, T.J.; Goulson, D. The environmental risks of neonicotinoid pesticides: A review of the evidence post 2013. *Environ. Sci. Pollut. Res.* **2017**, *24*, 17285–17325. [CrossRef]

52. Botías, C.; David, A.; Horwood, J.; Abdul-Sada, A.; Nicholls, E.; Hill, E.; Goulson, D. Neonicotinoid residues in wildflowers, a potential route of chronic exposure for bees. *Environ. Sci. Technol.* **2015**, *49*, 12731–12740. [CrossRef]

53. Tsvetkov, N.; Samson-Robert, O.; Sood, K.; Patel, H.S.; Malena, D.A.; Gajiwala, P.H.; Maciukiewicz, P.; Fournier, V.; Zayed, A. Chronic exposure to neonicotinoids reduces honey bee health near corn crops. *Science* **2017**, *356*, 1395–1397. [CrossRef] [PubMed]

54. David, A.; Botías, C.; Abdul-Sada, A.; Nicholls, E.; Rotheray, E.L.; Hill, E.M.; Goulson, D. Widespread contamination of wildflower and bee-collected pollen with complex mixtures of neonicotinoids and fungicides commonly applied to crops. *Environ. Int.* **2016**, *88*, 169–178. [CrossRef]

55. European Commission. Commission implementing regulation (EU) 2018/783 of 29 may 2018 amending implementing regulation (EU) No 540/2011 as regards the conditions of approval of the active substance imidacloprid. *Off. J. Eur. Union* **2018**, *132*, 31.

56. European Commission. Commission implementing regulation (EU) 2018/784 of 29 may 2018 amending implementing regulation (EU) No 540/2011 as regards the conditions of approval of the active substance clothianidin. *Off. J. Eur. Union* **2018**, *132*, 35.

57. European Commission. Commission implementing regulation (EU) 2018/785 of 29 may 2018 amending implementing regulation (EU) No 540/2011 as regards the conditions of approval of the active substance thiamethoxam. *Off. J. Eur. Union* **2018**, *132*, 40.

58. Van der Sluijs, J.P.; Simon-Delso, N.; Goulson, D.; Maxim, L.; Bonmatin, J.M.; Belzunces, L.P. Neonicotinoids, bee disorders and the sustainability of pollinator services. *Curr. Opin. Environ. Sustain.* **2013**, *5*, 293–305. [CrossRef]

59. Bonmatin, J.M.; Giorio, C.; Girolami, V.; Goulson, D.; Kreutzweiser, D.P.; Krupke, C.; Liess, M.; Long, E.; Marzaro, M.; Mitchell, E.A.; et al. Environmental fate and exposure; neonicotinoids and fipronil. *Environ. Sci. Pollut. Res.* **2015**, *22*, 35–67. [CrossRef]

60. Hladik, M.L.; Main, A.R.; Goulson, D. Environmental risks and challenges associated with neonicotinoid insecticides. *Environ. Sci. Technol.* **2018**, *52*, 3329–3335. [CrossRef]

61. Jones, A.; Harrington, P.; Turnbull, G. Neonicotinoid concentrations in arable soils after seed treatment applications in preceding years. *Pest Manag. Sci.* **2014**, *70*, 1780–1784. [CrossRef]

62. Lima, M.A.P.; Martins, G.F.; Oliveira, E.E.; Guedes, R.N.C. Agrochemical-induced stress in stingless bees: Peculiarities, underlying basis, and challenges. *J. Comp. Physiol.* **2016**, *202*, 733–747. [CrossRef]

63. La, N.; Lamers, M.; Bannwarth, M.; Nguyen, V.; Streck, T. Imidacloprid concentrations in paddy rice fields in northern Vietnam: Measurement and probabilistic modeling. *Paddy Water Environ.* **2014**, *13*, 191–203. [CrossRef]

64. Garibaldi, L.A.; Steffan-Dewenter, I. Wild Pollinators Enhance Fruit Set of Crops Regardless of Honey Bee Abundance. *Science* **2013**, *339*, 1608–1611. [CrossRef] [PubMed]

65. Wusmart, J.; Spivak, M. Sub-lethal effects of dietary neonicotinoid insecticide exposure on honey bee queen fecundity and colony development. *Sci. Rep.* **2016**, *6*, 32108. [CrossRef] [PubMed]

66. Woodcock, B.A.; Bullock, J.M.; Shore, R.F.; Heard, M.S.; Pereira, M.G.; Redhead, J.; Ridding, L.; Dean, H.; Sleep, D.; Henrys, P.; et al. Country-specific effects of neonicotinoid pesticides on honey bees and wild bees. *Science* **2017**, *356*, 1393–1395. [CrossRef]

67. Decourtye, A.; Devillers, J.; Genecque, E.; Menach, K.L.; Budzinski, H.; Cluzeau, S.; Pham-Delgue, M.H. Comparative sublethal toxicity of nine pesticides on olfactory learning performances of the honeybee Apis mellifera. *Arch. Environ. Contam. Toxicol.* **2015**, *48*, 242–250. [CrossRef]

68. El Hassani, A.K.; Dacher, M.; Gary, V.; Lambin, M.; Gauthier, M.; Armengaud, C. Effects of sublethal doses of acetamiprid and thiamethoxam on the behavior of the honeybee (*Apis mellifera*). *Arch. Environ. Contam. Toxicol.* **2008**, *54*, 653–661. [CrossRef]

69. Henry, M.; Béguin, M.; Requier, F.; Rollin, O.; Odoux, J.F.; Aupinel, P.; Aptel, J.; Tchamitchian, S.; Decourtye, A. A common pesticide decreases foraging success and survival in honey bees. *Science* **2012**, *336*, 348–350. [CrossRef]

70. Yang, E.C.; Chang, H.C.; Wu, W.Y.; Chen, Y.W. Impaired olfactory associative behavior of honeybee workers due to contamination of imidacloprid in the larval stage. *PLoS ONE* **2012**, *7*, e49472. [CrossRef]

71. Tan, K.; Chen, W.; Dong, S.; Liu, X.W.; Wang, Y.C.; Nieh, J.C. Imidacloprid alters foraging and decreases bee avoidance of predators. *PLoS ONE* **2014**, *9*, e102725. [CrossRef]

72. Rundlöf, M.; Andersson, G.K.S.; Bommarco, R.; Fries, I.; Hederstrem, V.; Herbertsson, L.; Jonsson, O.; Klatt, B.K.; Pedersen, T.R.; Yourstone, J.; et al. Seed Coating with a Neonicotinoid Insecticide Negatively Affects Wild Bees. *Nature* **2015**, *521*, 77–94. [CrossRef]

73. McArt, S.H.; Fersch, A.A.; Milano, N.J.; Truitt, L.L.; Böröczky, K. High pesticide risk to honey bees despite low focal crop pollen collection during pollination of a mass blooming crop. *Sci. Rep.* **2017**, *7*, 46554. [CrossRef] [PubMed]

74. Sandrock, C.; Tanadini, L.G.; Pettis, J.S.; Biesmeijer, J.C.; Potts, S.G.; Neumann, P. Sublethal neonicotinoid insecticide exposure reduces solitary bee reproductive success. *Agric. For. Entomol.* **2014**, *16*, 119–128. [CrossRef]

75. Stanley, D.A.; Michael, P.; Garratt, D.; Wickens, J.B.; Wickens, V.J.; Potts, S.G.; Raine, N.E. Neonicotinoid pesticide exposure impairs crop pollination services provided by bumblebees. *Nature* **2015**, *528*, 548–550. [CrossRef] [PubMed]

76. Mitchell, E.A.D.; Mulhauser, B.; Mulot, M.; Mutabazi, A.; Glauser, G.; Aebi, A. Aworldwide survey of neonicotinoids in honey. *Science* **2017**, *358*, 109–111. [CrossRef]

77. Christen, V.; Mittner, F.; Fent, K. Molecular effects of neonicotinoids in honey bees (*Apis mellifera*). *Environ. Sci. Technol.* **2016**, *50*, 4071–4081. [CrossRef]

78. Babelova, J.; Šefčíková, Z.; Čikoš, S.; Špirková, A.; Kovaříková, V.; Koppel, J.; Makarevich, A.V.; Chrenek, P.; Fabian, D. Exposure to neonicotinoid insecticides induces embryotoxicity in mice and rabbits. *Toxicology* **2017**, *392*, 71–80. [CrossRef]

79. Kapoor, U.; Srivastava, M.K.; Srivastava, L.P. Toxicological impact of technical imidacloprid on ovarian morphology, hormones and antioxidant enzymes in female rats. *Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc.* **2011**, *49*, 3086–3089. [CrossRef]

80. Bal, R.; Naziroglu, M.; Turk, G.; Yilmaz, O.; Kuloglu, T.; Etem, E.; Baydas, G. Insecticide imidacloprid induces morphological and DNA damage through oxidative toxicity on the reproductive organs of developing male rats. *Cell Biochem. Funct.* **2012**, *30*, 492–499. [CrossRef]

81. Bal, R.; Turk, G.; Tuzcu, M.; Yilmaz, O.; Kuloglu, T.; Baydas, G.; Naziroglu, M.; Yener, Z.; Etem, E.; Tuzcu, Z. Effects of the neonicotinoid insecticide, clothianidin, on the reproductive organ system in adult male rats. *Drug Chem. Toxicol.* **2013**, *36*, 421–429. [CrossRef]

82. Bal, R.; Turk, G.; Tuzcu, M.; Yilmaz, O.; Kuloglu, T.; Gundogdu, R.; Gur, S.; Agca, A.; Ulas, M.; Cambay, Z.; et al. Assessment of imidacloprid toxicity on reproductive organ system of adult male rats. *J. Environ. Sci. Health Part B* **2012**, *47*, 434–444. [CrossRef]

83. Bal, R.; Turk, G.; Yilmaz, O.; Etem, E.; Kuloglu, T.; Baydas, G.; Naziroglu, M. Effects of clothianidin exposure on sperm quality, testicular apoptosis and fatty acid composition in developing male rats. *Cell Biol. Toxicol.* **2012**, *28*, 187–200. [CrossRef] [PubMed]

84. Hirano, T.; Yanai, S.; Omotehara, T.; Hashimoto, R.; Umemura, Y.; Kubota, N.; Minami, K.; Nagahara, D.; Matsuo, E.; Aihara, Y.; et al. The combined effect of clothianidin and environmental stress on the behavioral and reproductive function in male mice. *J. Vet. Med. Sci.* **2015**, *77*, 1207–1215. [CrossRef] [PubMed]

85. Bhardwaj, S.; Srivastava, M.K.; Kapoor, U.; Srivastava, L.P. A 90 days oral toxicity of imidacloprid in female rats: Morphological, biochemical and histopathological evaluations. *Food Chem. Toxicol.* **2010**, *48*, 1185–1190. [CrossRef] [PubMed]

86. Toor, H.K.; Sangha, G.K.; Khera, K.S. Imidacloprid induced histological and biochemical alterations in liver of female albino rats. *Pestic. Biochem. Phys.* **2013**, *105*, 1–4. [CrossRef] [PubMed]

87. Vohra, P.; Khera, K.S.; Sangha, G.K. Physiological, biochemical and histological alterations induced by administration of imidacloprid in female albino rats. *Pestic. Biochem. Phys.* **2014**, *110*, 50–56. [CrossRef]

88. Kapoor, U.; Srivastava, M.K.; Trivedi, P.; Garg, V.; Srivastava, L.P. Disposition and acute toxicity of imidacloprid in female rats after single exposure. *Food Chem. Toxicol.* **2014**, *68*, 190–195. [CrossRef]

89. Arfat, Y.; Mahmood, N.; Tahir, M.U.; Rashid, M.; Anjum, S.; Zhao, F.; Li, D.J.; Sun, Y.L.; Hu, L.; Zhihao, C.; et al. Effect of imidacloprid on hepatotoxicity and nephrotoxicity in male albino mice. *Toxicol. Rep.* **2014**, *1*, 554–561. [CrossRef]

90. Calderon-Segura, M.E.; Gomez-Arroyo, S.; Villalobos-Pietrini, R.; Martinez-Valenzuela, C.; Carbajal-Lopez, Y.; Calderon-Ezquerro Mdel, C.; Cortes-Eslava, J.; Garcia-Martinez, R.; Flores-Ramirez, D.; Rodriguez-Romero, M.I.; et al. Evaluation of genotoxic and cytotoxic effects in human peripheral blood lymphocytes exposed in vitro to neonicotinoid insecticides news. *J. Toxicol.* **2012**, *2012*, 612647. [CrossRef]

91. Kocaman, A.Y.; Rencuzogullari, E.; Topaktas, M. In vitro investigation of the genotoxic and cytotoxic effects of thiacloprid in cultured human peripheral blood lymphocytes. *Environ. Toxicol.* **2014**, *29*, 631–641. [CrossRef]

92. Galdikova, M.; Sivikova, K.; Holeckova, B.; Dianovsky, J.; Drazovska, M.; Schwarzbacherova, V. The effect of thiacloprid formulation on DNA/chromosome damage and changes in GST activity in bovine peripheral lymphocytes. *J. Environ. Health Sci. Part B* **2015**, *50*, 698–707. [CrossRef]

93. Kataria, S.K.; Chhillar, A.K.; Kumar, A.; Tomar, M.; Malik, V. Cytogenetic and hematological alterations induced by acute oral exposure of imidacloprid in female mice. *Drug Chem. Toxicol.* **2016**, *39*, 59–65. [CrossRef] [PubMed]

94. Amaral, M.J.; Bicho, R.C.; Carretero, M.A.; Sanchezhernandez, J.C.; Faustino, A.M.; Soares, A.M.; Mann, R.M. The use of a lacertid lizard as a model for reptile ecotoxicology studies: Part 2-biomarkers of exposure and toxicity among pesticide exposed lizards. *Chemosphere* **2012**, *87*, 765–774. [CrossRef] [PubMed]

95. Randhawa, M.A.; Anjum, M.N.; Butt, M.S.; Yasin, M.; Imran, M. Minimization of imidacloprid residues in cucumber and bell pepper through washing with citric acid and acetic acid solutions and their dietary intake assessment. *Int. J. Food Prop.* **2014**, *17*, 978–986. [CrossRef]

96. Mingo, V.; Lotters, S.; Wagner, N. Risk of pesticide exposure for reptile species in the European Union. *Environ. Pollut.* **2016**, *215*, 164–169. [CrossRef] [PubMed]

97. Bicho, R.C.; Amaral, M.J.; Faustino, A.M.; Power, D.M.; Rema, A.; Carretero, M.A.; Soares, A.M.; Mann, R.M. Thyroid disruption in the lizard Podarcis bocagei exposed to a mixture of herbicides: A field study. *Ecotoxicology* **2013**, *22*, 156–165. [CrossRef]

98. Park, H.; Suk, H.Y.; Jeong, E.; Park, D.; Lee, H.; Min, M. Population genetic structure of endangered Mongolian racerunner (*Eremias argus*) from the Korean Peninsula. *Mol. Biol. Rep.* **2014**, *41*, 7339–7347. [CrossRef]

99. Zhu, Y.; Ma, X.F.; Su, G.Y.; Yu, L.Q.; Robert, J.L.; Hou, J.; Yu, H.X.; John, P.G.; Liu, C. Environmentally Relevant Concentrations of the Flame-Retardant Tris (1,3-dichloro-2-propyl) Phosphate (TDCIPP) Inhibits Growth of Female Zebrafish and Decreases Fecundity. *Environ. Sci. Technol.* **2015**, *49*, 14579–14587. [CrossRef]

100. Miles, J.C.; Hua, J.; Sepulveda, M.S.; Krupke, C.H.; Hoverman, J.T. Effects of clothianidin on aquatic communities: Evaluating the impacts of lethal and sublethal exposure to neonicotinoids. *PLoS ONE* **2017**, *13*, e0194634. [CrossRef]

101. Pereira, A.S.; Cerejeira, M.J.; Daam, M.A. Ecological risk assessment of imidacloprid applied to experimental rice fields: Accurateness of the RICEWQ model and effects of ecosystem structure. *Ecotoxicol. Environ. Saf.* **2017**, *142*, 431–440. [CrossRef]

102. Main, A.R.; Webb, E.B.; Goyne, K.W.; Mengel, D. Neonicotinoid insecticides negatively affect performance measures of non-target terrestrial arthropods: A meta-analysis. *Ecol. Appl.* **2018**, *28*, 1232–1244. [CrossRef]

103. Riens, J.R.; Schwarz, M.S.; Mustafa, F.; Hoback, W.W. Aquatic macroinvertebrate communities and water quality at buffered and non-buffered wetland sites on federal waterfowl production areas in the Rainwater Basin, Nebraska. *Wetlands* **2013**, *33*, 1025–1036. [CrossRef]

104. Smit, C.E.; Posthuma-Doodeman, J.A.M.; van Vlaardingen, P.L.A.; de Jong, F.M.W. Ecotoxicity of imidacloprid to aquatic organisms: Derivation of water quality standards for peak and long-term exposure. *Hum. Ecol. Risk Assess.* **2015**, *21*, 1608–1630. [CrossRef]

105. Anderson, T.A.; Salice, C.J.; Erickson, R.A.; McMurry, S.T.; Cox, S.B.; Smith, L.M. Effects of landuse and precipitation on pesticides and water quality in playa lakes of the southern high plains. *Chemosphere* **2013**, *92*, 84–90. [CrossRef] [PubMed]

106. Sánchez-Bayo, F.; Goka, K.; Hayasaka, D. Contamination of the aquatic environment with neonicotinoids and its implication for ecosystems. *Front. Environ. Sci.* **2016**, *4*, 291–303. [CrossRef]

107. Evelsizer, V.; Skopec, M. Pesticides, including neonicotinoids, in drained wetlands of Iowa's prairie pothole region. *Wetlands* **2018**, *38*, 221–232. [CrossRef]

108. Anderson, J.C.; Dubetz, C.; Palace, V.P. Neonicotinoids in the Canadian aquatic environment: A literature review on current use products with a focus on fate, exposure, and biological effects. *Sci. Total Environ.* **2015**, *505*, 409–422. [CrossRef]

109. Schepker, T.J.; Webb, E.B.; Tillitt, D.; LaGrange, T. Neonicotinoid insecticide concentrations in agricultural wetlands and associations with aquatic invertebrate communities. *Agric. Ecosyst. Environ.* **2020**, *287*, 106–109. [CrossRef]

110. Cimino, A.M.; Boyles, A.L.; Thayer, K.A. Effects of Neonicotinoid Pesticide Exposure on Human Health: A Systematic Review. *Environ. Health Perspect.* **2017**, *125*, 155–162. [CrossRef]

111. Ueyama, J.; Nomura, H.; Kondo, T.; Saito, I.; Ito, Y.; Osaka, A.; Kamijima, M. Biological monitoring method for urinary neonicotinoid insecticides using LCMS/MS and its application to Japanese adults. *J. Occup. Health* **2014**, *56*, 461–468. [CrossRef]

112. Ueyama, J.; Harada, K.H.; Koizumi, A.; Sugiura, Y.; Kondo, T.; Saito, I.; Kamijima, M. Temporal levels of urinary neonicotinoid and dialkylphosphate concentrations in Japanese women between 1994 and 2011. *Environ. Sci. Technol.* **2015**, *49*, 14522–14528. [CrossRef]

113. Osaka, A.; Ueyama, J.; Kondo, T.; Nomura, H.; Sugiura, Y.; Saito, I.; Nakane, K.; Takaishi, A.; Ogi, H.; Wakusawa, S.; et al. Exposure characterization of three major insecticide lines in urine of young children in Japanneonicotinoids, organophosphates, and pyrethroids. *Environ. Res.* **2016**, *147*, 89–96. [CrossRef] [PubMed]

114. Tao, Y. Exposure Characteristics of Neonicotinoid Imidacloprid towards Human Body Based on Metabolomics. Ph.D. Thesis, Chinese Academy of Agricultural Sciences, Beijing, China, May 2019.

115. Kavvalakis, M.P.; Tzatzarakis, M.N.; Theodoropoulou, E.P.; Barbounis, E.G.; Tsakalof, A.K.; Tsatsakis, A.M. Development and application of LC-APCIMS method for biomonitoring of animal and human exposure to imidacloprid. *Chemosphere* **2013**, *93*, 2612–2620. [CrossRef] [PubMed]

116. Tadashi, Y.; Hikoto, O.; Mika, A.; Baisuke, W. Simultaneous determination of neonicotinoid insecticides in human serum and urine using diatomaceous earth-assisted extraction and liquid chromatography–tandem mass spectrometry. *J. Chromatogr. B* **2014**, *969*, 85–94.

117. Sagiv, S.K.; Harris, M.H.; Gunier, R.B.; Kogut, K.R.; Harley, K.G.; Deardorff, J.; Bradman, A.; Holland, N.; Eskenazi, B. Prenatal Organophosphate Pesticide Exposure and Traits Related to Autism Spectrum Disorders in a Population Living in Proximity to Agriculture. *Environ. Health Perspect.* **2018**, *126*, 47–59.

118. Mercadante, R.; Polledri, E.; Moretto, A.; Fustinoni, S. Long-term occupational and environmental exposure to penconazole and tebuconazole by hair biomonitoring. *Toxicol. Lett.* **2018**, *298*, 19–24. [CrossRef]

119. Lozano-Paniagua, D.; Parron, T.; Alarcon, R.; Requena, M.; Gil, F.; López-Guarnido, O.; Lacasaña, M.; Hernández, A.F. Biomarkers of oxidative stress in blood of workers exposed to non- cholinesterase inhibiting pesticides. *Ecotoxicol. Environ. Saf.* **2018**, *162*, 121–128. [CrossRef]

120. Wei, Y.; Carmichael, S.L.; Roberts, E.M.; Susan, E.K.; Amy, M.P.; Paul, B.E.; Gary, M.S. Residential Agricultural Pesticide Exposures and Risk of Neural Tube Defects and Orofacial Clefts Among Offspring in the San Joaquin Valley of California. *Am. J. Epidemiol.* **2014**, *179*, 740–748.

121. Keil, A.P.; Daniels, J.L.; Hertz-Picciotto, I. Autism spectrum disorder, flea and tick medication, and adjustments for exposure misclassification: The CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. *Environ. Health* **2014**, *13*, 3–13. [CrossRef]

122. Koureas, M.; Tsezou, A.; Tsakalof, A.; Orfanidou, T.; Hadjichristodoulou, C. Increased levels of oxidative DNA damage in pesticide sprayers in Thessaly Region (Greece). Implications of pesticide exposure. *Sci. Total Environ.* **2014**, *496*, 358–364. [CrossRef]

123. Marfo, J.T.; Fujioka, K.; Ikenaka, Y.; Nakayama, S.M.; Mizukawa, H.; Aoyama, Y.; Ishizuka, M.; Taira, K. Relationship between urinary N-Desmethyl-Acetamiprid and typical symptoms including neurological findings: A prevalence case-control study. *PLoS ONE* **2015**, *10*, e0142172. [CrossRef]

124. Seltenrich, N. Catching Up with Popular Pesticides: More Human Health Studies Are Needed on Neonicotinoids. *Environ. Health Perspect.* **2017**, *125*, 41–42. [CrossRef] [PubMed]

125. Mesnage, R.; Bisemi, M.; Genkova, D. Evaluation of neonicotinoid insecticides for oestrogenic, thyroidogenic and adipogenic activity reveals imidacloprid causes lipid accumulation. *J. Appl. Toxicol.* **2018**, *38*, 1483–1491. [CrossRef] [PubMed]

126. Main, A.R.; Headley, J.V.; Peru, K.M.; Michel, N.L.; Cessna, A.J.; Morrissey, C.A. Widespread use and frequent detection of neonicotinoid insecticides in wetlands of Canada's Prairie Pothole Region. *PLoS ONE* **2014**, *9*, e92821. [CrossRef] [PubMed]

127. Sadaria, A.; Supowit, S.D.; Halden, R.U. Mass balance assessment for six neonicotinoid insecticides during conventional wastewater and wetland treatment: Nationwide reconnaissance in United States wastewater. *Environ. Sci. Technol.* **2016**, *50*, 6199–6206. [CrossRef]

128. Yamamoto, A.; Terao, T.; Hisatomi, H.; Kawasaki, H.; Arakawa, R. Evaluation of river pollution of neonicotinoids in Osaka City (Japan) by LC/MS with dopant-assisted photoionisation. *J. Environ. Monit.* **2012**, *14*, 2189–2194. [CrossRef]

129. Moschet, C.; Wittmer, I.; Simovic, J.; Junghans, M.; Piazzoli, A.; Singer, H.; Stamm, C.; Leu, C.; Hollender, J. How a complete pesticide screening changes the assessment of surface water quality. *Environ. Sci. Technol.* **2014**, *48*, 5423–5432. [CrossRef] [PubMed]

130. Zhang, C.; Tian, D.; Yi, X.H.; Zhang, T.; Ruan, J.J.; Wu, R.R.; Chen, C.; Huang, M.Z.; Ying, G.G. Occurrence, distribution and seasonal variation of five neonicotinoid insecticides in surface water and sediment of the Pearl Rivers, South China. *Chemosphere* **2019**, *217*, 437–446. [CrossRef]

131. Qi, Q.X.; Singer, H.; Berg, M.; Müller, B.; Pernet-Coudrier, B.; Liu, H.J.; Qu, J.H. Elimination of polar micropollutants and anthropogenic markers by wastewater treatment in Beijing, China. *Chemosphere* **2015**, *119*, 1054–1061. [CrossRef]

132. Chen, M.; Yi, Q.; Hong, J. Simultaneous determination of 32 antibiotics and 12 pesticides in sediment using ultrasonic-assisted extraction and high-performance liquid chromatography-tandem mass spectrometry. *Anal. Methods* **2015**, *7*, 1896–1905. [CrossRef]

133. Bradley, P.M.; Journey, C.A.; Romanok, K.M.; Barber, L.B.; Buxton, H.T.; Foreman, W.T.; Furlong, E.T.; Glassmeyer, S.T.; Hladik, M.L.; Iwanowicz, L.R.; et al. Expanded target-chemical analysis reveals extensive mixed-organic-contaminant exposure in U.S. streams. *Environ. Sci. Technol.* **2017**, *51*, 4792–4802. [CrossRef]

134. de Perre, C.; Murphy, T.M.; Lydy, M.J. Fate and effects of clothianidin in fields using conservation practices. *Environ. Toxicol. Chem.* **2015**, *34*, 258–265. [CrossRef]

135. Benton, E.P.; Grant, J.F.; Mueller, T.C.; Webster, R.J.; Nichols, R.J. Consequences of imidacloprid treatments for hemlock woolly adelgid on stream water quality in the southern Appalachians. *For. Ecol. Manag.* **2016**, *360*, 152–158. [CrossRef]

136. Huseth, A.S.; Groves, R.L. Environmental fate of soil applied neonicotinoid insecticides in an irrigated potato agroecosystem. *PLoS ONE* **2014**, *9*, e97081. [CrossRef] [PubMed]

137. Main, A.R. Snowmelt transport of neonicotinoid insecticides to Canadian prairie wetlands. *Agric. Ecosyst. Environ.* **2016**, *215*, 76–84. [CrossRef]

138. Samson-Robert, O.; Labrie, G.; Chagnon, M.; Fournier, V. Neonicotinoid-contaminated puddles of water represent a risk of intoxication for honey bees. *PLoS ONE* **2014**, *9*, e108443. [CrossRef] [PubMed]

139. Schaafsma, A.; Limay-Rios, V.; Baute, T.; Smith, J.; Xue, Y. Neonicotinoid insecticide residues in surface water and soil associated with commercial maize (corn) fields in southwestern Ontario. *PLoS ONE* **2015**, *10*, e0118139. [CrossRef]

140. Dijk, T.C.V.; Staalduinen, M.A.V.; Sluijs, J.P.V.D. Macroinvertebrate decline in surface water polluted with imidacloprid. *PLoS ONE* **2015**, *9*, e89837.

141. Englert, D.; Bakanov, N.; Zubrod, J.P.; Schulz, R.; Bundschuh, M. Modeling remobilization of neonicotinoid residues from tree foliage in streams—A relevant exposure pathway in risk assessment. *Environ. Sci. Technol.* **2017**, *51*, 1785–1794. [CrossRef]

142. López-Doval, J.C.; Montagner, C.C.; de Alburquerque, A.F.; Moschini-Carlos, V.; Umbuzeiro, G.; Pompêo, M. Nutrients, emerging pollutants and pesticides in a tropical urban reservoir: Spatial distributions and risk assessment. *Sci. Total Environ.* **2016**, *575*, 1307–1324. [CrossRef]

143. Gonzalez-Rey, M.; Tapie, N.; Le, M.K.; Dévier, M.H.; Budzinski, H.; Bebianno, M.J. Occurrence of pharmaceutical compounds and pesticides in aquatic systems. *Mar. Pollut. Bull.* **2015**, *96*, 384–400. [CrossRef]

144. Székács, A.; Mörtl, M.; Darvas, B. Monitoring pesticide residues in surface and ground water in Hungary: Surveys in 1990–2015. *J. Chem.* **2015**, *2015*, 717948. [CrossRef]

145. Masiá, A.; Campo, J.; Vázquez-Roig, P.; Blasco, C.; Picó, Y. Screening of currently used pesticides in water, sediments and biota of the Guadalquivir River Basin (Spain). *J. Hazard. Mater.* **2013**, *263*, 95–104. [CrossRef] [PubMed]

146. Kreutzweiser, D.P.; Thompson, D.G.; Scarr, T.A. Imidacloprid in leaves from systemically treated trees may inhibit litter breakdown by non-target invertebrates. *Ecotoxicol. Environ. Saf.* **2009**, *72*, 1053–1057. [CrossRef] [PubMed]

147. Dankyi, E.; Gordon, C.; Carboo, D.; Formsgaard, T.S. Quantification of neonicotinoid insecticide residues in soils from cocoa plantations using a QuEChERS extraction procedure and LC-MS/MS. *Sci. Total Environ.* **2014**, *499*, 276–283. [CrossRef] [PubMed]

148. Limayrios, V.; Forero, L.G.; Xue, Y.; Smith, J.; Baute, T.; Schaafsma, A. Neonicotinoid insecticide residues in soil dust and associated parent soil in fields with a history of seed treatment use on crops in Southwestern Ontario. *Environ. Toxicol. Chem.* **2016**, *35*, 303–310. [CrossRef]

149. Xu, T.; Dyer, D.G.; Mcconnell, L.L.; Bondarenko, S.; Allen, R.; Heinemann, O. Clothianidin in agricultural soils and uptake into corn pollen and canola nectar after multiyear seed treatment applications. *Environ. Toxicol. Chem.* **2016**, *35*, 311–321. [CrossRef]

150. Abdel-Ghany, M.F.; Hussein, L.A.; El Azab, N.F.; El-Khatib, A.H.; Linscheid, M.W. Simultaneous determination of eight neonicotinoid insecticide residues and two primary metabolites in cucumbers and soil by liquid chromatography–tandem mass spectrometry coupled with QuEChERS. *J. Chromatogr. B* **2016**, *1031*, 15–28. [CrossRef] [PubMed]

151. Zhou, Y.; Lu, X.X.; Fu, X.F.; Wang, D.; Zhao, C.; Zhang, Q.; Tan, Y.; Wang, X.Y. Development of a fast and sensitive method for measuring multiple neonicotinoid insecticide residues in soil and the application in parks and residential areas. *Anal. Chim. Acta* **2018**, *1016*, 19–28. [CrossRef]

152. Stewart, S.D.; Lorenz, G.M.; Catchot, A.L. Potential exposure of pollinators to neonicotinoid insecticides from the use of insecticide seed treatments in the mid-southern United States. *Environ. Sci. Technol.* **2014**, *48*, 9762–9769. [CrossRef]

153. Li, T.T.; Zheng, S.S.; Wang, J. A review on occurence and transformation behaviors of neonicotinoid pesticides. *Asian J. Ecotoxicol.* **2018**, *13*, 9–21.

154. Hoffmann, E.J.; Vandervoort, C.; Wise, J.C. Plum Curculio (Coleoptera: Curculionidae) adult mortality and associated fruit injury after exposure to field-aged insecticides on tart cherry branches. *J. Econ. Entomol.* **2010**, *103*, 1196–1205. [CrossRef]

155. Girolami, V.; Marzaro, M.; Vivan, L.; Mazzon, L.; Giorio, C.; Marton, D.; Tapparo, A. Aerial powdering of bees inside mobile cages and the extent of neonicotinoid cloud surrounding corn drillers. *J. Appl. Entomol.* **2013**, *137*, 35–44. [CrossRef]

156. Xue, Y.; Limay-Rios, V.; Smith, J.; Baute, T.; Forero, L.G.; Schaafsma, A. Quantifying neonicotinoid insecticide residues escaping during maize planting with vacuum planters. *Environ. Sci. Technol.* **2015**, *49*, 13003–13011. [CrossRef] [PubMed]

157. Botías, C.; David, A.; Hill, E.M.; Goulson, D. Contamination of wild plants near neonicotinoid seed-treated crops, and implications for non-target insects. *Sci. Total Environ.* **2016**, *566*, 269–278. [CrossRef] [PubMed]

158. Jiang, W.; Gan, J. Conversion of pesticides to biologically active products on urban hard surfaces. *Sci. Total Environ.* **2016**, *556*, 63–69. [CrossRef] [PubMed]

159. Roessink, I.; Merga, L.B.; Zweers, H.J. The Neonicotinoid Imidacloprid Shows High Chronic Toxicity to Mayfly Nymphs. *Environ. Toxicol. Chem.* **2013**, *32*, 1096–1100. [CrossRef] [PubMed]

160. Gibbons, D.; Morrissey, C.; Mineau, P. A Review of the Direct and Indirect Effects of Neonicotinoids and Fipronil on Vertebrate Wildlife. *Environ. Sci. Pollut. Res.* **2015**, *22*, 103–118. [CrossRef]

161. Chen, Z.L. Molecular Mechanism of Enantioselective Environmental Behavior and Toxicity Difference of Furosemide. Ph.D. Thesis, Chinese Academy of Agricultural Sciences, Beijing, China, May 2017.

162. Kessler, S.; Tiedeken, E.J.; Simcock, K.L.; Derveau, S.; Mitchell, J.; Softley, S.; Stout, J.C.; Wright, G.A. Bees Prefer Foods Containing Neonicotinoid Pesticides. *Nature* **2015**, *521*, 74–76. [CrossRef]

163. Forrester, M. Neonicotinoid Insecticide Exposures Reported to Six Poison Centers in Texas. *Hum. Exp. Toxicol.* **2014**, *33*, 568–573. [CrossRef]

164. Wei, Z.S.; Li, W.; Zhao, D.Y.; Seo, Y.; Spinney, R.; Dionysiou, D.D.; Wang, Y.; Zeng, W.Z.; Xiao, R.Y. Electrophilicity index as a critical indicator for the biodegradation of the pharmaceuticals in aerobic activated sludge processes. *Water Res.* **2019**, *160*, 10–17. [CrossRef]