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 (Khankanaw 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 food and environmental samples.

Abbreviations: ACE, Acetamiprid; CLO, Clothianidin; CYC, Cycloxaprid; DIN, Dinotefuran; FLO, Flonicamid; FLU, Flupyradifurone; GUA, Guadinpy; IMI, Imidacloprid; IMI-guanidine, Imidacloprid guanidine/Desnitro imidacloprid; IMI-olefin, Imidacloprid olefin; IMI-urea, Imidacloprid-urea; IMID, Imidaclothiz; NIT, Nitipyrinam; PCQ, Paichongding; SUL, Sulfoxaflor; THX, Thiamethoxam; THI, Thiacloprid; THIAC, Thiaclocrid amide; IMI-guanidine-olefin, Imidacloprid guanidine olefin; N-dm-ACE, N-desmethyl-acetamiprid; CPMA, N-(6-chloro-3-pyridylmethyl)acetoacetamide; CPMD, N-(6-chloro-3-pyridylmethyl)pyridylacetamide; CPMF, N-(6-chloro-3-pyridylmethylpyridylmethyl)-N-ethyl-N-methylformamidine; CPF, N-(6-chloro-3-pyridylmethyl)-N-ethylformamide; TZMU, N-(2-chloro-1, 3-thiaizole-5-methyl)-N-methylurea; MNG, 1-Methyl-3-nitroguanidine; UF, 1-methyl-3-(tetrahydro-3-furylmethyl) urea; DN, 1-methyl-3-(tetrahydro-3-furylmethyl) guanidium dihydrogen; TFPA, 4-trifluoromethylnicotinic acid; 5-GH-MI, 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 imidaloprid 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 (Anjos 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.
| 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 | 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) |
| Tea plant (Ge et al., 2020), soil (Sharma & Singh 2014), cardamom (Pratheeshkumar et al., 2016), tomato (Li et al., 2019) | IMI-urea | 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) |
| Tea plant (Ge et al., 2020), soil (Sharma & Singh 2014), cardamom (Pratheeshkumar et al., 2016), tomato (Li et al., 2019) | IMI-olefin | 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) |
| Tea plant (Ge et al., 2020), soil (Sharma & Singh 2014), tomato (Li et al., 2019) | OH-IMI | Tea plant (Ge et al., 2020), soil (Sharma & Singh 2014), cardamom (Pratheeshkumar et al., 2016), tomato (Li et al., 2019) |
| 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) | 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) |
| Tea plant (Ge et al., 2020), soil (Sharma & Singh 2014), tomato (Li et al., 2019) | 6-CNA | Tea plant (Ge et al., 2020), soil (Sharma & Singh 2014), tomato (Li et al., 2019) |
| Article (Simon-Delso et al., 2015; Casida 2011) | IMI-6 | 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) |
| Cotton (Wu et al., 2019), tea plant (Ge et al., 2020) | N-dm-ACE | Cotton (Wu et al., 2019), tea plant (Ge et al., 2020) |
| Tea plant (Ge et al., 2020), soil (Liu et al., 2011) | ACE-2 | Tea plant (Ge et al., 2020), soil (Liu et al., 2011) |
| 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) |
| Tea plant (Ge et al., 2020) | THX | Cotton (Wu et al., 2019), tea plant (Ge et al., 2020), soil (Liu et al., 2011) |
| Neonicotinoid insecticides | Metabolites | Related articles |
|---------------------------|-------------|-----------------|
| THX-2                     | ![THX-2](image) | Tea plant (Ge et al., 2020) |
| THX-3                     | ![THX-3](image) | Tea plant (Ge et al., 2020) |
| THX-4                     | ![THX-4](image) | Tea plant (Ge et al., 2020) |
| THX-5                     | ![THX-5](image) | Article (Simon-Delso et al., 2015; Casida 2011) |
|                           | 19 metabolites | Drinking water (Noestheden et al., 2016) |
| NIT                       | ![NIT](image) | Soil (Liu et al., 2011) |
| THI                       | ![THI](image) | Review article (Simon-Delso et al., 2015; Casida 2011) |
|                           | Metabolites | Peach tree (Xu et al., 2021), fruit juice (Li et al., 2020) |
| DIN                       | ![DIN](image) | Peach tree (Xu et al., 2021), fruit juice (Li et al., 2020) |
| DN                        | ![DN](image) | Article (Simon-Delso et al., 2015; Casida 2011) |
|                           | Metabolites | Tea plant (Ge et al., 2020), lettuce, and celery (Tao et al., 2021) |
| IMID                      | ![IMID](image) | Tea plant (Ge et al., 2020), soil (Liu et al., 2011) |
|                           | 5-OH-IMID | Lettuce, celery, and radish (Tao et al., 2021) |
|                           | IMID-olefin | (continued on next page) |
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, CHCl₃ or CH₂Cl₂ 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 MgSO₄/NaCl for extraction (Anastastades 2003), (2) the American standard (AOAC) which involves the use of 1% acetic acid (HOAc) in ACN and anhydrous MgSO₄/NaOAc (AOAC Official Method, 20070.01), (3) the European standard, EN 15662, which involves the use of acetonitrile and anhydrous MgSO₄/sodium citrate and disodium citrate hydrogenate sesquihydrate (NF EN 15662, 2009.01). For most food and environmental samples, the anhydrous MgSO₄/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 (Tan- ner & 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).
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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, polyvinylpolypyrrolidone (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

Sorptive 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.

Sorptive materials have a significant influence on extraction efficiency. Many novel adsorption materials (methylamine modified graphene (CH$_2$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, THIX). 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.
UIO-66 (Cao et al., 2018) was used as the dSPE sorbent to extract IMI, groups on UIO-66 (UIO-66-NH₂, pore volume, and excellent stability in the water and acid conditions, secticides have been listed in Table 4. Due to the high surface area, large –

Several established dSPE for detecting 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 in insecticides (IMI, ACE, THI, THX, DIN, CLO) in milk samples. In this work, the ionic liquid (C₁₀MIMPF₆) 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

| Analyte    | Sample                                                                 | Extraction | Clean-up | Detection | LOQ or LOD | Recovery (%) | Ref.          |
|------------|------------------------------------------------------------------------|------------|----------|-----------|------------|--------------|---------------|
| DIN, NIT, THX, CLO, IMI, ACE, THI, FLO, IMI-olefin, IMI-urea, UP, N-dm-ACE, CPMF, CFP, 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-N₂O₂-IMI | Honey | 1% acetonitrile (20% TEA) and ethyl acetate (82: 8: 8/v/v) in water | Strata X-CW cartridge | LC-MS/MS | 0.1–0.5 ng/ mL | 88.6–109.2 | Gliblik et al. (2015) |
| IMI, ACE, THX, 5-OH-IMI, IMI-urea, d-N₂O₂-IMI-olefin, d-N₂O₂-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 | Kamel (2010) |
| ACN, 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, IMID | 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, 6-CNA | 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, 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, CLO | Honey | / | Oasis HLB SPE | LC-MS/MS | 0.15–3.25 ng/ g | 70.7–113.6 | Mralik et al. (2019) |
| IMI, ACE, THI, THX | Bovine milk | / | Chem Elut cartridge | LC-DAD | 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, 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, CLO, NIT, CLO, IMID | Sediment | CH₃OH-water | Oasis HLB SPE | LC-MS/MS | 0.031–0.091 µg/kg | 75.5–98.5 | Wang et al. (2020) |
| PYM, IIM, ACE, THI, THX, DIN, NIT, IMID, CLO, FLO, TFNA, N-dm-ACE | Royal-jelly, honey | CH₂OH (royal-jelly) | Oasis HLB SPE | LC-MS/MS | 0.25–5.0 µg/kg | 72.8–106.5 | Hou et al. (2019) |
| IIM, ACE, THI, THX, DIN, CLO | Cucumber, eggplant | Water | Oasis HLB SPE and Envi-Carb/ LC-NH₂ | LC-DAD | 0.003–0.019 µg/ g | 82–114 | Watanabe et al. (2015) |
| IIM, ACE, THI, THX, 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) |
| IIM, ACE, THI, THX, DIN, CLO | Royal jelly-based products | Water (10 mL ammonium formate) | Strata ® cartridge | LC-MS/MS | 2.5–8.0 µg/kg | 83–109 | Valverde et al. (2015) |
| DIN, NIT, CLO, CLO, IMI, 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.
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, 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, CLO | Fruit juice     | Montmorillonite (30 mg)         | 0.03 g Na2SO4 | 4       | 4  | 0.15 mL 70% ACN | HPLC-DAD        | –        | Khwanakiew et al. 2018 |
| IMI, THI         | Fruit           | ACN Uio-66-NH2 (50 mg)          | /         | 9, 5            | 8  | 3 mL ACN (0.1% methanoic acid) | UPLC-MS/MS       | 86-107 | Xu et al., (2020) |
| IMI, ACE, THI, CLO, CLO | 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, CLO | Water           | Fe3O4/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 | Selable et al., (2020) |
| IMI, ACE, THI, CLO | Water, peanut milk | Ionic liquid (C(6MIMPF6) | /         | 6               | –  | 0.6 mLACN | LC-DAD         | 96.74-112.40      | Liu et al., (2015) |
| IMI, ACE, THI, CLO, DINO | Milk         | Magnetic nanocellulose (50 mg) | /         | –               | 1  | 0.5 mL ACN | LC-MS          | 91.0-109.5       | Adelantado et al., (2018) |
| IMI, ACE, THI, CLO, CLO, CLO, CLO | Vegetable | ACN Fe3O4/COF-(NO3)2 (10 mg) | /         | 7               | 6  | 0.1 mL ACN | LC-UV          | 77.5-110.2       | Lu et al. (2020) |
| IMI, ACE, THI, CLO, CLO, CLO, CLO | Fruit, water (1:10, v/v) | CoFe3O4@SiO2/GO/MIL-101(Cr)-NH2 (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/l. 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 π-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 KH$_2$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

![Chemical structures of neonicotinoid insecticides and hapten molecules.](image-url)
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 Glauer (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 & Glauer, 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.

Immunochemiluminescent 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) (Ganesanurthi 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 (IM) 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.

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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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