

Annual Review of Food Science and Technology

Status and Perspective on Green Pesticide Utilizations and Food Security

Runjiang Song,¹ Yuping Zhang,¹ Ping Lu,¹ Jian Wu,¹
Qing X. Li,² and Baoan Song¹

¹National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang, China; email: basong@gzu.edu.cn

²Department of Molecular Biosciences and Bioengineering, University of Hawaii at Manoa, Honolulu, Hawaii, USA; email: qingl@hawaii.edu

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Annu. Rev. Food Sci. Technol. 2024. 15:473–93

First published as a Review in Advance on
December 22, 2023

The *Annual Review of Food Science and Technology* is
online at food.annualreviews.org

<https://doi.org/10.1146/annurev-food-072023-034519>

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Keywords

dietary risk, ecological risk, environmental risk, food security, health risk,
green pesticide, pesticide, sustainable pesticide

Abstract

Pesticides protect crops against pests, and green pesticides are referred to as effective, safe, and eco-friendly pesticides that are sustainably synthesized and manufactured (i.e., green chemistry production). Owing to their high efficacy, safety, and ecological compatibility, green pesticides have become a main direction of global pesticide research and development (R&D). Green pesticides attract attention because of their close association with the quality and safety of agricultural produce. In this review, we briefly define green pesticides and outline their significance, current registration, commercialization, and applications in China, the European Union, and the United States. Subsequently, we engage in an in-depth analysis of the impact of newly launched green pesticides on the environment and ecosystems. Finally, we focus on the potential risks of dietary exposure to green pesticides and the possible hazards of chronic toxicity and carcinogenicity. The status of and perspective on green pesticides can hopefully inspire green pesticide R&D and applications to ensure agricultural production and safeguard human and ecological health.

1. BACKGROUND

Advancement of sustainable agriculture is hampered by pests such as destructive insects, weeds, parasitic nematodes, and microbial pathogens (e.g., bacteria, fungi, and viruses). Pesticides are a widely used and effective means to control pests. However, rapid development of pesticide resistance is a huge concern because of the long-term and widespread use of conventional pesticides. Another major concern is the adverse impact of pesticides on the environment, ecosystems, food safety, and public health. The innovation and sustainable industrialization of green pesticides are of significance to providing pest management solutions and food security.

The term “green pesticide” is popularly used by the public and yet is in fact controversial, with diverse aliases and concepts such as eco-friendly agrochemicals, ecological pesticides, and risk-reduced pesticides depending on the viewpoint (Ataei et al. 2021, Karunamoorthi 2012, Qian et al. 2010). Providing a precise or uniform definition of green pesticide is challenging because of the subjective nature of individual perspectives on the term. As commonly understood, the pursuit of nontoxic or perfectly safe substances, whether in the form of pesticides or medicines, is widely perceived as an unattainable goal. The notion of “green” is therefore a relative concept. Today, sustainability has become a common goal of science and technology, and it is commonly accepted that green pesticides must be effective tools to serve the purpose of sustainable agriculture (Edwards 1990, Reganold et al. 1990, Velten et al. 2015). Consequently, green pesticides discussed in this review are largely based on the principle of sustainability and are also called sustainable pesticides. In general, green or sustainable pesticide refers to pesticides with high efficacy in controlling and managing pests and ensuring the safety of nontarget organisms and humans (Li et al. 2023). In addition to being biodegradable and leaving low residues in the environment, their synthesis and manufacturing process ought to be sustainable.

Typically, a green pesticide satisfies multiple characteristics of, but is not limited to, the following: (a) high pest management performance, meaning that its efficacy is considerably superior to that of conventional agrochemicals, which may be achieved with a reduced dosage in comparison to traditional pesticides while maintaining equivalent levels of effectiveness; (b) friendliness to nontargets because of high selectivity, i.e., they are toxic to pests but have low nontarget toxicity, high tolerability, and rapid degradation; (c) inspired by nature but not restricted to natural products only, yet ultimately returning to nature, i.e., their molecular designs are inspired by nature, but their production can be through fermentation and synthesis, and the degradation products exhibit minimal ecological consequences; (d) industrial sustainability, which means their manufacturing process should be sustainable, characterized by mild conditions, high yield, cost effectiveness, and minimal pollution; and (e) reduced probability for resistance development, i.e., they do not offer easy opportunities for pests to develop resistance. This review presents a comparative analysis of the current status of green pesticide research and development (R&D) in China, the European Union, and the United States. Our perspectives are explained with the chosen examples in the hope of promoting green pesticide R&D.

2. STATUS OF INNOVATIONS, REGISTRATION, PRODUCTION, AND CONSUMPTION OF GREEN PESTICIDES IN CHINA, THE EUROPEAN UNION, AND THE UNITED STATES

2.1. Green Pesticide Innovations in China, the European Union, and the United States

Multinational corporations such as BASF, Bayer, Corteva, FMC, and Syngenta have been at the forefront of global green pesticide R&D, continuously achieving new progress and breakthroughs.

Continuous discovery of new targets and innovation of chemical structures remain important avenues in pesticide R&D. More than 70 pesticide active ingredients (a.i.) targeting 20 distinct targets have been released globally since 2005, and numerous other candidates have been reported (Umetsu & Shirai 2020, Wu & Song 2020). Most of these newly launched pesticides share common targets, including succinate dehydrogenase inhibitors, nicotinic acetylcholine receptors, ryanodine receptors, gamma amino butyric acid receptors, etc. Nevertheless, some newly released a.i. demonstrate unique mechanisms of action or targets. For example, afidopyropen, dihydro jasmonate, and oxathiapiprolin target the vanilloid receptor channel complex (Kandasamy et al. 2017), jasmonic acid receptor (Asami & Nakagawa 2018), and oxidized sterol-binding protein (Pasteris et al. 2016), respectively.

In recent years, China has made remarkable progress in pesticide innovation (Li et al. 2023). More than 20 novel a.i. have been registered, and many leads and/or candidates with novel structures were reported (Shao et al. 2020, Wu & Song 2020). Some eco-friendly pesticides, such as dufulin, cypyrfluone, and phenamacril, have become available in the Chinese market to meet diverse needs. Guvermectin, a potential plant growth regulator, can promote biomass and grain yield of rice by 6.2–19.6% in field experiments (Liu et al. 2022). Moreover, several new targets, including myosin protein, hairpin binding protein-1, and dihydrolipoyl succinyltransferase, have been reported (Wu & Song 2020). New strategies and tools, e.g., computer-aided pesticide design, target-oriented innovative strategy, intermediate derivatization method, and natural product-based exploration, have been established to aid pesticide innovations (Li et al. 2023, Shao et al. 2020, Zhang et al. 2022). For instance, the auto core fragment in *in silico* screening, a fragment-based drug/pesticide discovery web server made by Yang's group (Hao et al. 2016), was employed to produce the first selective herbicide benquitrione for sorghum fields. This open-access website has been utilized by more than 5,000 researchers as of May 2023. Chinese scientists have built various databases such as CIPDB (Yang et al. 2023) and delved into the crystal structure of pest proteins (enzymes) and identified their eutectic structures with certain compounds as well as the functions of these proteins (Shao et al. 2020). Recently, Yang and coworkers resolved the crystal structures of chitin synthase (W. Chen et al. 2022), providing one of the most valuable resources for the invention of chitin synthase inhibitor insecticides.

2.2. Pesticide Registration Status in China, the European Union, and the United States

By March 2023, there were 45,253 validly registered pesticide products in China (ICAMA P.R. China 2023), and there were 40,132 in the European Union (Eur. Comm. 2023) and 57,739 in the United States (EPA 2023). Over the past three years (2020–2022), China issued 4,358 registrations of pesticide products, the US Environmental Protection Agency (EPA) approved a total of 2,200 product registrations, and the EU granted 4,319 items (Cao 2023).

In 2021, 15 a.i. were first registered in China, of which five were fungicides (isofetamid, bixafen, picarbutrazox, fenpropimorph, and fenhexamid), one was an insecticide (thiorantraniliprole), and six were herbicides (bixlozone, tembotrione, terbacil, eradicane, prosulfuron, and prosulfocarb). Three a.i. (Z-8-dodecen-1-yl acetate, Z-8-dodecen-1-ol, and E-8-dodecen-1-ol) were insect sex pheromones (ICAMA P.R. China 2023).

In 2022, a total of 438 pesticide products were registered in China, but no new a.i. were registered. However, three herbicides (flufenoximacil, fluchloraminopyr, and flusulfinam) discovered by KingAgroot® (Qingdao, China) were launched in Cambodia and will be registered in China in the near future. In contrast, 616 registered products in the United States involved more than 200 a.i., but most of the a.i. were reregistered. With its strong support for the progression of biopesticides,

the United States has implemented various incentives (such as exemption from data requirements and minimal review fees) for the registration of biopesticides. Nineteen new a.i. applications were submitted to the EPA in 2022, 14 of which were biopesticides and the rest were metamitron, spi-doxamat, isocycloseram, cyclobutrifluram, and acynonapyr; however, only 11 a.i. were approved (7 biopesticides and 4 chemical pesticides) by the EPA. Owing to very strict registration poli-cies, the European Commission did not grant approval for any novel a.i. for plant protection in 2022 (Cao 2023). As China, the United States, and the European Union become increasingly stringent with their new a.i. registration policies, the process of registering new a.i. entities will inevitably grow more arduous. When innovating new a.i., companies must not only consider po-tential adverse effects on mammals, such as residues, proxy products, and dietary risks, but also assess impacts on the environment and ecosystems. This evaluation should encompass factors such as soil, water, microorganisms, aquatic organisms, pollinators, and natural enemy organisms.

2.3. Overview of Consumption of Green Pesticides in China, the European Union, and the United States

The annual consumption of pesticides in the United States is approximately 400,000 tons of a.i., of which about 80% is for agricultural purposes. Herbicides have the highest usage, with an annual usage of about 200,000 tons. The consumption of insecticides has slightly decreased in recent years. Specifically, before 2000, approximately 100,000 tons of insecticide were used yearly, which decreased to approximately 75,000 tons in 2022. The consumption of fungicides has been approximately 20,000 tons year-to-year (Cao 2023).

In general, pesticide consumption in Europe has decreased since 2011. In 2020, pesticide sales in the European Union declined by 7.3% in comparison with 2011. Eurostat statistics showed a downward trend of pesticide consumption in Italy and France but an upward trend in Spain, Germany, and Poland (Cao 2023, Zhu et al. 2017). The Sustainable Use of Pesticides regulation intends to scale back the quantity of pesticides deployed by 50% by 2030. However, the European Union has delayed this plan to halve pesticide use over fears that the implementation may slash food production and raise the prices of essentials in the bloc (Brookins 2022). The possibility exists that the consumption of pesticides in certain European Union member states may increase in the near future.

The pesticide consumption in China (including Hong Kong, Macao, and Taiwan) was approx-imately 339,782 tons in 2010, which accounted for approximately 13% of the global consumption (Cao 2023). The consumption in 2020 in China (including the three territories) decreased to 273,760 tons (262,700 tons in mainland China), which was approximately 10% of the global consumption (Cao 2023). Moreover, there was an increase in green usage from 8,917 tons in 2000 to 18,744 tons in 2019 and to 18,845 tons in 2020 (in mainland China) (Qin et al. 2021).

2.4. Status of Maximum Residue Level Standards for Agricultural Products in China, the European Union, and the United States

Maximum residue levels (MRLs) are used as the standard to manage and ensure the safety of agricultural products worldwide. The Codex Alimentarius Commission, the United States, and the European Union have all been actively involved in the process of developing and revising MRL standards, which are founded on scientific risk assessment data (FAO 2023). The European Food Safety Authority (EFSA) is responsible for establishing the unified pesticide MRL standards across the European Union. These standards currently encompass 660 pesticides (a.i.) in 315 dif-ferent food and agricultural products. In the European Union, there are currently 227,613 MRL

Table 1 Comparison of the numbers of pesticide maximum residue level (MRL) standards in China and the European Union

Pesticide	China	European Union
Flonicamid	34 MRL standards for rice, wheat, maize, other crops, and fruits	380 MRL standards for crops, flowers, trees, animals, birds, poultry, offal, eggs, milk, etc.
Ethametsulfuron-methyl	33 MRL standards for crops, vegetables, fruits, medicinal plants, etc.	375 MRL standards for crops, flowers, trees, animals, birds, poultry, offal, eggs, milk, etc.
Fenarimol	20 MRL standards for crops, fruits, animals, etc.	377 MRL standards for crops, flowers, trees, animals, birds, poultry, offal, eggs, milk, etc.
Flupyradifurone	47 MRL standards for crops, vegetables, fruits, animal offal, etc.	380 MRL standards for crops, flowers and trees, animals, birds, poultry, offal, eggs, milk, etc.
Spirotetramat	61 MRL standards for crops, vegetables, fruits, medicinal plants, etc.	381 MRL standards for crops, flowers, trees, animals, birds, poultry, offal, eggs, milk, etc.
Pyraclostrobin	117 MRL standards for crops, vegetables, fruits, medicinal plants, etc.	380 MRL standards for crops, flowers and trees, animals, birds, poultry, offal, eggs, milk, etc.
Triflumezopyrim	Not yet available	380 MRL standards for crops, flowers and trees, animals, birds, poultry, offal, eggs, milk, etc.

standards and approximately 640 a.i. are subjected to long-term monitoring (Eur. Comm. 2023). The EPA is responsible for establishing MRLs in the United States. The number of MRLs for more than 450 pesticides (a.i.) was over 50,000 items. Additionally, approximately 500 a.i. were subject to basket surveys (Qin et al. 2021).

In 2016, the National Health Commission, Ministry of Agriculture and Rural Affairs, and State Administration for Market Regulation joined forces to establish a unified system for MRLs in China, releasing a standard titled “National Food Safety Standard Maximum Residue Limits for Pesticides in Food” (GB 2763-2021). In total, this standard has outlined 10,092 MRLs for 564 a.i. on 106 agricultural products. The total number of MRL standards in China is significantly lower than that of both the European Union and the United States. **Table 1** compares MRLs for seven a.i. in the European Union and China, and the former is 8.5-fold of the latter (312 versus 2,653 items). The current list of China’s MRL standards (GB 2763-2021) does not encompass some recently registered agents, such as triflumezopyrim.

3. ENVIRONMENTAL AND ECOLOGICAL SAFETY STATUS OF GREEN PESTICIDES

3.1. Compatibility of Green Pesticides with Soil

The earthworm is one of the most important soil invertebrates and is a suitable indicator species for ecotoxicological assessment of soil pollution. A research report (Zhang et al. 2023) indicates that the insecticides chlorantraniliprole, flubendiamide, and cyantraniliprole have LD₅₀ (lethal dose, 50%) values above 100 mg/kg to earthworms. The LD₅₀ of the fungicides trifloxystrobin (Ouyang et al. 2017), isopyrazam (Lv et al. 2022), and benzovindiflupyr (Yao et al. 2021) are above 100 mg/kg, above 500 mg/kg, and 416 mg/kg, respectively. This fulfills green pesticide’s criteria of low toxicity and impact on the soil organisms. However, subchronic exposure of earthworms to benzovindiflupyr at 50 mg/kg in soil can activate antioxidant enzymes, such as catalase and peroxidase, which is an active defense mechanism employed against xenobiotics (Yao et al. 2021). In real-world applications, the residual concentration of green pesticides in the soil is remarkably lower than 50 mg/kg (see Section 3.4), which also indicates that green pesticides have a low risk to soil-sensitive organisms such as earthworms.

3.2. Low Aquatic Toxicity of Green Pesticides

Representative aquatic organisms for risk evaluation mainly include algae, daphnia, and fish. Green pesticides need to have low toxicity to all aquatic organisms. A few pesticides that one may consider as green pesticides have high toxicity to some aquatic organisms. However, their rapid degradation or low concentration in water notably reduced the toxicity of the pesticides to aquatic organisms. Spinosad and flonicamid, eco-friendly pesticides with an LD₅₀ of 242 and 91 mg/L, respectively, possess minimal toxicity toward zebrafish (Y. Luo et al. 2022, Xu et al. 2013), whereas spinetoram and tebuconazole demonstrate moderate toxicity, with a 96-h LD₅₀ of 9.7 and 4.8 mg/L, respectively (Kong et al. 2018, Wang et al. 2022). Pyraclostrobin, however, exhibits high toxicity toward zebrafish, with an LD₅₀ of 0.0756 mg/L (Li et al. 2017). The degradation half-life ($t_{1/2}$) of pyraclostrobin in paddy water is approximately 6.9–11.5 days (Z. Luo et al. 2022), which renders it relatively eco-sustainable for aquatic organisms. Flubendiamide has a low bioconcentration factor in fish, e.g., 1.1–2.0 in zebrafish (Meng et al. 2022). Therefore, the threat of flubendiamide to human health through the food chain would be minimal.

3.3. Long-Range Atmospheric Transport and Deposition of Green Pesticides

Pesticides disperse into the air, drift with the wind, enter the atmosphere, and travel over long distances. Organochlorine pesticides are well known for their long-distance migration. For example, toxaphene, which was banned in 1982 in the United States, can be transported from application sites through the atmosphere. Toxaphene residues that remain in the soil in the United States are a primary source of toxaphene residues detected in the Great Lakes in Canada (Li & Jin 2013). The vapor pressure of a pesticide is an important measure of long-range transport. Pesticides in the air mainly come from volatilization. X. Zhang et al. (2022) detected the presence of multiple pesticides, such as α -HCH, penconazole, propoxur, and tebuconazole, in air from the western Pacific to the Southern Ocean. Coscollà et al. (2014) detected the particle size distributions of currently used pesticides such as dimethoate, chlorpyrifos, carbendazim, penconazole, omethoate, and malathion in the ambient air of an agricultural Mediterranean area. Most of the detected pesticides in the atmosphere presented high or medium volatility. **Figure 1** depicts that most of the pesticides detected in the atmosphere or as ultrafine particles are volatile, easily escaping from the soil and plant surfaces. By contrast, most green pesticides, e.g., spinosad, have relatively low vapor pressure and are nonvolatile and readily degradable, resulting in less atmospheric pollution.

Semivolatile pesticides are often detected in the atmosphere because they are stable. For example, difenoconazole, which has a vapor pressure of 3.3×10^{-8} Pa at 25°C, has been detected with concentrations ranging from 0.15 ng/m³ to 0.80 ng/m³ in atmospheric samples collected in northeastern France (Schummer et al. 2010). The $t_{1/2}$ of difenoconazole in the atmosphere was less than one day, whereas its $t_{1/2}$ in aerosol particles can be more than one month, meaning that difenoconazole can be transported over long distances (Rashidi et al. 2011, Socorro et al. 2016). Pesticides in the air can undergo chemical or photo-chemical oxidation. Chemically stable pesticides such as difenoconazole, tetraconazole, and deltamethrin are usually persistent and may be transported over long distances (Socorro et al. 2016).

3.4. Residues of Green Pesticides in the Environment

Green pesticides have high efficacy, low application rate, low residue, and fast degradation in the environment. **Figure 2** shows the application dosage of 14 green pesticides in the field, ranging from 10 g a.i./ha to 337.5 g a.i./ha (Devi et al. 2019; Fang 2021; W. Guo et al. 2021; Hou et al. 2019; Kaushik et al. 2019; Liang et al. 2012; Lin et al. 2017; Liu et al. 2013, 2018; Qian et al. 2019; Sharma et al. 2014; Sun et al. 2012; Wang et al. 2018; Xie et al. 2020; Zhang et al. 2015).

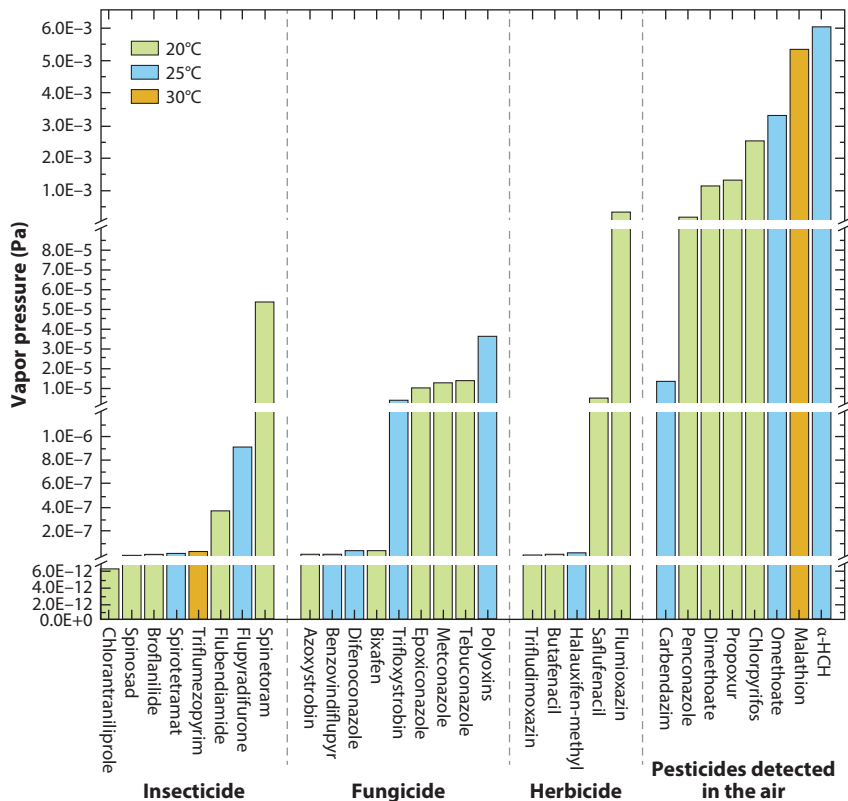


Figure 1
Vapor pressure of green pesticides and detected pesticides in the atmosphere.

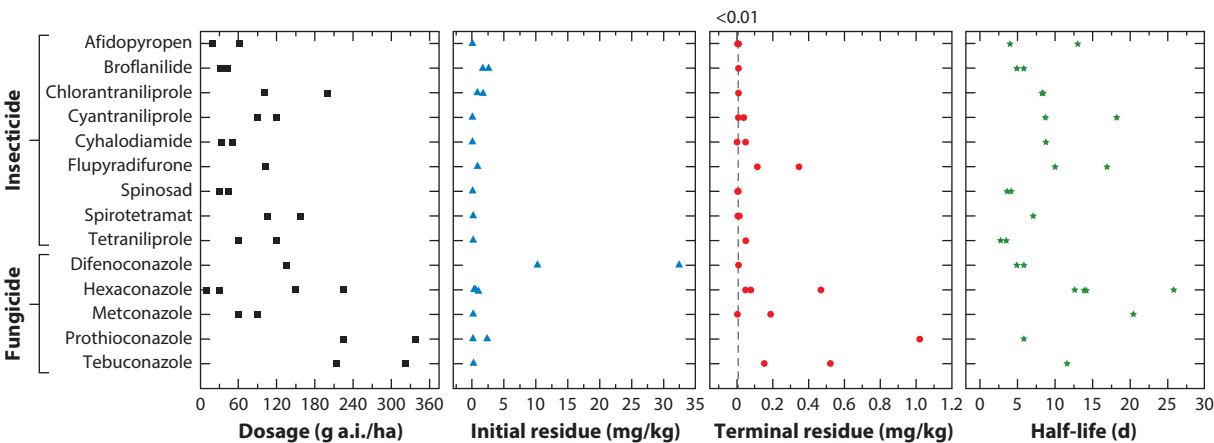


Figure 2
Dissipation and residue data of green pesticides in soil. Abbreviation: a.i., active ingredients.

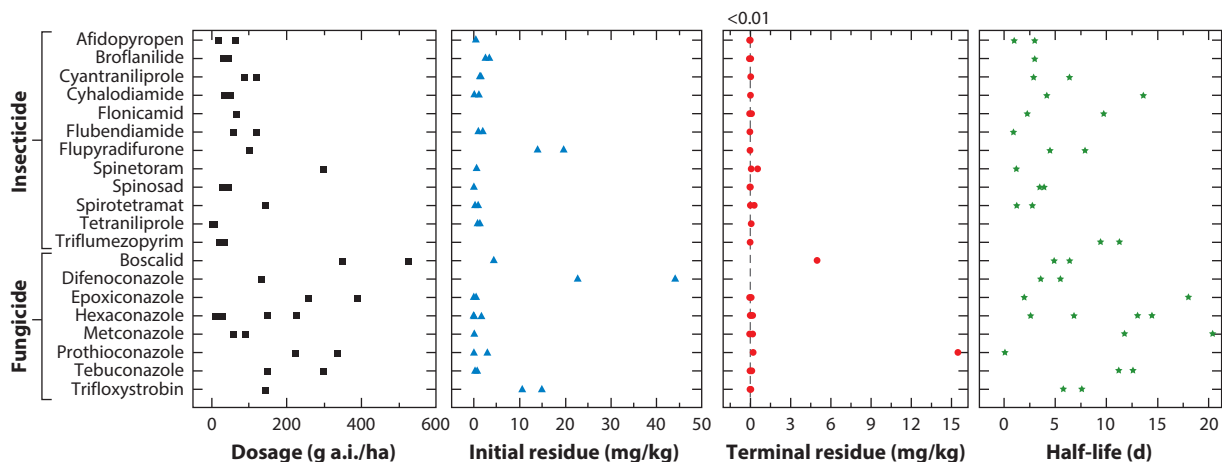


Figure 3

Dissipation and residue data of green pesticides in crops. Abbreviation: a.i., active ingredients.

When applied to bare soil, the initial residual amount in the soil after 2 h ranged from 0.06 mg/kg to 32.4 mg/kg for the pesticides. The residues of spinosad and spirotetramat, for example, in the soil samples collected 7–30 days after application ranged from <0.005 mg/kg to 0.015 mg/kg, whereas the residues of the fungicides tebuconazole and prothioconazole in the soil were between 0.002 and 1.02 mg/kg. The $t_{1/2}$ s of the pesticides in the soil ranged from 2.7 days to 25.8 days. In contrast, organochlorine pesticides (HCH and DDT) are persistent in the environment, typically with a $t_{1/2}$ of 4 weeks to 8 years (Niu et al. 2013, WHO 1989), and bioaccumulative, typically with a bioconcentration factor of 920–1,640 for HCH and 24–64 for DDT in zebrafish (Butte et al. 1991, Satyanarayan et al. 2005). Even after being banned in China for 20 years, residues of HCH and DDT can still be detected in soils, foods, and human milk in many areas (Wang et al. 2003).

The initial residual concentration of some green pesticides in crop plants ranged from 0.09 mg/kg to 44.1 mg/kg 2 h after application to various crops, such as rice, zucchini, scallions, and ginseng, at the recommended dosage (Chen & Zhang 2010; Devi et al. 2019; Fang 2021; Feng et al. 2022a,b; W. Guo et al. 2021; Y. Guo et al. 2021; Hou et al. 2019; Li et al. 2022; Liang et al. 2012; Lin et al. 2017; Liu et al. 2013, 2018; Malhat & Abdallah 2019; Matadha et al. 2021; Sahoo et al. 2009; Sun et al. 2012; Xie et al. 2020; Zhang et al. 2015; T. Zhang et al. 2022; Y. Zhang et al. 2022b). The residue levels of the insecticides ranged between 0.005 and 0.6 mg/kg in crop samples collected 1–30 days after the applications, whereas the residues of the fungicides ranged between 0.002 and 15.5 mg/kg (Figure 3).

4. SAFETY AND TOXICITY OF GREEN PESTICIDES IN MAMMALS

4.1. Acute Toxicity and Subchronic Toxicity of Green Pesticides

Green pesticides have low toxicity in humans. Among more than 150,000 deaths each year from pesticide poisoning, most deaths are due to homicidal ingestion. As highly toxic pesticides are gradually replaced by new and safe green pesticides in global agricultural practice, the fatality case of pesticide poisoning in general will likely fall (Eddleston 2020). In a specific case in India, a 26-year-old woman had no symptoms after homicidal ingestion of 10 mL of chlorantraniliprole. She developed a symptomatic Mobitz Type I atrioventricular block during observation. It is

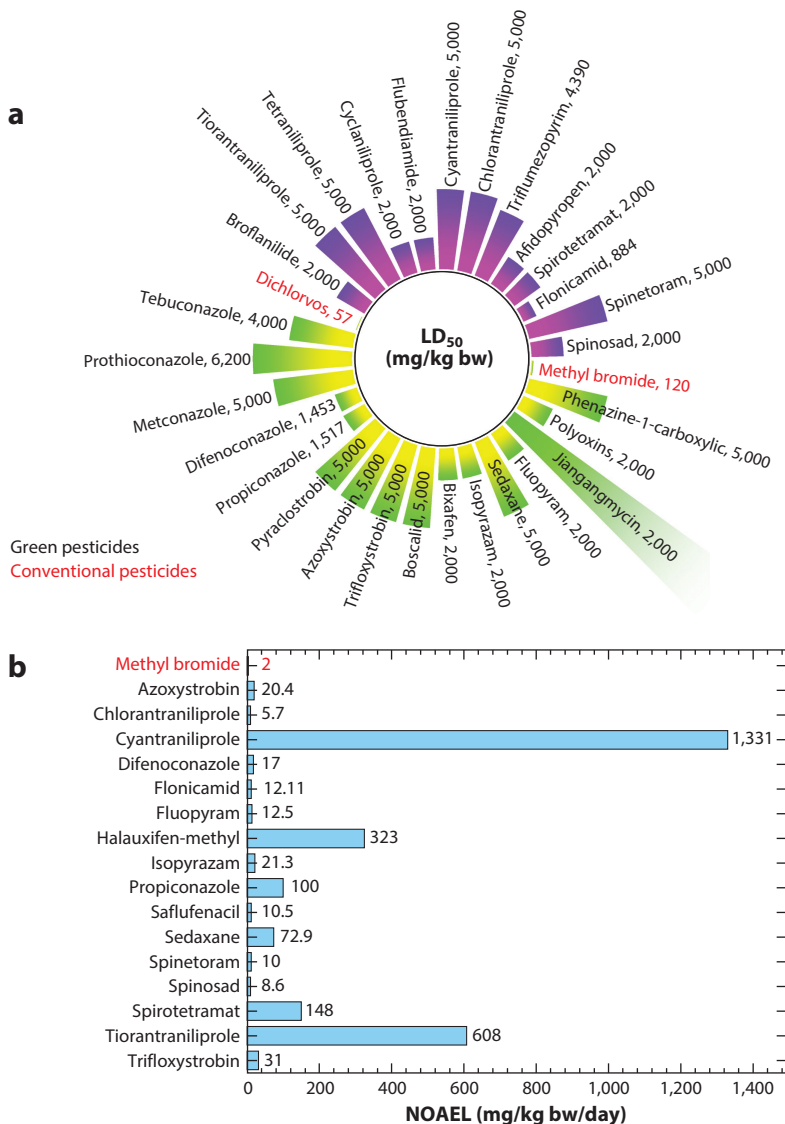


Figure 4

Comparative acute and subchronic toxicity of conventional pesticides (*red*) and green pesticides (*not red*). (a) Acute oral LD₅₀ values. (b) Subchronic no observed adverse effect level. Abbreviation: LD₅₀, lethal dose that kills 50 percent of sample; NOAEL, no observed adverse effect level.

speculated that chlorantraniliprole may cause conduction disorders by activating ryanodine receptors (Mishra et al. 2016).

Green pesticides have low toxicity in rodents, typically with an acute oral LD₅₀ value greater than 500 mg/kg bw. **Figure 4a** shows rat oral LD₅₀ values of the selected green pesticides (EPA 2021, FAO/WHO 2023). The LD₅₀ values of the green pesticides range from 840 mg/kg bw to 5,000 mg/kg bw, whereas the acute oral LD₅₀ values of the traditional pesticides dichlorvos and bromomethane are 57 and 120 mg/kg bw, respectively. **Figure 4b** shows that the no observed

adverse effect levels (NOAELs) for the green pesticides range from 5.7 to 1,331 mg/kg bw/day for subchronic toxicity. For example, the NOAELs of cyaniliprole and tiorantraniliprole are 1,331 and 608 mg/kg bw/day, respectively, whereas the NOAEL for bromomethane is 2 mg/kg bw/day.

4.2. Neurotoxicity of Green Pesticides

Spinosad, spinetoram, and chlorantraniliprole exhibit negligible acute neuron toxicity upon oral administration at dosages of 2,000 mg/kg bw. The acute NOAEL values of cyantraniliprole, flonicamid, isopyrazam, spinosad, spinetoram, and trifloxystrobin to rats range from approximately 250 to 2,000 mg/kg bw. However, the conventional insecticide dichlorvos has an acute NOAEL of 0.5 mg/kg bw, indicating that the acute neurotoxicity of the green insecticides is approximately 500 times less than dichlorvos (EPA 2021, FAO/WHO 2023). In 2011, Su et al. (2011) reported the first case of acute exposure to a mixture of 80 mL of spinosad and 2–3 g of flonicamid in a patient, leading to symptoms, such as consciousness disorder and respiratory failure. The authors believed that the patient's clinical manifestations were not due to the neurotoxicity of the chemicals but rather because the amount of spinosad ingested was far beyond the physiological safety dose that can be handled by the human body. Therefore, although green pesticides are less toxic, they still require proper management and use to ensure their safety.

4.3. Chronic and Carcinogenic Effects of Green Pesticides

Green pesticides should have no chronic and carcinogenic toxicity. Some green pesticides have no adverse effects on the test animals at exposure doses of 4.1–1,022 mg/kg bw/day, indicating low chronic toxicity (EPA 2021, FAO/WHO 2023). For example, flumiclorac-pentyl, cyaniliprole, and spirotetramat did not exhibit any chronic toxicity reactions at dose levels of 731, 884, and 1,022 mg/kg bw/day, respectively. **Figure 5** shows the NOAEL values of 21 green pesticides on

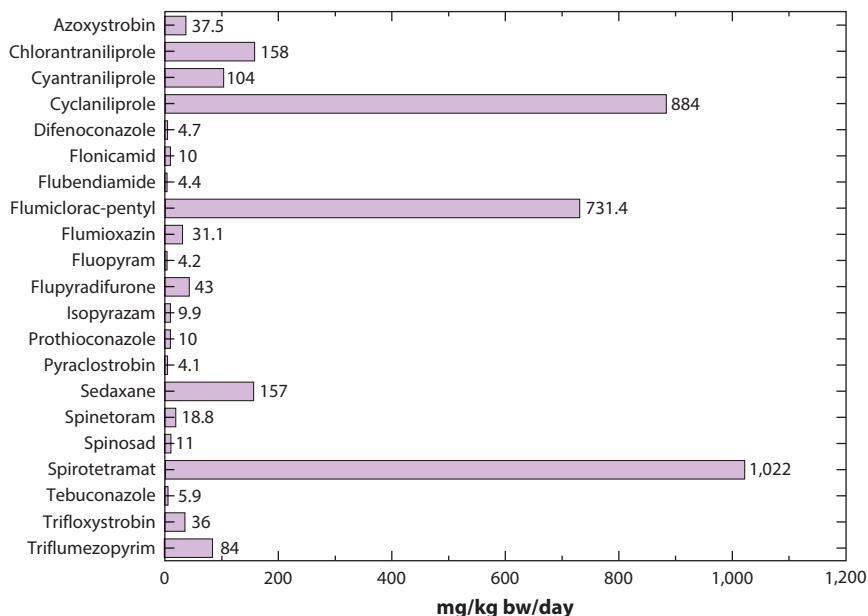


Figure 5

NOAEL (no observed adverse effect level) diagram for chronic toxicity of green pesticides in mice.

mice after long-term exposure (1.5–2 years). Achieving complete nontoxicity of green pesticides on the test animals over a prolonged period is a considerable challenge. Even with low-toxicity pesticides, long-term ingestion can cause harm and poisoning. Spinosad is classified as a low-toxicity pesticide based on its oral LD₅₀ of 3,738 mg/kg in male rats. However, in chronic toxicity and carcinogenicity studies, a high mortality rate was observed when rats were fed with spinosad at a daily dosage of 48 mg/kg bw/day for 21 months (Yano et al. 2002). Numerous pesticides, including traditional organochlorine and organophosphate pesticides, can disrupt endocrine systems, causing recurrent inflammation and disordering growth and development, metabolism, and reproduction (Patel & Sangeeta 2019). In particular, organochlorine pesticides possess the ability to persist in the environment over extended periods of time and accumulate within various organs or tissues of the human body through ecological pathways and the food chain (Butte et al. 1991, Patel & Sangeeta 2019, Satyanarayan et al. 2005). Consequently, they exert detrimental effects on human health, thereby compromising its integrity. Certain organochloride pesticides, such as DDT and lindane, have been subjected to bans or restrictions on their usage primarily because of their persistent nature, tendency to accumulate in organisms, and inherent toxicity (Patel & Sangeeta 2019).

4.4. Reproductive and Developmental Toxicity of Green Pesticides

The evaluation of green pesticides (e.g., those in **Figure 5**) conducted by the FAO and WHO revealed no significant mutagenicity and teratogenicity in rats and rabbits at exposure doses ranging from 33 to 1,683 mg/kg bw/day. However, the studies did indicate that some so-called green pesticides exhibited reproductive and developmental toxicity in the tested animals (EPA 2021, FAO/WHO 2023).

4.5. Exposure Route and Public Safety of Green Pesticides

Pesticide residues in the environment can ultimately enter the human body through respiration, drinking water, and food consumption, which threatens human health. Pesticides are usually dispersed in the atmosphere via drift, volatilization, and movement. Most commonly used pesticides with low volatility tend to adsorb on the surface of atmospheric particles. The $t_{1/2}$ s of 8 commonly used pesticides (difenoconazole, tetraconazole, fipronil, oxadiazon, deltamethrin, cyprodinil, permethrin, and pendimethalin) span from 9 to 24 days in aerosol particles (Socorro et al. 2016), which could be transported long distance through the atmosphere. The concentrations of pesticides in the atmosphere are on the order of several tens of nanograms per cubic meter (Guicherit et al. 1999, Schummer et al. 2010).

There have been many reports about organochlorine pesticide residues in surface water and groundwater (Chen et al. 2011, Jayashree & Vasudevan 2007, Wu et al. 2014, Shukla et al. 2006, Gilliom 2007). Some widely used pesticides such as triazines, organophosphorus pesticides, and tributylphosphate were detected in surface marine sediments from a Mediterranean coastal lagoon in Spain during 2009 and 2010 (Moreno & Leon 2017). There has been a noticeable rise in the concentration of glyphosate in surface water during the past two decades. For example, glyphosate and its metabolite aminomethylphosphonic acid (AMPA) are among the most often quantified compounds in river water in France (43% and 63% quantification frequency, respectively). The concentrations of AMPA and glyphosate in river water reached up to 558 µg/L and 164 µg/L, respectively (Carles et al. 2019). These facts show that the pollution of water resources caused by pesticides has seriously threatened the safety of humans, livestock, and other animals. Although the detection rate of green pesticides in aquatic ecosystems is relatively low, instances of their presence in river systems have been documented, including the detection of

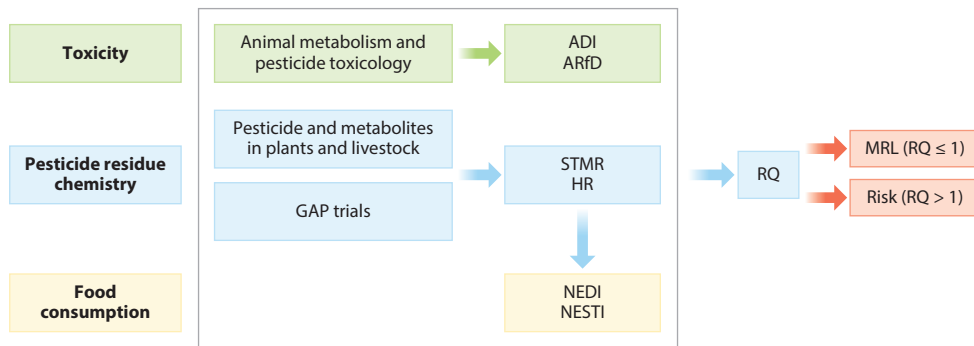


Figure 6

Procedure for pesticide risk assessment and maximum residue level setting based on the Codex Alimentarius Commission. Abbreviations: ADI, acceptable daily intake; ARfD, acute reference dose; GAP, Good Agricultural Practice; HR, highest residue; MRL, maximum residue level; NEDI, national estimated daily intake; NESTI, national estimated short-term intake; RQ, risk quotient; STMR, supervised trials median residue.

propiconazole and penconazole in headwater streams in the United Kingdom (Hurst & Sheahan 2003).

Occupational exposure may occur to workers during the production, packaging, transportation, and application of pesticides. Several conventional herbicides, such as atrazine, alachlor, and cyanazine, can cause genome damage and exhibit potential genotoxicity among manufacturing workers (Garaj & Zeljezic 2002). Although eco-friendly pesticides may not result in mutagenesis, carcinogenesis, or teratogenesis, their chronic toxicity is challenging to evade.

5. DIETARY EXPOSURE AND RISK OF GREEN PESTICIDES

Risk from dietary exposure is influenced by the interplay of pesticide toxicity, pesticide residue concentration, and dietary consumption. This risk assessment serves as the foundation for establishing MRLs for pesticides, as illustrated in **Figure 6** (MARA 2015). Evaluating the residues and associated risks linked to green pesticides in food is not only a critical aspect of pesticide development research but also an indispensable prerequisite for responsible and science-based utilization.

5.1. Pesticide Residues in Food

Pesticide residues have been associated with health problems because of their toxicity, and thus controlling and regulating the use of pesticides in agriculture and monitoring their levels in agricultural produce are of great concern in consumer health and international trade (J. Wang et al. 2017). Flonicamid, a new low-toxicity pyridinamide insecticide, was detected in peaches, cucumbers, and cabbages below the limit-of-quantitation threshold. However, in apples, the final residue levels ranged from <0.01 to 0.14 mg/kg (Liu et al. 2014, T. Zhang et al. 2022). Additionally, cyantraniliprole residues in brown rice and tomatoes were determined to be lower than the MRL values (Paramasivam et al. 2014). Similarly, the residual concentrations of difenoconazole in wheat, bananas, and leafy vegetables (Gao et al. 2022, Zhang et al. 2015, Zheng et al. 2020), as well as the residual concentrations of epoxiconazole in wheat and citrus crops used for managing fungal diseases, were found to be below the established MRLs (Zhang et al. 2022b, Zhao et al. 2021). When pyraclostrobin was used as a fungicide during the storage period of bananas, the residue

levels were within the MRL (Lin et al. 2022). It is noteworthy that during the initial stages of agricultural processing, the presence of pesticide residues in food can be minimized, and the effect of food processing on pesticide degradation has also been the focus of recent study (Kong et al. 2012, Y. Wang et al. 2017). The aforementioned studies regarding dissipation kinetics have demonstrated that green pesticides exhibit shorter $t_{1/2}$ s and safer interval periods compared to conventional insecticides when administered under Good Agricultural Practice (GAP) conditions. Furthermore, the presence of pesticide residues in pertinent agricultural commodities remains within acceptable thresholds.

5.2. Acute Reference Dose, Acceptable Daily Intake of Pesticides

Acute reference dose (ARfD) and acceptable daily intake (ADI) are two concepts in toxicology and risk assessment and are mainly used for assessing health effects from short-term and lifetime exposure, respectively, to environmental chemicals, including pesticides (WHO 2021). The ARfD of a chemical is an estimate of the amount of a substance in food and/or drinking water, normally expressed on a body weight basis, that can be ingested in a period of 24 h or less without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation (JMPR 2002), which provides an exposure measure related to the hazards that occur during short-term exposure. The purpose of ADI is to determine the possible daily exposure levels that may occur throughout a lifetime. For pesticide residues, ARfD and ADI are mainly used for risk assessment of acute dietary intake. Pesticide ADI is determined by considering the ratio of NOAEL or the benchmark dose lower confidence limit to an uncertainty factor (de Andrade et al. 2023, MARA 2012). Because ADI values are derived from toxicological data obtained from animal studies, these values generally exhibit consistency across different countries. The ADI value for difenoconazole established by the Codex Alimentarius Commission, European Union, China, and the United States is 0.01 mg/kg bw/day. However, differences in the evaluation of toxicological data by different countries and organizations can lead to variations in ADI values for the same pesticide. The ADI values of diamide insecticides, such as cyantraniliprole, chlorantraniliprole, and flubendiamide, prescribed by the European Union may be stricter than China and the United States. ADI values of some newly developed pesticides, such as cyhalodiamide, benzfendione, cinidon-ethyl, and triazinone, cannot be obtained now because of the lack of health-based guidance values. Tiafenacil, developed by FarmHannong Co., Ltd., South Korea, was given an ADI value of 0.011 mg/kg bw/day based on the toxicological data, but other countries and organizations have not formulated relevant ADI values (Park et al. 2018). In general, the establishment of ADI values for fungicides is relatively comprehensive, but further work is needed to develop ADI values for insecticides and herbicides.

5.3. Dietary Risk Assessment of Green Pesticides in Food

The process of evaluating the risk of pesticide residue in the diet involves analyzing potential hazards to human health that may arise from exposure to pesticides through dietary consumption. This assessment typically employs a risk quotient (RQ), which is calculated by dividing the estimated daily intake at the national level by the ARfD and ADI. Researchers have conducted dietary risk evaluations for many insecticides, such as spinosad and spinetoram on vegetables (Gao et al. 2007, Lin et al. 2020, Tang et al. 2021); flonicamid on Japanese honeysuckle (*Lonicera japonica*) (Li et al. 2018); spirotetramat on pineapple (Liang et al. 2020); afidopyropen on cucumber, nectarine, and tea (Guo et al. 2023, Xie et al. 2019); triflumezopyrim on rice (Y. Zhang et al. 2022a); and chlorantraniliprole on sugarcane and rice (Cheng & Hu 2022). Dietary risks have also been assessed for fungicides, including tebuconazole (G. Chen et al. 2022), prothioconazole (Dong &

Hu 2023, Dong et al. 2019, Liang et al. 2021), propiconazole (J. Wang et al. 2017), pyraclostrobin (Malhat et al. 2019, Zhao et al. 2020), pydiflumetofen (Bian et al. 2021), fluopyram (Feng et al. 2022a, Mohapatra et al. 2018, Sharma et al. 2022, Yang et al. 2022), boscalid (Chen et al. 2019, Niu & Hu 2018), and metconazole (W. Guo et al. 2021), on various crops, such as rice, pomegranate, wheat, cucumber, ginseng, strawberry, onion, carrot, cantaloupe, grape, and mango. Additionally, a rare assessment of the potential risks associated with the consumption of soybean crops treated with the herbicide flumioxazin has been conducted. The dietary exposure RQ for the aforementioned pesticide residues was found to be less than 1, indicating acceptable risk. However, the RQ for the application of tebuconazole on loquat yielded a value greater than 1, suggesting a potential risk associated with its use. Implementing a series of techniques to transform raw agricultural commodities into consumable food items has the potential to significantly reduce the levels of residual pesticides and mitigate the hazards associated with dietary exposure (Ahammed et al. 2023; Cámara et al. 2020; Feng et al. 2022b,c; Li et al. 2021). The acute and chronic dietary risks of target pesticides in food are low. The residual concentrations of the pesticides in agricultural products were all lower than MRL values, and %ARfD and %ADI values were far lower than 100%, indicating acceptable dietary risks.

Dietary risk assessment of pesticides has received extensive attention in recent years. In the past 20 years, the number of relevant articles archived in the SciFinder database has approximately tripled (**Figure 7a**). The primary focus of risk assessment of the abovementioned pesticides in terms of environmental sustainability has been directed toward insecticides and fungicides, whereas herbicides represent a relatively smaller fraction of the overall assessment. Commodities assessed mainly included grains, fruits, and vegetables, and diet risk assessments of a small variety of agricultural products like herb and tea were rare (**Figure 7b**). As for the new pesticides, toxicological data are often insufficient to establish accurate ADI. Moreover, there is a delay in the process of setting and updating MRLs for environmentally friendly pesticides. It is noteworthy that the determination of MRLs focuses on primary agricultural commodities. However, considering the changes in pesticide residues that may occur during postharvest handling and processing of agricultural commodities is crucial to ensure that potential hazards to consumers through their diet are effectively managed and kept within acceptable thresholds.

6. SUMMARY AND PERSPECTIVE

6.1. Green Pesticides and Food Security

In general, the above briefly elucidated the dissipation, residues, and environmental impact of various green pesticides widely used in recent decades, such as the microbial insecticide spinosad, non-neonicotinoids for preventing piercing-sucking pests, and new mesoionic insecticides. In general, these green pesticides have good degradability in natural water, soil, and other environments, and are eco-friendly. In addition, the a.i. exhibit low toxicity to nontarget organisms. These pesticides appear to have low mammalian acute toxicity, chronic toxicity, and neurotoxicity and negligible genotoxicity and carcinogenicity. Nevertheless, it is imperative to continuously monitor the chronic toxic effects of green pesticides when used over extended periods at the recommended dosage. Additionally, a re-evaluation of registered green pesticides is necessary, with a particular focus on potential disruptions to the endocrine system.

Owing to the recent introduction of green pesticides to the market, there is limited availability of toxicological data, including ADI value information. Moreover, there are relatively few examples of residue monitoring in both agricultural products under GAP conditions and market monitoring data in agro-food products. The establishment of MRL values for pesticides is primarily focused on primary agricultural products. However, to conduct a comprehensive residue risk assessment,



Figure 7

Comparison of the number of references for pesticides about diet risk assessment in the journals. (a) Number of references on pesticide and diet risk assessment from 2002 to 2022. (b) Number of references on risk assessment of typical green pesticides. Abbreviations: EBIs, ergosterol biosynthesis inhibitors; SDHI, succinate dehydrogenase inhibitor.

it is imperative to consider the potential changes in residue levels during postharvest processing of agricultural products to ensure that the risk posed to consumers remains at relatively low levels.

6.2. Prospects for Future Development of Green Pesticides and Food Security

Pesticides need to exhibit low toxicity toward nontargeted species. However, prolonged and continuous use of pesticides, even low-toxicity ones, may pose certain risks. It is indispensable to conduct ongoing investigations regarding the safety of eco-friendly pesticides on organisms that provide ecological benefits, which hold significant value in terms of promoting the judicious and regulated application of such pesticides, safeguarding the ecological environment, and fostering sustainable development within the realm of modern agriculture.

Balancing food security and health safety has led to a decrease in the use of conventional pesticides and a subsequent acceleration in the adoption of green pesticides. As a result, many researchers in the world have directed their scientific efforts toward green pesticide R&D. This

review has scrutinized green pesticides based on the sustainability principle. It is important to note that the inclusion of these pesticides in this review does not preclude the existence of other risk-reduced pesticides that may also qualify as green pesticides. We hope this review shall draw attention to the innovation of efficacious and eco-friendly agrochemicals with sustainable methods to align the balance between ecological milieu, food security, and human health.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The authors are grateful to the National Natural Science Foundation of China (32172457; 32272590), National Key Research and Development Program of China (2022YFD1700300), and the USDA (Hatch project HAW5044-R) for financial support.

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