

# A comprehensive review on the pretreatment and detection methods of neonicotinoid insecticides in food and environmental samples

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## ABSTRACT

In recent years, the residues of neonicotinoid insecticide in food and environmental samples have attracted extensive attention. Neonicotinoids have many adverse effects on human health, such as cancer, chronic disease, birth defects, and infertility. They have substantial toxicity to some non-target organisms (especially bees). Hence, monitoring the residues of neonicotinoid insecticides in foodstuffs is necessary to guarantee public health and ecological stability. This review aims to summarize and assess the metabolic features, residue status, sample pretreatment methods (solid-phase extraction (SPE), Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS), and some novel pretreatment methods), and detection methods (instrument detection, immunoassay, and some innovative detection methods) for neonicotinoid insecticide residues in food and environmental samples. This review provides detailed references and discussion for the analysis of neonicotinoid insecticide residues, which can effectively promote the establishment of innovative detection methods for neonicotinoid insecticide residues.

## 1. Introduction

Neonicotinoid insecticides act as modulators at the nicotinic acetylcholine receptors (nAChR) of the insect's central nervous system, and they are utilized extensively in different fields as crop protection and pest control. Because of their high efficacy against a wide range of insect pests (whiteflies, aphids, beetles, and some Lepidoptera species) and their versatility of use, neonicotinoid insecticides have become the most widely used insecticides in terms of the global market (above 25% in 2014) (Bass et al., 2015).

Although they have the advantage of pest control and food production, neonicotinoids have many adverse effects on human health, such as cancer, chronic disease, birth defects, and infertility (Han et al., 2018),

and they have substantial toxicity to many non-target organisms (especially bees) (Ihara & Matsuda, 2018). Neonicotinoids are widely persistent in human surroundings: They extensively occur in soil (park and residential soil (Zhou et al., 2018), planting soil (Wang et al., 2012b)), water (irrigation water (Hua et al., 2017), surface water (Yi et al., 2019), tap water (Ghiasi et al., 2020), etc.), drinking (fruit juice (Li et al., 2020), milk (Liu et al., 2015), wine (Rodríguez-Cabo et al., 2016), etc.), foods (fruits (Khawkaew et al., 2018), vegetables (Watanabe et al., 2015), grains (Wu et al., 2020b, etc.) and even biological samples (plasma and urine (Tadashi et al., 2014)), which dramatically increases the risk of the humans being exposed to neonicotinoid insecticides. Therefore, many countries and organizations have established maximum residue limits (MRLs) for neonicotinoid insecticides in

**Abbreviations:** ACE, Acetamidiprid; CLO, Clothianidin; CYC, Cycloxaprid; DIN, Dinotefuran; FLO, Flonicamid; FLU, Flupyradifurone; GUA, Guadipyr; IMI, Imidacloprid; IMI-guanidine, Imidacloprid guanidine/Desnitro imidacloprid; IMI-olefin, Imidacloprid olefin; IMI-urea, Imidacloprid-urea; IMID, Imidaclothiz; NIT, Nitenpyram; PCD, Paichongding; SUL, Sulfoxaflo; THX, Thiamethoxam; THI, Thiachloprid; THIAC, Thiachloprid amide; IMI-guanidine-olefin, Imidacloprid guanidine olefin; N-dm-ACE, N-desmethyl-acetamidiprid; CPMA, N-[(6-chloro-3-pyridinyl)methyl]acetamide; CPMF, N-(6-chloro-3-pyridinylmethyl)pyridinylmethyl)-N-ethyl-N-methylformamidine; CPF, N-(6-chloro-3-pyridinylmethyl)-N-ethylformamide; TZMU, N-(2-chloro-1, 3-thiazole-5-ylmethyl)-N-methylurea; MNG, 1-Methyl-3 nitroguanidine; UF, 1-methyl-3-(tetrahydro-3-furylmethyl) urea; DN, 1-methyl-3-(tetrahydro-3-furylmethyl) guanidium dihydrogen; TFNA, 4-trifluoromethylnicotinic acid; 5-OH-IMI, 5-hydroxy imidacloprid; 6-CNA, 6-chloronicotinic acid.

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fruits, vegetables, cereal products, and other edible products. However, the residue levels and detection rates of neonicotinoid insecticides are high in numerous reports (Yi et al., 2019; Sánchez-Bayo & Hyne, 2014; Li et al., 2020; Song et al., 2018; Dankyi et al., 2014), and in some cases residues are even over the MRLs (Zhang et al., 2020b; Wang et al., 2012a).

Therefore, it is crucial to monitor the residues of neonicotinoid insecticides. Since the early 1990s, when the first neonicotinoid (IMI) was introduced, numerous analytical methods have been devised to quantify neonicotinoid insecticides, such as high-performance liquid chromatography (HPLC) with either ultraviolet (UV), diode-array-detector (DAD) detection or mass spectrometry (MS) detection, immunoassays, optical and electrochemical sensor. Moreover, efficient sample pretreatment methods are required to remove the matrix interferences and improve the enrichment factors, such as solid-phase extraction (SPE), liquid-liquid extraction (LLE), Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS), and numerous novel sample preparation methods. Eventually, these proposed analysis methods have been applied to extract and determine neonicotinoid insecticides in many sample matrices, including foodstuffs (fruits, vegetables, grains, and edible commodities), and environmental samples (water and soil).

This review focuses on the articles about neonicotinoid insecticides analysis in foodstuffs and environmental samples. The main point of this review is to summarize and discuss the metabolism, residue status, sample pretreatment and detection methods for neonicotinoid insecticides analysis. This review maybe a valuable database to provide a reference for neonicotinoid insecticide residues analysis.

## 2. Neonicotinoid insecticides and their metabolites

Seven neonicotinoids are commercially available worldwide: IMI, ACE, THI, THX, CLO, DIN, and NIT. The neonicotinoids (Fig. 1.) are classified into three generations, including the chloropyridinyl compounds (first generation, IMI, NIT, ACE, THI), chlorothiazolyl compounds (second generation, THX, CLO), tetrahydrofuryl compounds (third generation, DIN), and other introduced neonicotinoids (IMID, FLO, PCD, SUL, FLU, GUA, CYC). Research have shown that some of their metabolites exhibit comparable or even higher toxicity than the parent compounds, such as CLO, which is 1.36 times as toxic as its parent THX to bees (*Apis mellifera*) (Iwasa et al., 2004); IMI-olefin, which is twice as toxic as the original IMI to bees (*Apis mellifera*) (Codling et al., 2016); 4-hydroxy imidacloprid is as active as IMI to whitefly (Nauen et al., 1999). Moreover, they are highly persistent in the environment, with half-lives of several months or even years under natural conditions.

The main metabolites of the most commonly used neonicotinoid insecticides that have been identified in agricultural and environmental samples are shown in Table 1. The frequent metabolic reactions included nitro reduction, demethylation, cyano hydrolysis, hydroxylation, olefin, guanidine and urea formation, ring-opening, etc. Moreover, some articles have discussed the metabolic pathways of neonicotinoid insecticides in plants (Motaung 2020) (spinach (Ford & Casida 2008), pistachio (Faraji et al., 2017), and onion (Thurman et al., 2013)) and environments (Faraji et al., 2017) (soil (Anjari et al., 2021; Ma et al., 2021) and water (Carla et al., 2014; Matthew et al., 2016)) using high-resolution mass spectrometry (HRMS). There are differences in the metabolism, translocation, and accumulation of neonicotinoid metabolites in various substrates. These differences mainly depend on the types of microbial and enzymes in the subjects. Hence, the metabolites of neonicotinoid insecticides are also of interest to many researchers, and it is also a hot spot for neonicotinoid insecticides analysis.

## 3. Residue status and regulation

Due to the widespread use and persistence of neonicotinoid insecticides, the detection rate and level are generally high. In this review, positive samples (excluding artificial and laboratory samples) from 45 reports (including 19 countries and more than 30 matrices) were collected through the PubMed database. Table 2 lists the maximum residue levels of different neonicotinoid insecticides in various positive samples from different countries. Among them, ten neonicotinoid insecticides (IMI, ACE, NIT, THI, THX, CLO, DIN, IMID, SUL, FLU) and some metabolites are detected in food and environmental samples, and the most commonly detected neonicotinoid insecticides are IMI (22.5%), ACE (19.5%), THX (17.5%). Multiple neonicotinoid residues were present in honey/honey-based products, field soil, tea, and environmental samples (water and soil) with high residue levels. Neonicotinoid insecticides were detected in honey or honey-based products from ten countries. Eight neonicotinoid insecticides (ACE, IMI, THX, THI, CLO, DIN, NIT, IMID) were simultaneously detected in honey samples from China, and the residue levels (0.041–0.120 mg/kg) were very high. SUL and FLU were also determined in honey samples from the US. Several metabolites of neonicotinoid insecticides have also been detected in edible foods. Overall, neonicotinoid insecticides exist widely in human surroundings. Thus, neonicotinoid insecticide residues in food and environmental samples should be widely concerned.

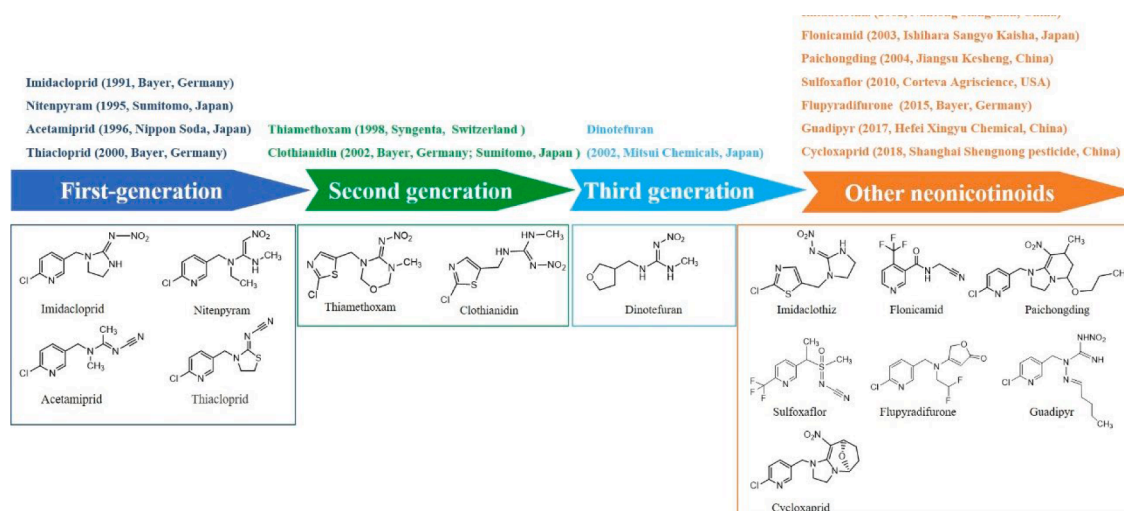


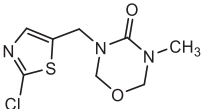
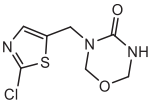
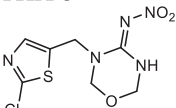
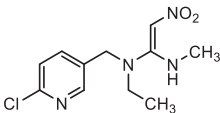
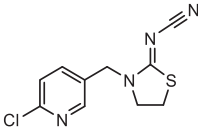
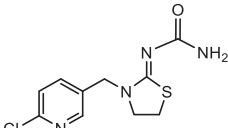
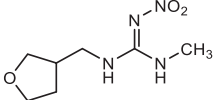
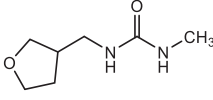
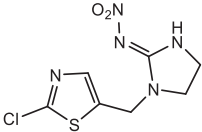
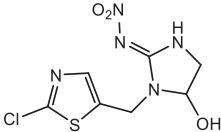
Fig. 1. The market introduction of neonicotinoid insecticides.

**Table 1**  
Main metabolites of the most commonly used neonicotinoid insecticides.

Neonicotinoid insecticides	Metabolites	Related articles
		Cotton (Wu et al., 2019), tea plant (Ge et al., 2020), casing soil, and mushroom (Zhang et al., 2020a), apple tree (Wu et al., 2020a), soil (Sharon et al., 2006), cardamom (Pratheeshkumar et al., 2016), tomato (Li et al., 2019)
IMI	IMI-urea	
		Cotton (Wu et al., 2019), tea plant (Ge et al., 2020), casing soil and mushroom (Zhang et al., 2020a), apple tree (Wu et al., 2020a), soil (Liu et al., 2011), cardamom (Pratheeshkumar et al., 2016), tomato (Li et al., 2019)
	IMI-olefin	
		Tea plant (Ge et al., 2020), soil (Sharma & Singh 2014), cardamom (Pratheeshkumar et al., 2016), tomato (Li et al., 2019), fruit juice (Li et al., 2020)
	OH-IMI	
		Tea plant (Ge et al., 2020), soil (Sharon et al., 2006), cardamom (Pratheeshkumar et al., 2016), tomato (Li et al., 2019)
	IMI-guanidine	
		Cotton (Wu et al., 2019), casing soil, and mushroom (Zhang et al., 2020a), soil (Sharma & Singh 2014), cardamom (Pratheeshkumar et al., 2016), tomato (Li et al., 2019)
	6-CNA	
		Tea plant (Ge et al., 2020), soil (Sharma & Singh 2014), tomato (Li et al., 2019)
	IMI-6	
		Article (Simon-Delso et al., 2015; Casida 2011)
ACE	ACE	Cotton (Wu et al., 2019), tea plant (Ge et al., 2020), apple tree (Wu et al., 2020a), fruit juice (Li et al., 2020), honey (Hou et al., 2019)
	N-dm-ACE	Cotton (Wu et al., 2019), tea plant (Ge et al., 2020)
	ACE-2	Tea plant (Ge et al., 2020), soil (Liu et al., 2011)
	ACE-3	Tea plant (Ge et al., 2020), soil (Liu et al., 2011)
		Review article (Carla et al. 2014; Simon-Delso et al., 2015; Casida 2011)
	ACE-4	Cotton (Wu et al., 2019), tea plant (Ge et al., 2020)
THX	THX	
		Tea plant (Ge et al., 2020)
	CLO	

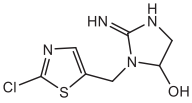
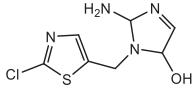
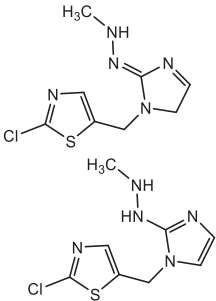
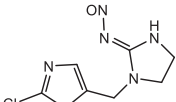
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Table 1 (continued)

Neonicotinoid insecticides	Metabolites	Related articles
		
	THX-2	Tea plant (Ge et al., 2020)
		
	THX-3	Tea plant (Ge et al., 2020)
		
	THX-4	Tea plant (Ge et al., 2020)
	THX-5 Metabolites 19 metabolites	Article (Simon-Delso et al., 2015; Casida 2011) Drinking water (Noestheden et al., 2016)
		
NIT		
		Soil (Liu et al., 2011)
THI	THIAC Metabolites	Review article (Simon-Delso et al., 2015; Casida 2011) Peach tree (Xu et al., 2021), fruit juice (Li et al., 2020)
		
DIN	UF	Peach tree (Xu et al., 2021), fruit juice (Li et al., 2020)
		Article (Simon-Delso et al., 2015; Casida 2011) Tea plant (Ge et al., 2020), lettuce, and celery (Tao et al., 2021)
IMID	5-OH-IMID	Tea plant (Ge et al., 2020), soil (Liu et al., 2011)
	IMID-olefin	Lettuce, celery, and radish (Tao et al., 2021)

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Table 1 (continued)

Neonicotinoid insecticides	Metabolites	Related articles
		
		
	<p>IMID-3</p> 	Celery (Tao et al., 2021)
	<p>IMID-4</p> 	Soil (Liu et al., 2011)
	<p>IMID-5</p> <p>Metabolites</p>	Article (Ma et al., 2021; Tao et al., 2021)

#### 4. Sample pretreatment

In order to satisfy the analysis concentration and eliminate the interference of the matrix, sample pretreatment is a vital step before instrument detection. Many traditional and novel extraction methods have been established for isolating neonicotinoid insecticides from different samples, such as solvent extraction (solid–liquid extraction, SLE; LLE), SPE, QuEChERS and other novel miniaturized and automated methods (liquid–liquid microextraction, LLME; dispersive solid-phase extraction, dSPE; magnetic solid-phase extraction, MSPE; solid-phase microextraction, SPME; matrix solid-phase dispersion, MSPD). In 2021, Watanabe (2021) enumerated the sample pretreatment methods that used for neonicotinoid insecticides analysis. Unlike the above review, this work focuses on the following two points: (1) critical factors of the commonly used sample preparation methods; (2) novel sample pretreatment techniques for the analysis of neonicotinoid insecticides.

##### 4.1. Solvent extraction

Solvent extraction is based on the principle of similar phase dissolution. The extraction process involves the application of an extractant with high solubility for the target analytes from the sample. Due to the high polarity of neonicotinoid insecticides, solvents with high polarity can better dissolve and extract the analytes from matrices. For solid matrix, methanol and acetonitrile are ordinarily employed in neonicotinoid insecticides extraction for direct detection with enzyme-linked immunosorbent assay (ELISA), electrochemical and optical sensor detection, which have high recognition ability to the target analytes. As for chromatographic detection, acetonitrile aqueous solution is universally utilized to extract neonicotinoid insecticides in fruits and agricultural products, and a further purification process is needed to reduce interferences of the co-extractives. LLE and LLME are frequently used to

separate the neonicotinoid insecticides from liquid samples by using acetonitrile as the dispersant,  $\text{CHCl}_3$  or  $\text{CH}_2\text{Cl}_2$  as the extractant, and the appropriate addition of NaCl can promote the extraction efficiency (Pastor-Belda et al., 2016). However, a highly selective method is needed to avoid the interference of co-extracts by using LLE and LLME, so there are limited reports on the direct application of LLE or LLME for the analysis of neonicotinoid insecticides.

##### 4.2. QuEChERS-like method

QuEChERS is the preferred method for pesticide analysis, including neonicotinoids. At present, three QuEChERS protocols are typically used: (1) the original QuEChERS method which is performed with acetonitrile and anhydrous  $\text{MgSO}_4/\text{NaCl}$  for extraction (Anastasiades 2003), (2) the American standard (AOAC) which involves the use of 1% acetic acid (HOAc) in ACN and anhydrous  $\text{MgSO}_4/\text{NaOAc}$  (AOAC Official Method, 20070.01), (3) the European standard, EN 15662, which involves the use of acetonitrile and anhydrous  $\text{MgSO}_4/\text{sodium citrate}$  and disodium citrate hydrogenate sesquihydrate (NF EN 15662, 2009.01). For most food and environmental samples, the anhydrous  $\text{MgSO}_4/\text{NaCl}$  or AOAC method can obtain satisfactory methodological results in the analysis of neonicotinoid insecticides. Moreover, a large number of reports have proved that citrate salts (EN 15662) provide the best recovery and relative standard deviations (RSDs) for the extraction of neonicotinoid insecticides in honey and honey-based products (Tanner & Czerwenka 2011; Kammoun et al., 2019; Jovanov et al., 2014). For extraction solvent additives, although the addition of acetic acid had no benefit to the recovery of the target analytes, it allows to obtain a smaller RSD (Wu et al., 2020b). Moreover, the addition of triethylamine (TEA) can adjust the pH of the extraction solvent, which prevents the binding of 6-CNA with primary-secondary amine (PSA) (Giroud et al., 2013).

**Table 2**  
The pollution status and regulation of neonicotinoid insecticides.

Countries	Matrices/max level (mg/kg or µg/L) <sup>EU MRIs (mg/kg)</sup>
Austria	Honey (Tanner & Czerwenka 2011) (ACE: 0.015 <sup>-0.05*</sup> , THI: 0.027 <sup>-0.2</sup> , total: 0.027)
Benin	River water (Selahle et al., 2020) (total: 7.70)
Japan	River water (Selahle et al., 2020) (total: 0.025) Honey (Kammoun et al., 2019) (DIN: 0.002) Tea (Yoshinori et al., 2018) (ACE: 0.472 <sup>-0.05*</sup> , CLO: 0.233 <sup>-0.7</sup> , DIN: 3.004, IMI: 0.139 <sup>-0.05*</sup> , NIT: 0.054, THI: 0.650 <sup>-10</sup> , THX: 0.910 <sup>-20</sup> , metabolites: 0.100) and tea beverage (ACE: 0.002, CLO: 0.002, DIN: 0.059, IMI: 0.002, THI: 0.002, THX: 0.006, metabolites: 0.002)
Canada	River water (Selahle et al., 2020) (total: 5.95)
China	River water (Selahle et al., 2020) (total: 0.193), coastal bay water (Li et al., 2019) (total: 0.003), surface water (Yi et al., 2019) (IMI: 0.154, THX: 0.070, CLO: 0.038, ACE: 0.077, THI: 0.003, total: 0.321) and sediment (THX: 0.0002, CLO: 0.0002, ACE: 0.002, THI: 0.0004, total: 0.003), sediment (Wang et al., 2020) (ACE: 0.167, THX: 0.133), field water (Zhang et al., 2017) (ACE: 0.023, CLO: 0.005, DIN: 0.007, IMI: 0.193, THI: 0.002, THX: 0.002) Agricultural samples (Wen et al., 2011) (ACE/IMI: 3.6), brown rice (Wang et al., 2012a) (THX: 0.102 <sup>-0.01*</sup> ) and oat (THX: 0.028 <sup>-0.02*</sup> ) and maize (IMI: 0.037 <sup>-0.1</sup> ), chrysanthemum (Qin et al., 2020) (IMI: 0.398 <sup>-2</sup> , ACE: 1.570 <sup>-3</sup> , THX: 0.017 <sup>-2</sup> ), Cucumber (Zhang et al., 2012) (ACE: 0.004 <sup>-0.3</sup> , THI: 0.006 <sup>-0.5</sup> ) and (Lu et al., 2020) (ACE: 0.3 <sup>-0.3</sup> ), rice and soil (Du et al., 2020) (IMI: 0.723), dendrobium officinale (Zheng et al., 2015) (ACE: 0.068, IMI: 0.046, THI: 0.002, THX: 0.018, NIT: 0.008, CLO: 0.003) Honey (Song et al., 2018; Hou et al., 2019; Tao et al., 2019, Hui et al., 2019) (DIN: 0.102, ACE: 0.068 <sup>-0.05*</sup> , CLO: 0.113 <sup>-0.05*</sup> , THI: 0.042 <sup>-0.2</sup> , THX: 0.120 <sup>-0.05*</sup> , IMI: 0.072 <sup>-0.05*</sup> , IMID: 0.112, NIT: 0.041), honey (Valverde et al., 2018) (THX: 0.144 <sup>-0.05*</sup> , CLO: 0.045 <sup>-0.05*</sup> ), honey (Gawel et al., 2019) (ACE: 0.13 <sup>-0.05*</sup> , THI: 0.20 <sup>-0.2</sup> ) Fruit juice (Li et al., 2020; Pastor-Belda et al., 2016; Liu et al., 2014) (ACE: 0.015, IMI: 0.005, CLO: 0.026, THI: 0.029, DIN: 0.008, NIT: 0.030, THX: 0.019, N-dm-ACE: 0.017, 5-OH-IMI: 0.014, DN: 0.012, UF: 0.014, total: 0.056) Tea (Zhang et al., 2020b; Liu et al., 2010; Hou et al., 2013) (ACE: 5.319 <sup>-0.05*</sup> , IMI: 1.173 <sup>-0.05*</sup> , THX: 0.153 <sup>-20</sup> , CLO: 0.465 <sup>-0.7</sup> , THI: 0.983 <sup>-10</sup> , NIT: 0.007, DIN: 0.022, N-dm-ACE: 0.141) Dietary samples (Li et al., 2019) (ACE: 0.051, IMI: 0.023, NIT: 0.0002, DIN: 0.0004, THI: 0.005, CLO: 0.002, total: 0.067) Peanut milk (Liu et al., 2015) (ACE: 3.69, THX: 8.67)
Chile	Honey (Raquel et al., 2018) (ACE: 0.078 <sup>-0.05*</sup> , THI: 0.063 <sup>-0.2</sup> , IMI: 0.007 <sup>-0.05*</sup> , total: 0.148)
US	Honey (Giroud et al., 2013) (IMI: 0.068 <sup>-0.05*</sup> , THX: 0.002 <sup>-0.05*</sup> , CLO: 0.001 <sup>-0.05*</sup> , SUL: 0.005 <sup>-0.05*</sup> , FLU: 0.046, total: 0.061) River water (Selahle et al., 2020) (total: 3.29)
France	Beebread (Giroud et al., 2013) (IMI: 0.001 <sup>-0.05*</sup> , ACE: 0.171 <sup>-0.05*</sup> , THI: 0.177 <sup>-0.2</sup> , THX: 0.001 <sup>-0.05*</sup> , total: 0.177) Royal jelly (Giroud et al., 2019) (THX: 0.0002 <sup>-0.05*</sup> )
Ghana	Cocoa bean (Dankyi et al., 2016) (IMI: 0.036 <sup>-0.05*</sup> , ACE: 0.012 <sup>-0.05*</sup> ) Cocoa soil (Dankyi et al., 2014) (IMI: 0.251, CLO: 0.023)
India	Rice (Karthikeyan et al., 2019) (THX: 0.07 <sup>-0.01*</sup> )
Ireland	Honey (Kavanagh et al., 2021) (IMI: 0.018 <sup>-0.05*</sup> )
New Zealand	Maize field Soil (Pook & Gritcan 2019) (IMI: 0.014, CLO: 0.109)
Philippines	Field soil (Bonmatin et al., 2021) (total: 0.113)
Serbia	Honey liqueur (Jovanov et al., 2014) (CLO: 2.7 <sup>-0.05*</sup> )
Spain	Beewax (Yáñez et al., 2013) (THX: 0.153 <sup>-0.05*</sup> , ACE: 0.061 <sup>-0.05*</sup> , IMI: 0.039 <sup>-0.05*</sup> ) Wine (Rodríguez-Cabo et al., 2016) (IMI: 0.014)
Slovenia	Honey (Mrzlikar et al., 2019) (ACE: 0.002 <sup>-0.05*</sup> , THI: 0.010 <sup>-0.2</sup> )
South Africa	River water (Selahle et al., 2020) (IMI: 0.109, ACE: 0.021, THI: 0.008, CLO: 0.008)
Thailand	Five fruit juice (Vichapong et al., 2013) (IMI: 0.006, ACE: 0.0001, THX: 0.003, CLO: 0.00004, NIT: 0.001)
Switzerland	Milk (Lachat and Glauser, 2018) (IMI: 0.022 <sup>-0.1</sup> , ACE: 0.019 <sup>-0.2</sup> , THX: 0.020 <sup>-0.05</sup> , CLO: 0.023 <sup>-0.02</sup> , THI: 0.005 <sup>-0.05</sup> , total: 0.049)

\*Indicates the lower limit of analytical determination.

For sample clean-up, PSA (Jovanov et al., 2014) and PSA/C18 (Kammoun et al., 2019) can satisfy the purification of a small amount of pigment. Agricultural products with high pigment can be de-pigmented by adding graphitized carbon black (GCB) (Karthikeyan et al., 2019). For tea samples, polyvinylpyrrolidone (PVPP) exhibits an excellent

adsorption effect on the elimination of polyphenols, and a robust cationic exchange adsorbent (PCX) can efficiently remove alkaloids (Zhang et al., 2020b). In this study, PVPP/PCX replaced the conventionally used PSA/C18 as the clean-up sorbents to reduce the matrix effects of neonicotinoid insecticides (ACE, IMI, THI, CLO, THX, NIT, DIN, IMID, and N-dm-ACE) from tea (oolong tea, black tea, green tea, white tea, yellow tea, and dark tea) by the effective elimination of interferences.

#### 4.3. Solid-phase extraction

SPE is one of the most prevalent methods for pesticide extraction and clean-up of complex samples. It has plenty of merits, such as high enrichment factors, flexible selection of the sorbent, ease of use and speed. SPE has been widely used to extract neonicotinoid insecticides in various substrates. With the development of novel SPE techniques (dSPE, MSPE, MSPD, and SPME), SPE has become an attractive approach to isolate neonicotinoid insecticides from the complex matrices.

##### 4.3.1. Solid-phase extraction column

Sorbent medium packed in the SPE column plays a vital role in obtaining high enrichment factors and clean-up efficiency. Table 3 shows a partial list of the parameters of the packed SPE column for isolation of neonicotinoid insecticides in foodstuffs and environmental samples. Methanol and acetonitrile are generally applied to extract the homogenized solid sample because of their high dissolution power for neonicotinoid insecticides, low cost, and low toxicity. Anion exchanger-disposable pipette extraction and hydrophilic-lipophilic balance SPE cartridges (Oasis HLB SPE) can accomplish high-efficiency extraction of multiple neonicotinoid insecticides and their metabolites.

Sorbent materials have a significant influence on extraction efficiency. Many novel adsorption materials (methylamine modified graphene (CH<sub>3</sub>NH-G), molecularly imprinted polymers (MIPs)) (Shi et al., 2017; Tang et al., 2008; Yohannes et al., 2014) were encapsulated in empty columns as the SPE cartridges to perform the extraction process. Zhou et al. (2006) developed an SPE method by applying multi-walled carbon nanotubes (MWCNTs) as the packed sorbent for the enrichment of three neonicotinoid insecticides (IMI, ACE, THX). MWCNTs have unique tubular structures of nanometer diameter and their large length-to-diameter ratio, which allows the target analytes to be preserved in the tubular structures of the MWCNTs in an optimal structural form. Various parameters that influence the extraction efficiency, such as flow rate, sample pH and sample volume, were evaluated. The packed SPE column could be reused over 200 cycles. These novel sorbent materials allow regeneration and reuse of the packed column and can be further modified with special functional groups to obtain highly selective adsorbents to extract the neonicotinoid insecticides. However, it is still challenging to simultaneously adsorb multiple neonicotinoid insecticides by using these novel sorbents.

##### 4.3.2. Dispersive solid-phase extraction

The dSPE is different from the SPE of sorbent packed into a column, the extract solution is mixed and agitated with the dispersed adsorbent, and then separated by employing high-speed centrifugation. Because of the large specific surface area of the extraction sorbents, the equilibrium time between the sorbents and sample solution can be considerably shortened, and a small amount of adsorbent can satisfy the enrichment requirements. The parameters of the extraction procedure play a vital role in the enrichment efficiency. The pH of the aqueous solution influences the existing molecular form of analytes and the charge species and density on the adsorbent surface. The ion strength of the medium affects the ion-exchange interaction of the analytes towards the adsorption materials and the viscosity of the aqueous solution. Additionally, the types of extraction sorbent, elution solvent and the working time guarantee a sufficient extraction and elution of target analytes.

**Table 3**  
Overview of solid-phase extraction methods for the analysis of multiple neonicotinoid insecticides.

Analyte	Sample	Extraction	Clean-up	Detection	LOQ or LOD	Recovery (%)	Ref.
DIN, NIT, THX, CLO, IMI, ACE, THI, FLO, IMI-olefin, IMI-urea, UF, N-dm-ACE, CPMF, CPF, TZMU, MNG, TFNA, THIAC, CPMA	Fruits, vegetables, grains	ACN (0.1% HOAc)	PSA/GCB	LC-MS/MS	10 µg/kg	91.1–105.5	Wu et al. (2020b)
IMI, ACE, THX, THI, NIT, DIN, CLO, N-dm-ACE, THIAC, IMI-guanidine, IMI-urea, IMI-olefin, d-NO <sub>2</sub> -IMI	Honey	1% acetonitrile (20% TEA) and ethyl acetate (8:2, v/v) in water	Strata X-CW cartridge	LC-MS/MS	0.1–0.5 ng/mL	88.6–109.2	Gbylik-Sikorska et al. (2015)
IMI, IMI-olefin, 5-OH-IMI, IMI-urea, d-NO <sub>2</sub> -IMI-olefin, d-NO <sub>2</sub> -IMI, 6-CNA, DIN, UF, DN, THX, CLO	Honey	ACN (2% TEA)	C18 SPE cartridge	LC-MS/MS	0.2–15 ng/g	53.5–124.2 (39.4–49.6 d-NO <sub>2</sub> -IMI)	Kamel (2010)
ACE, N-dm-ACE, CLO, DIN, FLO, TFNA, IMI, NIT, THI, THX	Honey	ACN	PSA	LC-MS/MS	2–10 µg/kg	60–114.2	Tanner & Czerwenka (2011)
IMI, ACE, THX, THI, DIN, NIT, CLO, N-dm-ACE, 5-OH-IMI, UF, DN	Fruit juice	/	Anion exchanger-disposable pipette extraction	LC-MS/MS	0.01–0.1 ng/mL	71–104	Li et al. (2020)
IMI, ACE, THX, THI, DIN, NIT, CLO, IMID	Honey	/	Anion exchanger-disposable pipette extraction	LC-MS/MS	1–10 µg/kg	72–111	Song et al. (2018)
IMI, ACE, THX, THI, DIN, NIT, CLO	Water	/	SDB-RPS SPE disk	LC-MS/MS	0.25–0.5 ng/L	58.9–109.9	Li et al. (2019)
IMI, ACE, THX, THI, CLO	Wine	/	Oasis HLB SPE/Florisil column	LC-MS/MS	0.1–0.2 ng/mL	77–119	Rodríguez-Cabo et al. (2016)
IMI, ACE, THX, THI, CLO	Honey	/	Oasis HLB SPE	LC-MS/MS	0.15–3.25 ng/g	70.7–113.6	Mrzlikar et al. (2019)
IMI, ACE, THI, THX	Bovine milk	/	Chem Elut cartridge	LC-DAD	0.0–0.04 mg/kg	85.1–99.7	Seccia et al. (2008)
IMI, ACE, THX, 6-CNA	Water	/	Strata-X cartridges	MEKC	0.342–2.672 µg/g	85.5–99.1	Ettiene et al. (2012)
IMI, ACE, THX, THI, DIN, NIT, CLO, and 20 their metabolites	Tea	Water	Presep RPP/ENVIcarb/PSA cartridges	LC-MS/MS	1.33–33.3 ng/g	32.9–116.7	Yoshinori et al. (2018)
IMI, ACE, THX, THI, DIN, NIT, CLO, IMID	Sediment	CH <sub>3</sub> OH-water	Oasis HLB SPE	LC-MS/MS	0.031–0.091 µg/kg	75.5–98.5	Wang et al. (2020)
PYM, IMI, ACE, THI, THX, DIN, NIT, IMID, CLO, FLO, TFNA, N-dm-ACE	Royal-jelly, honey	CH <sub>3</sub> OH (royal-jelly)	Oasis HLB SPE	LC-MS/MS	0.25–5.0 µg/kg	72.8–106.5	Hou et al. (2019)
IMI, ACE, THX, THI, DIN, NIT, CLO	Cucumber, eggplant	Water	Oasis HLB SPE and Envi-Carb/LC-NH <sub>2</sub>	LC-DAD	0.003–0.019 µg/g	82–114	Watanabe et al. (2015)
IMI, ACE, THX, THI, DIN, CLO	Agricultural sample	ACN	Oasis HLB SPE	LC-MS/MS	0.01–0.02 mg/kg	82.1–108.5	Wen et al. (2011)
IMI, ACE, THX, THI, DIN, NIT, CLO	Royal jelly-based products	Water (10 mM ammonium formate)	Strata® cartridge	LC-MS/MS	2.5–8.0 µg/kg	83–109	Valverde et al. (2015)
DIN, NIT, THX, CLO, IMI, IMID, ACE, THI	Tea	ACN	PVPP/GCB	LC-MS/MS	10–50 µg/kg	66.3–108.0	Jiao et al. (2016)

MEKC: micellar electrokinetic chromatography; ACN: acetonitrile.

/: no solvent extraction.

Several established dSPE for detecting multiple neonicotinoid insecticides have been listed in Table 4. Due to the high surface area, large pore volume, and excellent stability in the water and acid conditions, UiO-66 (Cao et al., 2018) was used as the dSPE sorbent to extract IMI, ACE, THI, THX, CLO in water samples. Moreover, the addition of amino groups on UiO-66 (UiO-66-NH<sub>2</sub> (Xu et al., 2020)) may increase the electrostatic interactions between the sorbent and analytes, allowing efficient extraction of IMI and THX from fruit samples. The amount of adsorbent (≤50 mg) used for dSPE is significantly less than that of the SPE column, and the dSPE also has a satisfactory recovery. The main drawback of dSPE is the need for high-speed centrifugation to realize solid–liquid separation.

#### 4.3.3. Magnetic solid-phase extraction

MSPE uses magnetic materials as extraction sorbents and isolates the sorbent from the sample solution by an external magnetic field. In general, the adsorption capacity of prepared magnetic sorbent for the target analytes is equal to or higher than that of the original non-magnetic sorbent. Therefore, MSPE not only has all the advantages of dSPE but also can solve the drawbacks of the high-speed centrifugation required by dSPE. Table 4 lists reports on the use of MSPE for extracting multiple neonicotinoid insecticides in water, fruit, vegetable, and milk

samples. So far, graphene oxide (GO), metal–organic frameworks (MOFs), covalent organic frameworks (COFs), nanocellulose, porous porphyrin organic polymer and porous carbon have been modified by magnetic particles as magnetic extraction sorbents. Additionally, the frequently used extraction parameters for neonicotinoid insecticides are summarized as follows: (1) the amount of sorbent is less than 50 mg, (2) the pH value of the sample solution is controlled between 6 and 7, (3) no salt is added, (4) acetonitrile is used as the efficient eluent, (5) the volume of eluent is less than 1 mL, (6) many designed sorbents can be regenerated and reused.

Adelantado et al. (2018) developed an ionic liquid-based magnetic nanocellulose microextraction to determine six neonicotinoid insecticides (IMI, ACE, THI, THX, DIN, CLO) in milk samples. In this work, the ionic liquid (C<sub>4</sub>MIMPF<sub>6</sub>) was quickly dispersed in milk samples in a cloudy form, and the neonicotinoid insecticides were extracted into the fine droplets of ionic liquid. Then, the ionic liquid containing target analytes from the sample solution was separated by using magnetic nanocellulose. It was found that N, O, S atoms on the analytes could promote the adsorption between neonicotinoid insecticides and magnetic nanocellulose. It also speculated that the differences in adsorption of analytes by magnetic nanocellulose depended on the Cl, O, and S atoms and Van der Waals. Additionally, the 3D structure of

**Table 4**

Overview of dispersive and magnetic solid-phase extraction methods for the analysis of multiple neonicotinoid insecticides.

Analyte	Sample	Extractant	SPE	Salt	pH	Reuse	Elution	Detection	Recovery	Ref.
IMI, ACE, THI, THX, CLO	Water	/	UiO-66 (40 mg)	15% NaCl	9	10	3 mL acetone	LC-MS/MS	73.7–119.0	Cao et al., (2018)
IMI, ACE, THI, THX, CLO	Fruit juice, water	/	Montmorillonite (30 mg)	0.03 g Na <sub>2</sub> SO <sub>4</sub>	4	4	0.15 mL 70% ACN	HPLC-DAD	–	Khwankaew et al. 2018
IMI, THX	Fruit	ACN	UiO-66-NH <sub>2</sub> (50 mg)	/	9, 5	8	3 mL ACN (0.1% methanoic acid)	UPLC-MS/MS	86–107	Xu et al., (2020)
IMI, ACE, THI, THX	Lemon juice	/	Magnetic 3D-graphene (15 mg)	/	7	20	0.3 mL acetone	LC-UV	88.75–111.60	Liu et al., (2014)
IMI, ACE, THI, THX, CLO, DIN	Water	/	Fe <sub>3</sub> O <sub>4</sub> /GO/ZIF-67 (40 mg)	/	7	–	1 mL ACN	LC-MS/MS	83.5–117.0	Cao et al., (2017)
IMI, ACE, THI, CLO	Water	/	Magnetic porous porphyrin organic polymer (15 mg)	–	7	5	1.13 mL ACN	LC-DAD	91–99.3	Selahle et al., (2020)
IMI, ACE, THI, THX	Water, peanut milk	/	Magnetic ordered porous carbon (10 mg)	/	6	–	0.6 mL ACN	LC-DAD	96.74–112.40	Liu et al., (2015)
IMI, ACE, THI, THX, DIN, CLO	Milk	Ionic liquid (C <sub>4</sub> MIMPF <sub>6</sub> )	Magnetic nanocellulose (50 mg)	–	–	1	0.5 mL ACN	LC-MS	91.0–109.5	Adelantado et al., (2018)
IMI, ACE, THI, THX, CLO, IMID	Vegetable	ACN	Fe <sub>3</sub> O <sub>4</sub> @COF-(NO <sub>2</sub> ) <sub>2</sub> (10 mg)	/	7	6	0.1 mL ACN	LC-UV	77.5–110.2	Lu et al. (2020)
IMI, ACE	Fruit, water	ACN/water (1:10, v/v) (fruit)	CoFe <sub>2</sub> O <sub>4</sub> @SiO <sub>2</sub> /GO/MIL-101(Cr)-NH <sub>2</sub> (20 mg)	4% NaCl	6–7	20	1 mL TEA /ethanol (3:7, v/v)	LC-DAD	82.13–102.27	Ghiasi et al., (2020)

/: no solvent extraction; no salt addition. –: not mentioned in the articles.

neonicotinoid insecticides also affected the adsorption of analytes by magnetic nanocellulose.

#### 4.3.4. Other solid-phase extraction

Other novel solid-phase extraction methods have also been used to enrich neonicotinoid insecticides in different matrices. Matrix solid-phase dispersion (MSPD) is a widely applied technique for extracting pesticides from solid samples. This method consists of mechanical mixing of the sample with the dispersing sorbents, which improves the complete disruption of the sample matrix. Hence, compared with other solid-phase extraction methods, MSPD can omit the step of applying the extraction solvent to obtain the crude extraction solution. Furthermore, the extraction and elution procedures are performed in an SPE column using the optimized solvent. Ettiene's group (Ettiene et al., 2012) used C18 as an adsorbent in MSPD to extract neonicotinoid insecticides in soil. The acetonitrile/methanol (9:1, v/v) was the optimal eluent. After MSPD, the analytes (IMI, ACE, THX, 6-CNA) were detected by micellar electrokinetic chromatography (MEKC). It has good linearity, accuracy, and precision. The detection of limits (LOD) ranged from 0.17 to 0.37 µg/g. The prepared MIPs can also be used as the dispersant of MSPD for selective extraction of neonicotinoid insecticide residues (Chen, 2012).

SPME is a simple sample preparation method which combines extraction, separation and enrichment into a single step. In this method, the extraction sorbents are packed on a needle, and the constructed probes are used as the extraction device. The most significant advantage of SPME is the realization of real-time, online monitoring of neonicotinoid insecticide changes in plants under normal physiological conditions. The SPME can obtain the detection results of the same sample for different periods, which avoids batch-to-batch variation in samples. However, SPME also has disadvantages such as poor mechanical stability, low fiber volume, and sensitivity issues due to fiber saturation. A polyacrylonitrile/polyvinylpyrrolidone (PAN/PVPP) was applied as the SPME fiber for in vivo detection of seven commercial neonicotinoid insecticides in lettuce and soybean (Qiu et al., 2019) coupled with UPLC-MS/MS analysis. Neonicotinoids are polar compounds which require the SPME probe to have good water-swelling and

be biocompatible. Thus, the extraction fiber was prepared using PVPP and PAN. The in vivo assays provided the distribution characteristics of neonicotinoid insecticides over time in the same plants. What's more, the water-swelling SPME probe could be reused for 20 cycles.

These novel SPE methods (dsPE, SPME, MSPE, and MSPD) have been tried to separate neonicotinoid insecticides in various samples. MOFs, COFs, GO, and montmorillonite materials have demonstrated good extraction efficiency for neonicotinoid insecticides. The adsorption of neonicotinoid insecticides by these adsorbents is mainly dependent on the following aspects: (1) the adsorbents have a large surface area and suitable pore size, which allows neonicotinoid insecticides to be physically fixed in the cavities; (2) some special functional groups (aromatic ring, charge distribution, etc.) exist on the surface of the adsorbent, which can form interaction forces with neonicotinoid insecticides (pyridine ring or thiazole ring, halogen atoms and nitro functional group), such as  $\pi$ -bondings and Van der Waals forces; (3) MIPs can accomplish high selectivity adsorption of neonicotinoid insecticides by using them as the templates.

Based on the above, many novel sorbent materials and sample pretreatment techniques have been applied to extract and separate neonicotinoid insecticides. These new methods simplify the operation procedures, reduce the consumption of organic solvents and the time of sample preparation, and have great potential to promote the development of sample preparation. However, the application of these new methods to the analysis of multi-target analytes in complex matrices still needs further investigation and validation. At this stage, the conventional SPE and QuEChERS are still the most popular choices for analyzing multiple neonicotinoid insecticides and their metabolites in different samples.

## 5. Analysis method

Various detection methods have been applied to determine neonicotinoid insecticides in foodstuffs and environmental samples. LC combined with UV, DAD, MS, immunoassay, optical, and electrochemical detection methods have been established to the analysis of



neonicotinoid insecticides. Among these methods, LC-MS is the most commonly used method for simultaneously detecting multiple neonicotinoid insecticides and their metabolites; immunoassay methods can achieve rapid and specific detection of one or several neonicotinoid insecticides.

### 5.1. LC and LC-MS

LC-UV/DAD is widely used to detect the original neonicotinoid

insecticides, and LC-MS enables simultaneous qualitative and quantitative detection of multiple neonicotinoid insecticides and their metabolites. For LC-DAD, the addition of  $\text{KH}_2\text{PO}_4$  (0.05 M) in the water phase and small injection volume was influential in obtaining a sharp peak of NIT, which is highly water-soluble (Obana et al., 2002). For LC-MS, formic acid, acetic acid, ammonium formate, ammonium acetate or their mixtures are often used as mobile phase additives. As for the organic phase, acetonitrile can give a better response than methanol; in the inorganic phase, the addition of formic acid produced excellent peak

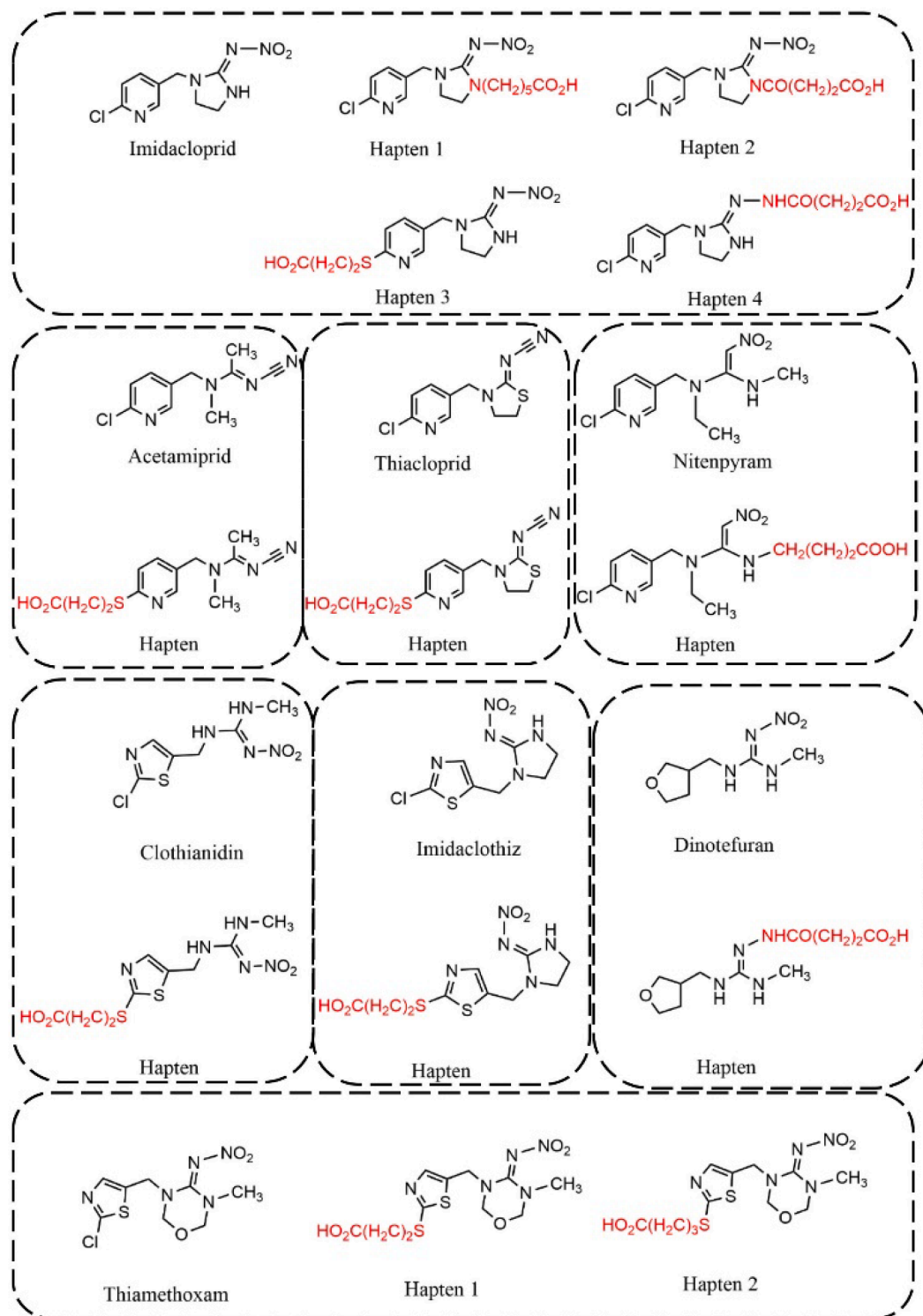


Fig. 2. Chemical structures of neonicotinoid insecticides and hapten molecules.

shapes and stability than ammonium acetate and pure water (Wu et al., 2020b). Jiao's team (2016) investigated several different mobile phase additives (for instance, 0.1% and 0.3% formic acid (FA), 5 mM ammonium formate, 5 mM ammonium formate with 0.1% formic acid, no additives, 0.02% formic acid, 0.02% acetic acid, 5 mM ammonium acetate and 5 mM ammonium acetate with 0.1% formic acid), and the results showed that the signals of all neonicotinoids (DIN, NIT, THX, CLO, IMI, IMID, ACE, THI) in MRM were significantly increased and the peak uniformity was also improved when 5 mM ammonium formate was added to the water phase. They also found that the signals of all eight neonicotinoid insecticides were slightly suppressed when both 0.1% formic acid and 5 mM ammonium formate were added to the water phase. Likewise, Lachat and Glauser (2018) found that the addition of 5 mM ammonium formate to the aqueous acidic mobile phase improved the intensity of five neonicotinoid insecticides (IMI, ACE, THI, THX, CLO). Collectively, the addition of ammonium formate to the mobile phase can increase the MS signals of neonicotinoid insecticides, but the enhancement levels are inconsistent on different instruments (Lachat & Glauser, 2018; Jiao et al., 2016; Kammoun et al., 2019). However, the effect of mobile phase additives on the MS signals of their metabolites has been rarely reported.

## 5.2. Immunoassay

Immunoassays have been proved to be the excellent analytical methods for rapid monitoring of neonicotinoid insecticides. It possesses such predominant benefits: satisfactory sensitivity and selectivity due to the characteristics of antibodies, obviating troublesome sample pretreatment procedures, adaptability to various matrices. Meanwhile, the most important influencing factor of the immunoassay is the properties of the proteins (antigens and antibodies). On one hand, the cross-reactivity of antibodies is unavoidable in immunoassay, especially endogenous components. On the other hand, the reagents used for immunoassay cannot affect the protein properties and have good solubility for the analyte.

To date, antibodies of several neonicotinoid insecticides have been developed, which promoted the advancement of neonicotinoid insecticides immunoassay. Fig. 2. lists the chemical structures of neonicotinoid insecticides (of which antibodies have been produced) and hapten molecules for immunization and assay development. For neonicotinoid insecticides with chloropyridine ring (IMI, ACE, and THI) and chlorothiazole ring (THX, CLO, and IMID), the design principle of hapten molecules is to replace the chlorine atom with a sulfur atom, and the chain is extended from the sulfur atom with two methylene groups and finally a carboxyl group is introduced. Besides, the branched structures of neonicotinoid insecticides can also be modified to form the hapten's arm (Zhao et al., 2019).

Enzyme-linked immunosorbent assay (ELISA) is a rapid and high-throughput screening method. The antibodies obtained from all of the above hapten molecules have been applied to establish the ELISA methods. The proposed methods have been widely used in different samples, including fruits, vegetables, and environmental samples. ELISA kits are commercially available for several neonicotinoid insecticides. In 2013, Watanabe et al. (2013) published a review paper on the application of ELISA for the detection of neonicotinoid insecticides. In this review, not only the design of the hapten molecules was elaborated, but also the sample pretreatment and the application of ELISA in various agro-environments matrices were summarized. After that, the developed antibodies were introduced to construct immunosensors, which significantly improved the sensitivity and reduced matrix interference compared with traditional ELISA.

Immunochromatographic assay (ICA) is a convenient and inexpensive on-site analysis method. The most frequently used extraction solvent is methanol and buffer solution. To date, ICA has been widely used for the rapid screening of neonicotinoid insecticides in fruit and vegetable samples. Fang et al. (2019) group used a high affinity nanogold-

biotinylated anti-IMI mono-antibody and nanogold-streptavidin probes dual labeling of the test lines on the strip to achieve signal amplification. The sensitivity of the proposed strip was significantly higher (10-fold or even 160-fold) than those of traditional ICA. Tan et al. (2020) developed two types of lateral flow immunoassay for IMI detection. The IMI mAb was conjugated to colloidal gold and Eu(III)-nanobeads, respectively. Both immunochromatographic methods obtained high sensitivity (0.02 ng/mL) for the determination of IMI in Chinese leeks. Although the ICA method is convenient and low-cost enough, its biggest drawback is the false-positive results, which require further confirmation using instrument detection.

## 5.3. Optical detection

At present, various optical sensors have been established for the detection of neonicotinoid insecticide residue in agricultural products, water and soil samples. It contains the following classes: surface plasmon resonance (SPR) (Ding et al., 2012), surface-enhanced Raman scattering (SERS) (Hassan et al., 2021), fluorescence resonance energy transfer (FRET) (Guo et al., 2020), fluorescence polarization immunoassay (FPIA) (Shim et al., 2009) and fluorescent detection (Liu et al., 2020).

SERS has been recognized as a promising tool for rapid and accurate detection in various fields. It has excellent sensitivity, non-invasive detection capability, and unique fingerprint effect. Gold and silver nanoparticles have been extensively used to develop the SERS methods for the detection of neonicotinoid insecticides in agricultural products. Mehedi et al. used reduced-graphene-oxide-gold-nano-star (rGO-NS) nano-composite (Mehedi et al., 2019) and flower-like silver nanoparticle (AgNP) (Hassan et al., 2021) to establish two SERS sensors for rapid detection of ACE in green tea. The SERS constructed by rGO-NS could provide higher sensitivity, and the pretreatment of green tea was more straightforward than the others. Zhao and colleagues (Zhao et al., 2020) developed a paper-based SERS based on 3D silver dendrites (SD)/electropolymerized molecular identifiers/silver nanoparticles (AgNPs) sandwich hybrid. In this assay, dendrite-like 3D silver materials and AgNPs formed the first and secondary enhancement of the amplification strategy, respectively, and molecular identifiers coated upon the SD layer as interlayer was used for IMI capture and enrichment. Owing to the strong identification ability of molecular identifiers, a simple sample pretreatment could meet the extraction of IMI in different samples (Chinese chives, crown daisy, soybean and cucumber).

Fluorescence analysis is one of the most popular optical techniques. A large number of chemical materials (quantum dots (Hua et al., 2017), metal-organic framework (Liu et al., 2020), AuNPs (Qi et al., 2016), etc.) were applied for signal enhancement. In addition, molecularly imprinted and aptamer were utilized for the accurate recognition of neonicotinoid insecticides. At the same time, fluorometric sensors can help to provide ultra-high sensitivities. Even for solid samples, the homogenization supernatants can be directly analyzed using these sensors.

## 5.4. Electrochemical detection

The electrochemical method has drawn great attention due to its low cost, rapid response and high sensitivity. In recent years, different kinds of electrochemical sensors have been designed for neonicotinoid insecticides testing, such as cyclic voltammetry (CV) (Shi et al., 2020), different pulse voltammetry (DPV) (Ganesamurthi et al., 2020), square-wave voltammetry (SWV) (Oliveira et al., 2018). Electrodes with additional nanomaterial decorations can realize signal amplification for the detection of target analytes, which has significant contribution to the sensitivity improvement of analytical methods. Electrochemical sensors have high sensitivity (fM) and a wide linear range. Moreover, the sample preparation procedure for electrochemical detection is also simple enough, and the target pesticides can be directly detected or extracted by using organic solvents (methanol, acetonitrile, acetone, etc.) with

low toxicity or buffer solution (PBS or PB solution). A novel dual signal amplification strategy for aptasensor employing reduced graphene with silver nanoparticles and Prussian blue-gold nanocomposites was developed to detect ACE (Shi et al., 2020). The reduced graphene oxide-silver nanoparticles (rGO-AgNPs) provided a large specific surface area for subsequent material immobilization and amplified current signal, and Prussian blue-gold nanoparticles (PB-AuNPs) significantly improved the electrical signal output and sensitivity of the aptasensor. The analysis experiment exhibited a super-high sensitivity to ACE with a detection limit of 0.30 pM (S/N = 3), which met the requirements of the vast majority of daily leaf vegetable testing.

Both optical and electrochemical sensors are powerful tools for signal amplification and significantly improving sensitivity, and their high selectivity does not require cumbersome sample pretreatment. However, the inability to simultaneously screen and quantify multiple neonicotinoid insecticides is their vital drawback, and these sensors need to be combined with special detection instruments. Thus, the miniaturization and multi-array chips of these sensors is a promising development for them to achieve rapid and on-site detection.

## 6. Conclusions and challenges

This review provides a concise summary of neonicotinoid insecticides and their metabolites and discusses the contamination status of neonicotinoid insecticides. Importantly, it presents an overview of recent progress in sample pretreatment technology and detection methods for the determination of neonicotinoid insecticide residues in foodstuffs and environmental samples. In addition, the vital conditions of each method have also been summarized. Among these methods, SPE, QuEChERS, LC-DAD and LC-MS/MS are the most ordinarily used methods for the extraction and detection of multiple neonicotinoid insecticides and their metabolites.

For sample preparation, various novel sample preparation (dSPE, SPME, MSPE, and MSPD) methods have been designed and some extraction sorbents have also been applied for extraction and enrichment of neonicotinoid insecticides from complex matrices. Compared with traditional sample pretreatment technologies, these methods use fewer adsorbents and organic solvents, convenient operation and low cost. Although these novel extraction methods have been applied to extract the analytes, the applicability and stability of the methods for a large number of real samples still need further investigation. At the same time, the screening of multiple neonicotinoid insecticides and their metabolites under the novel extraction procedures remains a challenge.

For sample detection, LC-UV/DAD is usually used for the detection of original neonicotinoid insecticides, and LC-MS/MS is an irreplaceable method for simultaneous determination of neonicotinoid insecticides and their metabolites. Many other methods (immunoassay, optical and electrochemical detection) have been established to achieve sensitive, rapid, real-time and on-site detection. However, the repeatability and robustness of these methods still need further confirmation. Additionally, applying of these techniques to achieve simultaneous detection of multiple neonicotinoid insecticides still presents significant challenges.

## CRedit authorship contribution statement

**Yudan Wang:** Investigation, Writing – original draft. **Yanwei Fu:** Conceptualization. **Yunyun Wang:** Software. **Qian Lu:** Data curation. **Haonan Ruan:** Visualization. **Jiaoyang Luo:** Conceptualization, Writing – review & editing. **Meihua Yang:** Supervision, Writing – review & editing.

## Declaration of Competing Interest

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

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## References

- Adelantado, C., Rios, A., & Zougagh, M. (2018). Magnetic nanocellulose hybrid nanoparticles and ionic liquid for extraction of neonicotinoid insecticides from milk samples prior to determination by liquid chromatography-mass spectrometry. *Food Additives and Contaminants Part A*, 35, 1755–1766. <https://doi.org/10.1080/19440049.2018.1492156>
- Anastasiades, M. (2003). Fast and easy multiresidue method employing acetonitrile extraction/partitioning and “dispersive solid-phase extraction” for the determination of pesticide residues in produce. *Journal of AOAC International*, 86, 412–431. <https://doi.org/10.1093/jaoac/86.2.412>
- Anjos, C. S., Lima, R. N., & Porto, A. (2021). An overview of neonicotinoids: Biotransformation and biodegradation by microbiological processes. *Environmental Science and Pollution Research*, 28, 37082–37109. <https://doi.org/10.1007/s11356-021-13531-3>
- AOAC Official Method, 2007.01, Pesticides residues in food by acetonitrile extraction and partitioning with magnesium sulphate, 2007.
- Bass, C., Denholm, I., Williamson, M., & Nauen, R. (2015). The global status of insect resistance to neonicotinoid insecticides. *Pesticide Biochemistry and Physiology*, 121, 78–87. <https://doi.org/10.1016/j.pestbp.2015.04.004>
- Bonmatin, J., Mitchell, E., Glauser, G., Lumawig-Heitzman, E., Claveria, F., et al. (2021). Residues of neonicotinoids in soil, water and people's hair: A case study from three agricultural regions of the Philippines. *Science of the Total Environment*, 757, Article 143822. <https://doi.org/10.1016/j.scitotenv.2020.143822>
- Cao, X., Jiang, Z., Wang, S., Hong, S., & Li, H. (2018). Metal-organic framework UiO-66 for rapid dispersive solid phase extraction of neonicotinoid insecticides in water samples. *Journal of Chromatography B*, 1077, 92–97. <https://doi.org/10.1016/j.jchromb.2017.11.034>
- Cao, X., Jiang, Z., Wang, S., Hong, S., Li, H., et al. (2017). One-pot synthesis of magnetic zeolitic imidazolate framework/graphene oxide composites for the extraction of neonicotinoid insecticides from environmental water samples. *Journal of Separation Science*, 4747–4756. <https://doi.org/10.1002/jssc.201700674>
- Carla, S., Ana, A., Irene, C., José, A., & Sánchez, P. (2014). Application of liquid chromatography quadrupole time-of-flight mass spectrometry to the identification of acetamiprid transformation products generated under oxidative processes in different water matrices. *Analytical and Bioanalytical Chemistry*, 406, 2549–2558. <https://doi.org/10.1007/s00216-014-7678-y>
- Casida, E. J. (2011). Neonicotinoid metabolism: Compounds, substituents, pathways, enzymes, organisms, and relevance. *Journal of Agricultural and Food Chemistry*, 59, 2923–2931. <https://doi.org/10.1021/jf102438c>
- Chen, L. (2012). Determination of imidacloprid in rice by molecularly imprinted-matrix solid-phase dispersion with liquid chromatography tandem mass spectrometry. *Journal of Separation Science*, 897, 32–36. <https://doi.org/10.1002/jssc.201700674>
- Codling, G., Naggar, Y. A., Giesy, J. P., & Robertson, A. J. (2016). Concentrations of neonicotinoid insecticides in honey, pollen and honey bees (*Apis mellifera* L.) in central Saskatchewan, Canada. *Chemosphere*, 144, 2321–2328. <https://doi.org/10.1016/j.chemosphere.2015.10.135>
- Dankyi, E., Carboo, D., Gordon, C., & Fomsgaard, I. (2016). Application of the QuEChERS procedure and LC-MS/MS for the assessment of neonicotinoid insecticide residues in cocoa beans and shells. *Journal of Food Composition and Analysis*, 44, 149–157. <https://doi.org/10.1016/j.jfca.2015.09.002>
- Dankyi, E., Gordon, C., Carboo, D., & Fomsgaard, I. S. (2014). Quantification of neonicotinoid insecticide residues in soils from cocoa plantations using a QuEChERS extraction procedure and LC-MS/MS. *Science of the Total Environment*, 499, 276–283. <https://doi.org/10.1016/j.scitotenv.2014.08.051>
- Ding, X., Wei, Z., Dan, C., He, J., & Yang, K. (2012). Oligopeptides functionalized surface plasmon resonance biosensors for detecting thiacloprid and imidacloprid. *Biosensors and Bioelectronics*, 35, 271–276. <https://doi.org/10.1016/j.bios.2012.02.060>
- Du, M., Yang, Q., Liu, W., Ding, Y., & Wang, M. (2020). Development of immunoassays with high sensitivity for detecting imidacloprid in environment and agro-products using phage-borne peptides. *Science of the Total Environment*, 723, Article 137909. <https://doi.org/10.1016/j.scitotenv.2020.137909>
- Ettiène, G., Bauza, R., Plata, M. R., Contento, A. M., & Rios, A. (2012). Determination of neonicotinoid insecticides in environmental samples by micellar electrokinetic chromatography using solid-phase treatments. *Electrophoresis*, 33, 2969–2977. <https://doi.org/10.1002/elps.201200241>
- Fang, Q., Wang, L., Cheng, Q., Cai, J., Wang, Y., et al. (2019). A bare-eye based one-step signal amplified semiquantitative immunochromatographic assay for the detection of imidacloprid in Chinese cabbage samples. *Analytica Chimica Acta*, 881, 82–89. <https://doi.org/10.1016/j.aca.2015.04.047>
- Faraji, M., Noorbakhsh, R., Shafieyan, H., & Ramezani, M. (2017). Determination of acetamiprid, imidacloprid, and spirotetramat and their relevant metabolites in pistachio using modified QuEChERS combined with liquid chromatography-tandem mass spectrometry. *Food Chemistry*, 240, 634–641. <https://doi.org/10.1016/j.foodchem.2017.08.012>

- Ford, K. A., & Casida, J. (2008). Comparative metabolism and pharmacokinetics of seven neonicotinoid insecticides in spinach. *Journal of Agricultural and Food Chemistry*, 56, 10168–10175. <https://doi.org/10.1021/jf8020909>
- Ganesamurthi, J., Keerthi, M., Chen, S. M., & Shanmugam, R. (2020). Electrochemical detection of thiamethoxam in food samples based on Co3O4 nanoparticle@Graphitic carbon nitride composit. *Ecotoxicology and Environmental Safety*, 189, Article 110035. <https://doi.org/10.1016/j.ecoenv.2019.110035>
- Gawel, M., Kiljanek, T., Niewiadowska, A., Semeniuk, S., Goliszek, M., et al. (2019). Determination of neonicotinoids and 199 other pesticide residues in honey by liquid and gas chromatography coupled with tandem mass spectrometry. *Food Chemistry*, 282, 36–47. <https://doi.org/10.1016/j.foodchem.2019.01.003>
- Gbylik-Sikorska, M., Sniogocki, T., & Posnyak, A. (2015). Determination of neonicotinoid insecticides and their metabolites in honey bee and honey by liquid chromatography tandem mass spectrometry. *Journal of Chromatography B*, 990, 132–140. <https://doi.org/10.1016/j.jchromb.2015.03.016>
- Ge, G., Gao, W., Yan, M., Song, W., Hou, R., et al. (2020). Comparison study on the metabolism destination of neonicotinoid and organophosphate insecticides in tea plant (*Camellia sinensis* L.). *Food Chemistry*, 344, Article 128579. <https://doi.org/10.1016/j.foodchem.2020.128579>
- Ghiasi, A., Malekpour, A., & Mahpishanian, S. (2020). Metal-organic framework MIL-101 (Cr)-NH2 functionalized magnetic graphene oxide for ultrasonic-assisted magnetic solid phase extraction of neonicotinoid insecticides from fruit and water samples. *Talanta*, 217, Article 121120. <https://doi.org/10.1016/j.talanta.2020.121120>
- Giroud, B., Bruckner, S., Straub, L., Neumann, P., Williams, G. R., et al. (2019). Trace-level determination of two neonicotinoid insecticide residues in honey bee royal jelly using ultra-sound assisted salting-out liquid liquid extraction followed by ultra-high-performance liquid chromatography-tandem mass spectrometry. *Microchemical Journal*, 151, 104249–104249. <https://doi.org/10.1016/j.microc.2019.104249>
- Giroud, B., Vauchez, A., Vulliet, E., Wiest, L., & Bulete, A. (2013). Trace level determination of pyrethroid and neonicotinoid insecticides in bee bread using acetonitrile-based extraction followed by analysis with ultra-high-performance liquid chromatography-tandem mass spectrometry. *Journal of Chromatography A*, 1316, 53–61. <https://doi.org/10.1016/j.chroma.2013.09.088>
- Guo, Y., Zou, R., Si, F., Liang, W., & Zhao, J. (2020). A sensitive immunoassay based on fluorescence resonance energy transfer from up-converting nanoparticles and graphene oxide for one-step detection of imidacloprid. *Food Chemistry*, 335, Article 127609. <https://doi.org/10.1016/j.foodchem.2020.127609>
- Han, W., Tian, Y., & Shen, X. J. C. (2018). Human exposure to neonicotinoid insecticides and the evaluation of their potential toxicity: An overview. *Chemosphere*, 192, 59–65. <https://doi.org/10.1016/j.chemosphere.2017.10.149>
- Hassan, M. M., Zareef, M., Jiao, T., Liu, S., Xu, Y., et al. (2021). Signal optimized rough silver nanoparticle for rapid SERS sensing of pesticide residues in tea. *Food Chemistry*, 338, Article 127796. <https://doi.org/10.1016/j.foodchem.2020.127796>
- Hou, J., Xie, W., Hong, D., Zhang, W., Li, F., et al. (2019). Simultaneous determination of ten neonicotinoid insecticides and two metabolites in honey and Royal-jelly by solid-phase extraction and liquid chromatography-tandem mass spectrometry. *Food Chemistry*, 270, 204–213. <https://doi.org/10.1016/j.foodchem.2018.07.068>
- Hou, R. Y., Jiao, W. T., Qian, X. S., Wang, X. H., Xiao, Y., et al. (2013). Effective extraction method for determination of neonicotinoid residues in tea. *Journal of Agricultural and Food Chemistry*, 61, 12565–12571. <https://doi.org/10.1021/jf404100x>
- Hua, X., Ding, Y., Yang, J., Ma, M., Shi, H., et al. (2017). Direct competitive fluoroimmunoassays for detection of imidacloprid in environmental and agricultural samples using quantum dots and europium as labels. *Science of the Total Environment*, 583, 222–227. <https://doi.org/10.1016/j.scitotenv.2017.01.056>
- Hui, D., Wang, R., Wei, L., Cheng, S., Ji, W., Zheng, Z., et al. (2019). A spherical metal-organic coordination polymer for the microextraction of neonicotinoid insecticides prior to their determination by HPLC. *Microchimica Acta*, 186, 1–8. <https://doi.org/10.1007/s00604-018-3210-y>
- Ihara, M., & Matsuda, K. (2018). Neonicotinoids: Molecular mechanisms of action, insights into resistance and impact on pollinators. *Current Opinion in Insect Science*, 30, 86–92. <https://doi.org/10.1016/j.cois.2018.09.009>
- Iwasa, T., Ambrose, J., Rose, R., Motoyama, N., & Roe, R. M. (2004). Mechanism for the differential toxicity of neonicotinoid insecticides in the honey bee, *Apis mellifera*. *Crop Protection*, 23, 371–378. <https://doi.org/10.1016/j.cropro.2003.08.018>
- Jiao, W., Xiao, Y., Qian, X., Tong, M., Hu, Y., et al. (2016). Optimized combination of dilution and refined QuEChERS to overcome matrix effects of six types of tea for determination eight neonicotinoid insecticides by ultra performance liquid chromatography–electrospray tandem mass spectrometry. *Food Chemistry*, 210, 26–34. <https://doi.org/10.1016/j.foodchem.2016.04.097>
- Jovanov, P., Guzsvany, V., Franko, M., Lazic, S., Sakac, M., et al. (2014). Development of multiresidue DLLME and QuEChERS based LC-MS/MS method for determination of selected neonicotinoid insecticides in honey liqueur. *Food Research International*, 55, 11–19. <https://doi.org/10.1016/j.foodres.2013.10.031>
- Kamel, A. (2010). Refined methodology for the determination of neonicotinoid pesticides and their metabolites in honey bees and bee products by liquid chromatography-tandem mass spectrometry (LC-MS/MS). *Journal of Agricultural and Food Chemistry*, 58, 5266–5931. <https://doi.org/10.1021/jf904120n>
- Kammoun, S., Mulhauser, B., Aebi, A., Mitchell, E., & Glauser, G. (2019). Ultra-trace level determination of neonicotinoids in honey as a tool for assessing environmental contamination. *Environmental Pollution*, 247, 964–972. <https://doi.org/10.1016/j.envpol.2019.02.004>
- Karthikeyan, S., Suganthi, A., Bhuvanewari, K., & Kennedy, J. (2019). Validation and quantification of neonicotinoid insecticide residues in rice whole grain and rice straw using LC-MS/MS. *Food Additives and Contaminants Part A*, 36, 1–8. <https://doi.org/10.1080/19440049.2018.1562229>
- Kavanagh, S., Henry, M., Stout, J. C., & White, B. (2021). Neonicotinoid residues in honey from urban and rural environments. *Environmental Science and Pollution Research*, 28, 28179–28190. <https://doi.org/10.1007/s11356-021-12564-y>
- Khwankaew, M., Yanawath, S., Supalax, S., & Jitlada, V. (2018). Preconcentration of trace neonicotinoid insecticide residues using vortex-assisted dispersive micro solid-phase extraction with montmorillonite as an efficient sorbent. *Molecules*, 23, 883. <https://doi.org/10.3390/molecules23040883>
- Lachat, L., & Glauser, G. (2018). Development and validation of an ultra-sensitive UHPLC-MS/MS method for neonicotinoid analysis in milk. *Journal of Agricultural and Food Chemistry*, 66, 8639–8646. <https://doi.org/10.1021/acs.jafc.8b03005>
- Li, D., Zhang, H., Chang, M., Shen, K., Zhang, W., et al. (2020). Neonicotinoid insecticide and their metabolite residues in fruit juices: Implications for dietary intake in China. *Chemosphere*, 261, Article 127682. <https://doi.org/10.1016/j.chemosphere.2020.127682>
- Li, J. F., Jiang, Y. W., & Li, D. (2019). Determination of imidacloprid and its relevant metabolites in tomato using modified QuEChERS combined with ultrahigh-pressure liquid chromatography/Orbitrap tandem mass spectrometry. *Journal of the Science of Food and Agriculture*, 99, 5211–5218. <https://doi.org/10.1002/jsfa.9769>
- Li, S., Chen, D., Lv, B., Li, J., Zhao, Y., et al. (2019). Enhanced sensitivity and effective cleanup strategy for analysis of neonicotinoids in complex dietary samples and the application in Total Diet Study. *Journal of Agricultural and Food Chemistry*, 67, 2732–2740. <https://doi.org/10.1021/acs.jafc.9b00113>
- Li, X., Chen, J., He, X., Wang, Z., Wu, D., et al. (2019). Simultaneous determination of neonicotinoids and fipronil and its metabolites in environmental water from coastal bay using disk-based solid-phase extraction and high-performance liquid chromatography-tandem mass spectrometry. *Chemosphere*, 234, 224–231. <https://doi.org/10.1016/j.chemosphere.2019.05.243>
- Liu, J., Xiong, W., Ye, L., Zhang, W., & Yang, H. (2020). Developing a novel nanoscale porphyrinic metal-organic framework: A bifunctional platform with sensitive fluorescent detection and elimination of nitenpyram in agricultural environment. *Journal of Agricultural and Food Chemistry*, 68, 5572–5578. <https://doi.org/10.1021/acs.jafc.0c01313>
- Liu, L., Feng, T., Wang, C., Wu, Q., & Wang, Z. (2014). Enrichment of neonicotinoid insecticides from lemon juice sample with magnetic three-dimensional graphene as the adsorbent followed by determination with high-performance liquid chromatography. *Journal of Separation Science*, 37, 1276–1282. <https://doi.org/10.1002/jssc.201301382>
- Liu, L., Hao, Y., Zhou, X., Wang, C., Wu, Q., et al. (2015). Magnetic porous carbon based solid-phase extraction coupled with high performance liquid chromatography for the determination of neonicotinoid insecticides in environmental water and peanut milk samples. *Analytical Methods*, 7, 2762–2769. <https://doi.org/10.1039/c4ay02990a>
- Liu, S., Zheng, Z., Wei, F., Ren, Y., Gui, W., et al. (2010). Simultaneous determination of seven neonicotinoid pesticide residues in food by ultra-performance liquid chromatography tandem mass spectrometry. *Journal of Separation Science*, 58, 3271–3278. <https://doi.org/10.1021/jf904045j>
- Liu, Z., Dai, Y., Huang, G., Gu, Y., Ni, J., et al. (2011). Soil microbial degradation of neonicotinoid insecticides imidacloprid, acetamiprid, thiacloprid and imidaclothiz and its effect on the persistence of bioefficacy against horsebean aphid *Aphis craccivora* Koch after soil application. *Pest Management Science*, 67, 1245–1252. <https://doi.org/10.1002/ps.2174>
- Lu, J., Wang, R., Luan, J., Li, Y., & Zhang, Y. (2020). A functionalized magnetic covalent organic framework for sensitive determination of trace neonicotinoid residues in vegetable samples. *Journal of Chromatography A*, 1618, Article 460898. <https://doi.org/10.1016/j.chroma.2020.460898>
- Ma, C., Liu, X., Wu, X., Dong, F., Xu, J., et al. (2021). Kinetics, mechanisms and toxicity of the degradation of imidaclothiz in soil and water. *Journal of Hazardous Materials*, 403, Article 124033. <https://doi.org/10.1016/j.jhazmat.2020.124033>
- Matthew, N., Simon, R., & Hao, C. (2016). Nitenpyram degradation in finished drinking water. *Rapid Communications in Mass Spectrometry*, 30, 1653–1661. <https://doi.org/10.1002/rcm.7581>
- Mehedi, H. M., Chen, Q., Kutsanedzie, F., Li, H., Muhammad, Z., et al. (2019). rGO-NS SERS-based coupled chemometric prediction of acetamiprid residue in green tea. *Journal of Food and Drug Analysis*, 27, 145–153. <https://doi.org/10.1016/j.jfda.2018.06.004>
- Motaung, T. E. (2020). Chloronicotinyl insecticide imidacloprid: Agricultural relevance, pitfalls and emerging opportunities. *Crop Protection*, 131, Article 105097. <https://doi.org/10.1016/j.cropro.2020.105097>
- Mrzlikar, M., Heath, D., Heath, E., Markelj, J., Borovšak, A., et al. (2019). Investigation of neonicotinoid pesticides in Slovenian honey by LC-MS/MS. *LWT-Food Science and Technology*, 104, 45–52. <https://doi.org/10.1016/j.lwt.2019.01.017>
- Nauen, R., Reckmann, U., Armborst, S., Stupp, H. P., & Elbert, A. (1999). Whitefly-active metabolites of imidacloprid: Biological efficacy and translocation in cotton plants. *Journal of Pest Science*, 55, 265–271. [https://doi.org/10.1002/\(SICI\)1096-9063\(199903\)55:3<265::AID-PS891>3.0.CO;2-C](https://doi.org/10.1002/(SICI)1096-9063(199903)55:3<265::AID-PS891>3.0.CO;2-C)
- NF EN 15662, 2009.01, Determination of pesticide residues using GC-MS and/or LC-MS/MS following acetonitrile extraction/partitioning and clean-up by dispersive SPE-QuEChERS-method. vol V03-061; NF EN 15662:2009-01-01. AFDNOR.
- Noestheden, M., Roberts, S., & Hao, C. (2016). Nitenpyram degradation in finished drinking water. *Rapid Communications in Mass Spectrometry*, 30, 1653–1661. <https://doi.org/10.1002/rcm.7581>
- Obana, H., Okihashi, M., Akutsu, K., Kitagawa, Y., & Hori, S. (2002). Determination of acetamiprid, imidacloprid, and nitenpyram residues in vegetables and fruits by high-performance liquid chromatography with diode-array detection. *Journal of Agricultural and Food Chemistry*, 50, 4464–4467. <https://doi.org/10.1021/jf025539q>
- Oliveira, A., Bettio, G. B., & Pereira, A. (2018). An electrochemical sensor based on electropolymerization of  $\beta$ -cyclodextrin and reduced graphene oxide on a glassy

- carbon electrode for determination of neonicotinoids. *Electroanalysis*, 30, 1918–1928. <https://doi.org/10.1002/elan.201800236>
- Pastor-Belda, M., Garrido, I., Campillo, N., Vinas, P., Hellín, P., et al. (2016). Determination of spirocyclic tetratric tetramic acid derivatives and neonicotinoid insecticides in fruits and vegetables by liquid chromatography and mass spectrometry after dispersive liquid–liquid microextraction. *Food Chemistry*, 202, 389–395. <https://doi.org/10.1016/j.foodchem.2016.01.143>
- Pook, C., & Gritcan, I. (2019). Validation and application of a modified QuEChERS method for extracting neonicotinoid residues from New Zealand maize field soil reveals their persistence at nominally hazardous concentrations. *Environmental Pollution*, 255, Article 113075. <https://doi.org/10.1016/j.envpol.2019.113075>
- Pratheeshkumar, N., Chandran, M., Beevi, S. N., Mathew, T. B., George, T., et al. (2016). Dissipation kinetics and effect of processing on imidacloprid and its metabolites in cardamom (*Elettaria cardamomum* Maton). *Environmental Monitoring and Assessment*, 188, 53. <https://doi.org/10.1007/s10661-015-5058-5>
- Qi, Y., Xiu, F. R., Zheng, M., & Li, B. (2016). A simple and rapid chemiluminescence aptasensor for acetamiprid in contaminated samples: Sensitivity, selectivity and mechanism. *Biosensors and Bioelectronics*, 83, 243–249. <https://doi.org/10.1016/j.bios.2016.04.074>
- Qin, J., Fu, Y., Lu, Q., Dou, X., Luo, J., et al. (2020). Matrix-matched monitoring ion selection strategy for improving the matrix effect and qualitative accuracy in pesticide detection based on UPLC-ESI-MS/MS: A case of Chrysanthemum. *Microchemical Journal*, 160, Article 105681. <https://doi.org/10.1016/j.microc.2020.105681>
- Qiu, J., Ouyang, G., Pawliszyn, J., Schlenk, D., & Gan, J. (2019). A novel water-swelling sampling probe for in vivo detection of neonicotinoids in plants. *Environmental Science and Technology*, 53, 9686–9694. <https://doi.org/10.1021/acs.est.9b01682>
- Raqueal, B., Arturo, L., Núñez, P., Ady, G., & Gloria, M. (2018). LC-MS/MS analysis of neonicotinoid insecticides: Residue findings in Chilean honeys. *Ciencia E Agrotecnología*, 42, 51–57. <https://doi.org/10.1590/1413-70542018421021117>
- Rodríguez-Cabo, T., Casado, J., Rodríguez, I., Ramil, M., & Cela, R. (2016). Selective extraction and determination of neonicotinoid insecticides in wine by liquid chromatography–tandem mass spectrometry. *Journal of Chromatography A*, 1460, 9–15. <https://doi.org/10.1016/j.chroma.2016.07.004>
- Sánchez-Bayo, F., & Hynes, R. V. (2014). Detection and analysis of neonicotinoids in river waters-Development of a passive sampler for three commonly used insecticides. *Chemosphere*, 99, 143–151. <https://doi.org/10.1016/j.chemosphere.2013.10.051>
- Seccia, S., Fidente, P., Montesano, D., & Morrica, P. (2008). Determination of neonicotinoid insecticides residues in bovine milk samples by solid-phase extraction clean-up and liquid chromatography with diode-array detection. *Journal of Chromatography A*, 1214, 115–120. <https://doi.org/10.1016/j.chroma.2008.10.088>
- Selähle, S. K., Waleng, N. J., Mpupa, A., & Nomngongo, P. N. (2020). Magnetic solid phase extraction based on nanostructured magnetic porous porphyrin organic polymer for simultaneous extraction and preconcentration of neonicotinoid insecticides from surface water. *Frontiers in Chemistry*, 8, Article 555847. <https://doi.org/10.3389/fchem.2020.555847>
- Sharma, S., & Singh, B. (2014). Persistence behaviour of imidacloprid and its metabolites in soil under sugarcane. *Pest Management Science*, 186, 2281–2288. <https://doi.org/10.1007/s10661-013-3536-1>
- Sharon, K., Papiernik, W., Koskinen, C., Lucia, C., & Pamela, J. (2006). Sorption–desorption of imidacloprid and its metabolites in soil and vadose zone materials. *Journal of Agricultural and Food Chemistry*, 54, 8163–8170. <https://doi.org/10.1021/jf061670c>
- Shi, X., Sun, J., Yao, Y., Liu, H., Huang, J., et al. (2020). Novel electrochemical aptasensor with dual signal amplification strategy for detection of acetamiprid. *Science of the Total Environment*, 705, Article 135905. <https://doi.org/10.1016/j.scitotenv.2019.135905>
- Shi, Z., Zhang, S., Huai, Q., Xu, D., & Zhang, H. (2017). Methylamine-modified graphene-based solid phase extraction combined with UPLC-MS/MS for the analysis of neonicotinoid insecticides in sunflower seeds. *Talanta*, 162, 300–308. <https://doi.org/10.1016/j.talanta.2016.10.042>
- Shim, W. B., Yakovleva, M. E., Kim, K. Y., Nam, B. R., Vylegzhaniya, E. S., et al. (2009). Development of fluorescence polarization immunoassay for the rapid detection of 6-chloronicotinic acid: Main metabolite of neonicotinoid insecticides. *Journal of Agricultural and Food Chemistry*, 57, 791–796. <https://doi.org/10.1021/jf802647v>
- Simon-Delso, N., Amaral-Rogers, V., Belzunces, L. P., Bonmatin, J. M., Chagnon, M., et al. (2015). Systemic insecticides (neonicotinoids and fipronil): Trends, uses, mode of action and metabolites. *Environmental Science and Pollution Research*, 22, 5–34. <https://doi.org/10.1007/s11356-014-3470-y>
- Song, S., Zhang, C., Chen, Z., He, F., Wei, J., et al. (2018). Simultaneous determination of neonicotinoid insecticides and insect growth regulators residues in honey using LC-MS/MS with anion exchanger-disposable pipette extraction. *Journal of Chromatography A*, 1557, 51–61. <https://doi.org/10.1016/j.chroma.2018.05.003>
- Tadashi, Y., Hikoto, O., Mika, A., & Daisuke, W. (2014). Simultaneous determination of neonicotinoid insecticides in human serum and urine using diatomaceous earth-assisted extraction and liquid chromatography–tandem mass spectrometry. *Journal of Chromatography B*, 969, 85–96. <https://doi.org/10.1016/j.jchromb.2014.06.008>
- Tan, G., Zhao, Y., Wang, M., Chen, X., Wang, B., et al. (2020). Ultrasensitive quantitation of imidacloprid in vegetables by colloidal gold and time-resolved fluorescent nanobead traced lateral flow immunoassays. *Food Chemistry*, 311, 126055.1–126055.7. <https://doi.org/10.1016/j.foodchem.2019.126055>
- Tang, J., Zhang, M., Cheng, G., & Lu, Y. (2008). Development and application of molecularly imprinted polymer as solid phase extraction of imidacloprid in environmental samples. *Journal of Liquid Chromatography and Related Technologies*, 32, 59–71. <https://doi.org/10.1080/10826070802548622>
- Tanner, G., & Czerwenka, C. (2011). LC-MS/MS analysis of neonicotinoid insecticides in honey: Methodology and residue findings in Austrian honeys. *Journal of Agricultural and Food Chemistry*, 59, 12271–12277. <https://doi.org/10.1021/jf202775m>
- Tao, T., Wang, C., Dai, W., Yu, S., Lu, Z., et al. (2019). An integrated assessment and spatial-temporal variation analysis of neonicotinoids in pollen and honey from noncrop plants in Zhejiang, China. *Environmental Pollution*, 250, 397–406. <https://doi.org/10.1016/j.envpol.2019.04.004>
- Tao, Y., Jia, C., Jing, J., Zhao, M., & Zhao, E. (2021). Uptake, translocation, and biotransformation of neonicotinoid imidacloprid in hydroponic vegetables: Implications for potential intake risks. *Journal of Agricultural and Food Chemistry*, 69, 4064–4073. <https://doi.org/10.1021/acs.jafc.0c07006>
- Thurman, E. M., Ferrer, I., Zavitsanos, P., & Zweigenbaum, J. (2013). Identification of imidacloprid metabolites in onion (*Allium cepa* L.) using high-resolution mass spectrometry and accurate mass tools. *Rapid Communications in Mass Spectrometry*, 27, 1891–1903. <https://doi.org/10.1002/rcm.6637>
- Valverde, S., Ares, A. M., Arribas, M., Bernal, J., Nozal, M. J., et al. (2015). Development and validation of UHPLC-MS/MS methods for determination of neonicotinoid insecticides in royal jelly-based products. *Journal of Food Composition and Analysis*, 70, 105–113. <https://doi.org/10.1016/j.jfca.2018.05.002>
- Valverde, S., Bernal, J. L., Nozal, M. J., Hernández, F., & Bernal, J. (2018). Development and validation of ultra high performance-liquid chromatography–tandem mass spectrometry based methods for the determination of neonicotinoid insecticides in honey. *Food Chemistry*, 15, 215–222. <https://doi.org/10.1016/j.foodchem.2018.06.004>
- Vichapong, J., Burakham, R., & Srijaranai, S. (2013). Vortex-assisted surfactant-enhanced-emulsification liquid–liquid microextraction with solidification of floating organic droplet combined with HPLC for the determination of neonicotinoid pesticides. *Talanta*, 117, 221–228. <https://doi.org/10.1016/j.talanta.2013.08.034>
- Wang, P., Yang, X., Wang, J., Cui, J., Dong, A. J., et al. (2012a). Multi-residue method for determination of seven neonicotinoid insecticides in grains using dispersive solid-phase extraction and dispersive liquid–liquid micro-extraction by high performance liquid chromatography. *Food Chemistry*, 134, 1691–1698. <https://doi.org/10.1016/j.foodchem.2012.03.103>
- Wang, R., Wang, Z., Hong, Y., Wang, Y., & Deng, A. (2012b). Highly sensitive and specific detection of neonicotinoid insecticide imidacloprid in environmental and food samples by a polyclonal antibody-based enzyme-linked immunosorbent assay. *Journal of the Science of Food and Agriculture*, 92, 1253–1260. <https://doi.org/10.1002/jsfa.4691>
- Wang, Z., Chen, J., Zhan, T., He, X., & Dong, B. (2020). Simultaneous determination of eight neonicotinoid insecticides, fipronil and its three transformation products in sediments by continuous solvent extraction coupled with liquid chromatography–tandem mass spectrometry. *Ecotoxicology and Environmental Safety*, 189, Article 110002. <https://doi.org/10.1016/j.ecoenv.2019.110002>
- Watanabe, E. (2021). Review of sample preparation methods for chromatographic analysis of neonicotinoids in agricultural and environmental matrices: From classical to state-of-the-art methods. *Journal of Chromatography A*, 1643, Article 462042. <https://doi.org/10.1016/j.chroma.2021.462042>
- Watanabe, E., Kobara, Y., Baba, K., & Eun, H. (2015). Determination of seven neonicotinoid insecticides in cucumber and eggplant by water-based extraction and high-performance liquid chromatography. *Analytical Letters*, 48, 213–220. <https://doi.org/10.1080/00032719.2014.938346>
- Watanabe, E., Miyake, S., & Yogo, Y. (2013). Review of enzyme-linked immunosorbent assays (ELISAs) for analyses of neonicotinoid insecticides in agro-environments. *Journal of Agricultural and Food Chemistry*, 61, 12459–12472. <https://doi.org/10.1021/jf403801h>
- Wen, X., Han, C., Qian, Y., Ding, H., Chen, X., et al. (2011). Determination of neonicotinoid pesticides residues in agricultural samples by solid-phase extraction combined with liquid chromatography–tandem mass spectrometry. *Journal of Chromatography A*, 1218, 4426–4433. <https://doi.org/10.1016/j.chroma.2011.05.026>
- Wu, C., Dong, F., Chen, X., Tao, Z., Mei, X., et al. (2020a). Spatial and temporal distribution, degradation, and metabolism of three neonicotinoid insecticides on different parts, especially pests' target feeding parts of apple tree. *Pest Management Science*, 76, 2190–2197. <https://doi.org/10.1002/ps.5756>
- Wu, C., Dong, F., Mei, X., Ning, J., & She, D. (2020b). Isotope-labeled internal standards and grouping scheme for determination of neonicotinoid insecticides and their metabolites in fruits, vegetables and cereals-A compensation of matrix effects. *Food Chemistry*, 311, 125871.1–125871.8. <https://doi.org/10.1016/j.foodchem.2019.125871>
- Wu, C., Dong, F., Mei, X., Ning, J., & She, D. J. (2019). Distribution, dissipation, and metabolism of neonicotinoid insecticides in the cotton ecosystem under foliar spray and root irrigation. *Journal of Agricultural and Food Chemistry*, 67, 12374–12381. <https://doi.org/10.1021/acs.jafc.9b04664>
- Xu, F., Du, G., Xu, D., Chen, L., Zha, X., et al. (2021). Residual behavior and dietary intake risk assessment of flonicamid, dinotefuran and its metabolites on peach trees. *Journal of the Science of Food and Agriculture*, 101, 5842–5850. <https://doi.org/10.1002/jsfa.11236>
- Xu, Y., Li, X., Zhang, W., Jiang, H., Pu, Y., et al. (2020). Zirconium(IV)-based metal-organic framework for determination of imidacloprid and thiamethoxam pesticides from fruits by UPLC-MS/MS. *Food Chemistry*, 344, Article 128650. <https://doi.org/10.1016/j.foodchem.2020.128650>
- Yáñez, K. P., Bernal, J. L., Nozal, M. J., Martín, M., & Bernal, J. (2013). Determination of seven neonicotinoid insecticides in beeswax by liquid chromatography coupled to electrospray-mass spectrometry using a fused-core column. *Journal of Chromatography A*, 1285, 110–117. <https://doi.org/10.1016/j.chroma.2013.02.032>

- Yi, X., Zhang, C., Liu, H., Wu, R., Tian, D., et al. (2019). Occurrence and distribution of neonicotinoid insecticides in surface water and sediment of the Guangzhou section of the Pearl River, South China. *Environmental Pollution*, 251, 892–900. <https://doi.org/10.1016/j.envpol.2019.05.062>
- Yohannes, D., Sarwana, S., Tolpygo, S. K., Sahu, A., Polyakov, Y. A., et al. (2014). Synthesis and characterization of a molecularly imprinted polymer for preconcentration of clothianidin in environmental samples. *Analytical Letters*, 47, 2613–2627. <https://doi.org/10.1080/00032719.2014.915404>
- Yoshinori, I., Kazutoshi, F., Tomonori, K., Takahiro, I., Nesta, B. S., et al. (2018). Contamination by neonicotinoid insecticides and their metabolites in Sri Lankan black tea leaves and Japanese green tea leaves. *Toxicology Reports*, 5, 744–749. <https://doi.org/10.1016/j.toxrep.2018.06.008>
- Zhang, J., Wei, Y., Li, H., Zeng, E. Y., & You, J. (2017). Application of Box-Behnken design to optimize multi-sorbent solid phase extraction for trace neonicotinoids in water containing high level of matrix substances. *Talanta*, 170, 392–398. <https://doi.org/10.1016/j.talanta.2017.04.031>
- Zhang, Q., Wang, X., Rao, Q., Chen, S., & Song, W. (2020a). Imidacloprid dissipation, metabolism and accumulation in Agaricus bisporus fruits, casing soil and compost and dietary risk assessment. *Chemosphere*, 254, Article 126837. <https://doi.org/10.1016/j.chemosphere.2020.126837>
- Zhang, S., Yang, X., Yin, X., Wang, C., & Wang, Z. (2012). Dispersive liquid–liquid microextraction combined with sweeping micellar electrokinetic chromatography for the determination of some neonicotinoid insecticides in cucumber samples. *Food Chemistry*, 133, 544–550. <https://doi.org/10.1016/j.foodchem.2012.01.028>
- Zhang, Y., Zhang, Q., Li, S., Zhao, Y., & Wu, Y. (2020b). Simultaneous determination of neonicotinoids and fipronils in tea using a modified QuEChERS method and liquid chromatography-high resolution mass spectrometry. *Food Chemistry*, 329, Article 127159. <https://doi.org/10.1016/j.foodchem.2020.127159>
- Zhao, F., Liu, J., & Luo, J. (2019). Development of a high-quality ELISA method for dinotefuran based on a novel and newly-designed antigen. *Molecules*, 24, 2426. <https://doi.org/10.3390/molecules24132426>
- Zhao, P., Liu, H., Zhang, L., Zhu, P., & Yu, J. (2020). Paper-based SERS sensing platform based on 3D silver dendrites and molecularly imprinted identifier sandwich hybrid for neonicotinoid quantification. *ACS Applied Materials and Interfaces*, 12, 8845–8854. <https://doi.org/10.1021/acsami.9b20341>
- Zheng, S., Wu, H., Li, Z., Wang, J., Hu, Z., & Qian, M. (2015). Ultrasound/microwave-assisted solid-liquid-solid dispersive extraction with high-performance liquid chromatography coupled to tandem mass spectrometry for the determination of neonicotinoid insecticides in *Dendrobium officinale*. *Journal of Separation Science*, 38, 121–127. <https://doi.org/10.1002/jssc.201400872>
- Zhou, Q., Ding, Y., & Xiao, J. (2006). Sensitive determination of thiamethoxam, imidacloprid and acetamiprid in environmental water samples with solid-phase extraction packed with multiwalled carbon nanotubes prior to high-performance liquid chromatography. *Analytical and Bioanalytical Chemistry*, 385, 1520–1525. <https://doi.org/10.1007/s00216-006-0554-7>
- Zhou, Y., Lu, X., Fu, X., Yu, B., Wang, D., et al. (2018). Development of a fast and sensitive method for measuring multiple neonicotinoid insecticide residues in soil and the application in parks and residential areas. *Analytica Chimica Acta*, 1016, 19–28. <https://doi.org/10.1016/j.aca.2018.02.047>