Bioaccessibility and health risk of neonicotinoids in apple and pear samples as affected by *in vitro* digestion

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OPEN ACCESS   **ORIGINAL ARTICLE**

Abstract

Previous studies have only focused on the bioaccessibility of single pesticide/metal without considering the potential impact of post-uptake interactions on bioaccessibility of pesticides/metals in the human digestive system. Hence, the influences of chromium (Cr) speciation on neonicotinoids bioaccessibility were investigated and the potential health risk based on the oral bioaccessibility was evaluated. Bioaccessibility of four neonicotinoids in apple and pear was measured using three common in vitro methods (SBRC, PBET, and IVG). Bioaccessibility of neonicotinoids in apple and pear varied between in vitro methods, which may reflect the difference of determination parameters (i.e., pH values, incubation time, and constituents). The neonicotinoids bioaccessibility was remarkably reduced by 17.21–81.21% and 11.61–73.70% with the addition of Cr(III) and Cr(VI), respectively. Risk assessment based on the hazard quotient (HQ) with bioaccessibility revealed that exposure to pesticide residues in the tested fruits were all below levels that might pose a health risk. These findings are of theoretical value for the safety evaluation of pesticide residues on food.

Keywords: bioaccessibility; fruits; in vitro methods; neonicotinoids; risk assessment

Introduction

Pesticide residues in food exposure for humans has been associated with various adverse health effects, including immunological and neurobehavioral development (Chang *et al.*, 2018), and carcinogenic and teratogenic effects (Lundqvist *et al.*, 2016). Oral ingestion is the major route for human exposure to pesticide residues, especially through fruits and vegetables (Szpyrka *et al.*, 2015). This is because fruits and vegetables are often eaten raw or semi-processed, resulting in higher levels of pesticide residues compared to other foods (Bempah *et al.*, 2016;

Hlihor *et al.*, 2019). There has been widespread concern about the control and evaluation of fruit and vegetable safety in recent years.

Several studies are investigating the health risk assessment of pesticide-contaminated fruits and vegetables (Yu *et al.*, 2016). *In vivo* bioavailability and *in vitro* bioaccessibility have been considered as important parameters for a more reasonable human exposure or health risk assessment (Wang *et al.*, 2016; Yager *et al.*, 2015). *In vitro* methods are widely used to measure bioaccessibility and assess human health risks, considering the time, cost, and

ethical factors associated with *in vivo* methods (Zhao *et al.*, 2019). To date, several *in vitro* methods have been developed for bioaccessibility measurement. These methods vary in the composition of gastrointestinal fluid as well as operation parameters, such as gastrointestinal pH (Xing *et al.*, 2017), digestion times (Ayala-Bribiesca *et al.*, 2016), and solid–liquid (*S/L*) ratio (Laird *et al.*, 2015). Bioaccessibility measurement is therefore method dependent. Moreover, poor correlations were also observed between the bioaccessibility of contaminants derived from some *in vitro* digestion model and the relative bioavailability of the tested contaminants (Ruby *et al.*, 2016). Among those *in vitro* methods, physiologically based extraction test (PBET) (Zhuang *et al.*, 2016), solubility/bioavailability research consortium (SBRC) (Dong *et al.*, 2016), and *in vitro* gastrointestinal (IVG) method (Li *et al.*, 2015a) have been commonly utilized to determine the bioaccessibility of contaminants in foods or soils, and their suitability to predict the bioavailability of contaminants, such as Chromium (Cr) (Bruzzoniti *et al.*, 2017), lead (Pb) (Fujimori *et al.*, 2018), and other organic pollution (Cui *et al.*, 2016), have been demonstrated. However, such comparison for pesticide residues in food is limited. This information helps to determine the key factors governing the bioaccessibility of pesticides and is consequently important for *in vitro* method standardization.

Furthermore, humans are often exposed to co-contaminants with pesticides and other contaminants, such as heavy metals, which are also extensively distributed in fruits and vegetables (Rahman *et al.*, 2018). However, previous studies have only focused on the bioaccessibility of a single pesticide/metal, without considering the possible impact of post-uptake interactions on bioaccessibility in the human digestive system. Diacomanolis *et al.* (2014), for example, have shown that the bioavailability of arsenic in rats decreased significantly with cadmium co-administration. Obuekwe and Semple (2013) reported that the presence of high concentrations of Cu and Al can impact on the mobility and accessibility of phenanthrene in soil, which may have implications for risk assessment. However, no studies have yet been conducted to show whether pesticides and heavy metals in fruits and vegetables affect each other's bioaccessibility and whether food properties affect this interaction. Thus, we require a better understanding of potential interaction effects of mixtures with regard to their bioaccessibility.

The occurrence and fate of neonicotinoids in the food and environment have become an important global issue. Epidemiologic studies have also linked human exposure to neonicotinoids with adverse developmental and neurological outcomes (Li and Kannan, 2020). Accordingly, neonicotinoids were selected as the representative pesticides. The objectives of this study were as follows: (i) to compare the differences in neonicotinoids bioaccessibility in apple and pear samples between three common *in vitro* methods (PBET, SBRC, and IVG); (ii) to assess the influences of Cr speciation on neonicotinoids bioaccessibility; and (iii) to evaluate the potential health risk based on the oral bioaccessibility of neonicotinoids in selected samples.

Materials and Methods

Chemicals and reagents

The pesticide standards thiamethoxam (purity ≥ 97%), imidacloprid (purity ≥ 96%), acetamiprid (purity ≥ 97%), and thiacloprid (purity ≥ 98%) were acquired from *ANPEL* (*ANPEL* Laboratory Technologies, China). The standard matrix-matching solution was prepared by adding appropriate stock solution to blank extracts of the selected fruits and vegetables. Cr(III) and Cr(VI) working solutions were prepared by diluting stock standard solutions at 100 mg/L (National Center of Analysis and Testing for Non-ferrous Metals & Electronic Materials, Beijing, China) in ultrapure water. The simulated gastric and intestinal fluids were prepared according to Yin *et al.* (2016), with details provided in Table 1. QuEChERS bulk sodium chloride along with sorbent [anhydrous $MgSO_4$, C18, and primary-secondary amine (PSA)] was obtained from Agilent Technologies (USA). All solvents and other chemicals used in the study were of high-performance liquid chromatography (HPLC) or analytical grade.

Sample preparation

In this study, apple (*Malus domestica*) and pear (*Pyrus* spp.) were obtained from local markets in the city of Hefei (China) as the main material. The subsamples were prepared for further examination as follows: cleansed, patted dry, peeled, homogenized, and lyophilized with an FD5-4 freeze-dryer (GOLD-SIM, USA) at –50°C. Preliminary experiments showed that the samples do not contain the selected neonicotinoids, and thus, the dried samples were spiked with test compounds prior to use. Briefly, 10 g samples were spiked with 0.2 mL of stock standard solution. Subsequently, the spiked samples were mixed at 30 rpm for 24 h to achieve homogenous distribution and a short-term aging effect.

Extraction was carried out following the QuEChERS multi-residue method as described in our previous study (Shi *et al.*, 2019). Briefly, 2 g of spiked samples were mixed with 20 mL of acetonitrile, followed by vigorous stirring on vortex for 2 min. Thereafter, 3 g of sodium chloride (NaCl) was added to the tube and the solution was intensively hand-shaken for 1 min, followed by centrifugation for 5

min at 4000 rpm. The supernatant (5 mL) was collected and purified by solid-phase dispersion extraction, containing 250 mg of PSA, 250 mg of C18, and 750 mg of magnesium sulfate (MgSO$_4$). The extract was intensively shaken on the vortex for 2 min and then centrifuged for 5 min at 4000 rpm. After centrifugation, 2 mL of the supernatant was evaporated to dryness and then reloaded into 2 mL of acetonitrile–water (1/1, v/v) for HPLC analysis.

In vitro bioaccessibility assay

In the study, three commonly used *in vitro* methods were selected for bioaccessibility assessment. They included PBET (Ning *et al.*, 2021), SBRC (Garau *et al.*, 2019), and IVG (Schroder *et al.*, 2004), and their composition and analysis parameters are provided in Table 1. In this study, the bioaccessible neonicotinoids fraction from the two types of fruit samples was investigated in the stomach and intestine phase using a static batch design. For gastric phase, 1 g of spiked samples (in triplicate) was mixed with the gastric phase solution in crimp top vial at solid–liquid (S/L) ratio of 1:10. The pH was adjusted to 2.5, 1.5, and 1.8 for PBET, SBRC, and IVG, respectively, using 0.1 M hydrochloric acid (HCl). To simulate the anaerobic conditions of the human body, nitrogen gas was added to the sample tubes. The mixtures were then horizontally shaken at 37°C and 150 rpm for 1h. Triplicate samples from each gastrointestinal fluid treatment were then collected and analyzed for target compounds, described in our previous study (Shi *et al.*, 2019). Following the gastric phase, the solution was modified to simulate the intestinal phase by adjusting pH to 7.0 (PBET and SBRC) and 5.5 (IVG) with 0.1 M NaHCO$_3$, and then adding bile and pancreatin. The *S/L* ratio of PBET, SBRC, and IVG was increased to 1:20 in the intestinal phase. After 1 h (IVG), 2 h (SBRC), or 4 h (PBET) of incubation, aliquots (10.00 mL) of the supernatants were collected after centrifugation for 5 min at 4000 rpm and used for HPLC analysis.

The pesticides in the gastric or intestinal fluids were defined as the bioaccessible fraction, and bioaccessibility (%) was calculated according to the Eq. (1):

$$\text{Bioaccessibility}\left(\text{BA, \%}\right) = \frac{C_1 V}{C_2 M} \times 100 \text{ \%} \qquad (1)$$

where C_1 is the neonicotinoids concentration (mg/L) in the gastric or intestinal fluid, V is the volume of the gastric or intestinal fluids (mL), C_2 is the neonicotinoids concentration (mg/kg) in the spiked samples, and M is the total mass (g) of the spiked samples used in the extraction.

Effects of chromium speciation on pesticide bioaccessibility

Heavy metals are often found to coexist with other contaminants, such as arsenic (As) and polyaromatic hydrocarbons (PAHs), and their interaction may significantly influence the bioaccessibility of contaminants on food (Xia *et al.*, 2016). To investigate the potential interaction effect of heavy metals on the bioaccessibility of neonicotinoids in the fruit and vegetable samples, Cr(III) and Cr(VI) were separately added at the beginning of the digestion process to simulate the co-ingestion of contaminant, respectively. The initial ratios of Cr and neonicotinoids were 1/2, 1/1, and 2/1, respectively. The treatments (in triplicate) were then carried out in a SHIME as previously described in our previous study (Shi *et al.*, 2019).

Instrumental analysis and quality control

The tested compounds in the final extracts were analyzed on an Agilent 1260 HPLC system (Agilent Technologies Inc., CA, USA). The HPLC settings were the same as those used in our previously reported method (Shi *et al.*,

Table 1. Composition and parameters for SBRC, PBET, and IVG methods.

In vitro Method	Phase	Composition (L^{-1})	pH	Solid/solution ratio	Duration (h)
SBRC	Gastric	30.03 g of glycine	1.5	1:10	1
	Intestinal	1.75 g of bile, 0.5 g of pancreatin	7.0	1:20	2
PBET	Gastric	1.25 g of pepsin, 0.5 g of sodium malate, 0.5 g of sodium citrate, 0.42 mL of lactic acid, 0.5 mL of acetic acid, 8.77 g of NaCl	2.5	1:10	1
	Intestinal	1.75 g of bile, 0.5 g of pancreatin	7.0	1:20	4
IVG	Gastric	10 g of pepsin, 8.77 g of NaCl	1.8	1:10	1
	Intestinal	3.5 g of bile, 0.35 g of pancreatin	5.5	1:20	1

SBRC, solubility/bioavailability research consortium; PBET, physiologically based extraction test; IVG, *in vitro* gastrointestinal.

2019). Briefly, the chromatographic system was equipped with UV detection (HPLC-UV) and a ZORBAX SB-C18 column (4.6 mm × 250 mm, 5 μm). The mobile phase was acetonitrile: water (v/v = 25: 75) at a flow rate of 1.0 mL/min with a column oven temperature of 30℃. The UV detection wavelength was 254 nm, and the injection volume was 10 μL.

Health risk assessment model

For pesticide residues in food, ingestion plays the most important role. Hence, we estimated the daily intake via ingestion (average daily dose, ADD) for each studied pesticide residue in fruits. The ADD (mg/kg·bw) is assessed according to the following model (Eq (2)), recommended by the US Environmental Protection Agency (Liu *et al.*, 2016).

$$ADD = \frac{C \times IngR \times EF \times ED}{bw \times AT} \times CF \times BA \qquad (2)$$

where *C* is the concentration of neonicotinoids (mg/kg) in apple and pear; *IngR* is the ingestion rate of selected fruits (mg/day); *EF* and *ED* are the exposure frequency (day/year) and duration (year), respectively; *bw* is the body weight (kg); *AT* is the averaging time (day, AT = ED × 365); *CF* is the unit conversion factor (= 10^{-6}); *BA* is the neonicotinoids bioaccessibility.

The potential health risks posed by pesticide exposure are characterized by the hazard quotient (HQ), which is the ratio of ADD of selected pesticides to the corresponding reference dose (RfD, expressed in mg/kg·bw) that is likely to be without deleterious effects. HQ values were calculated according to Eq (3).

$$HQ = \frac{ADD}{RfD} \qquad (3)$$

HQ indicates an unacceptable risk if it is higher than 1, and a higher value represents a higher risk. When HQ < 1, the risk is considered acceptable.

Statistical analysis

The results were expressed as means ± standard deviations (SD). IBM SPSS Statistics 22.0 (SPSS, Inc., Chicago, IL, USA) was used for the one-way analysis of variance (ANOVA) analysis and *t*-test. Differences were considered significant at P < 0.05. Figures were drawn using the software GraphPad Prism 7 (GraphPad Software, Inc., USA).

Results and Discussion

Method validation

The recoveries of neonicotinoids in the spiked samples ranged from 72.80 ± 1.92% to 106.61 ± 2.19%, and the recoveries for the simulated fluids ranged from 81.64 ± 3.53% to 110.08 ± 2.94%. Method quantification limits (MQLs) were determined for each enantiomer by spiking pesticide-free samples at the lowest concentration meeting the validation criteria. They determined that compounds were in the range of 0.02 to 0.05 mg/kg (Table 2). Instrumental calibration was verified by the injection of

Table 2. Recoveries of neonicotinoids in apple and pear at three different concentration levels.

Pesticides	Fortified level (mg/kg)	Average recovery ± RSD (%)			r^2	MQLs (mg/kg)
		Apple	**Pear**	**Simulated fluids**		
Thiamethoxam	0.5	83.52 ± 2.58	79.82 ± 4.91	95.59 ± 5.34	0.9944	0.02
	1.0	82.17 ± 6.02	80.62 ± 4.76	110.08 ± 2.94		
	5.0	85.89 ± 2.83	80.59 ± 7.49	91.05 ± 0.89		
Imidocloprid	0.5	106.61 ± 2.19	89.98 ± 5.82	88.39 ± 6.64	0.9994	0.04
	1.0	87.92 ± 1.08	85.07 ± 5.93	97.85 ± 2.30		
	5.0	90.95 ± 3.09	91.53 ± 5.52	81.64 ± 3.53		
Acetaniprid	0.5	95.29 ± 2.02	72.80 ± 1.92	97.05 ± 7.16	0.9997	0.05
	1.0	89.21 ± 1.39	75.25 ± 2.32	98.72 ± 3.13		
	5.0	90.15 ± 1.52	99.17 ± 2.60	94.28 ± 0.54		
Thiacloprid	0.5	93.33 3.1.36	94.91 ± 5.38	94.70 4.6.45	0.9989	0.05
	1.0	86.58 6.6.45	78.47 ± 4.01	95.24 5.4.34		
	5.0	90.02 0.2.51	89.79 ± 3.40	94.97 4.1.31		

MQL, Method quantification limits.

6-point calibration standards at concentrations ranging from 0.2 to 5 mg/L, and the linearity with correlation coefficients (r^2) > 0.994.

Variability in neonicotinoids bioaccessibility among different in vitro methods

Figure 1 showed the variability in neonicotinoids bioaccessibility among three *in vitro* methods. Based on the gastric phase, neonicotinoids bioaccessibility in apple using PBET, SBRC, and IVG was 60.00–92.17%, 69.79–91.98%, and 65.66–89.53%, respectively. The gastric bioaccessibility of neonicotinoids in pear using the three *in vitro* methods was 63.82–71.30%, 68.69–75.63%, and 59.73–77.14%, respectively. No statistically significant pesticide bioaccessibility was obtained among three *in vitro* methods. In contrast, the thiamethoxam and acetamiprid bioaccessibility in the apple samples using the SBRC method obtained a higher value (91.98 and 80.62%) than the PBET (71.75%) and IVG (68.28%) methods, respectively. For the intestinal phase, the neonicotinoids bioaccessibility in apple and pear were 56.41–64.29% and 57.53–59.00% using the PBET method, 77.13–88.90% and 76.40–90.85% for the SBRC method, and 62.44–73.62% and 56.91–82.08% for the IVG method, respectively. Generally, the disparity in

neonicotinoids bioaccessibility between methods was in the order of SBRC > IVG > PBET method, which may be related to differences in assay parameters (i.e., pH values, incubation time, and constituents) between *in vitro* methods. These observations agreed well with the study of Li *et al.* (2015b). Thus, we speculate that the differences in neonicotinoids bioaccessibility in the gastric and intestinal phases are a result of synergistic effects between the *in vitro* parameters and food matrix.

Effect of Cr speciation on the neonicotinoids bioaccessibility

Chromium is a transition metal and is found in two forms in the environment: Cr(III) and Cr(VI). Fruits are capable of accumulating chromium in their edible and inedible parts. In this study, we found that the neonicotinoids bioaccessibility was significantly affected by Cr in spiked apple and pear samples (Figure 2). Briefly, in the absence of Cr, the bioaccessibility values of thiamethoxam, imidacloprid, acetamiprid, and thiacloprid in apple were 59.02, 54.34, 51.74, and 53.82%, respectively. In contrast, when Cr was added to the incubation, the corresponding values decreased to 17.85–35.69%, 12.28–35.49%, 18.04–33.11%, and 10.11–20.59%, respectively. In most cases, increases in the ratio of Cr in the
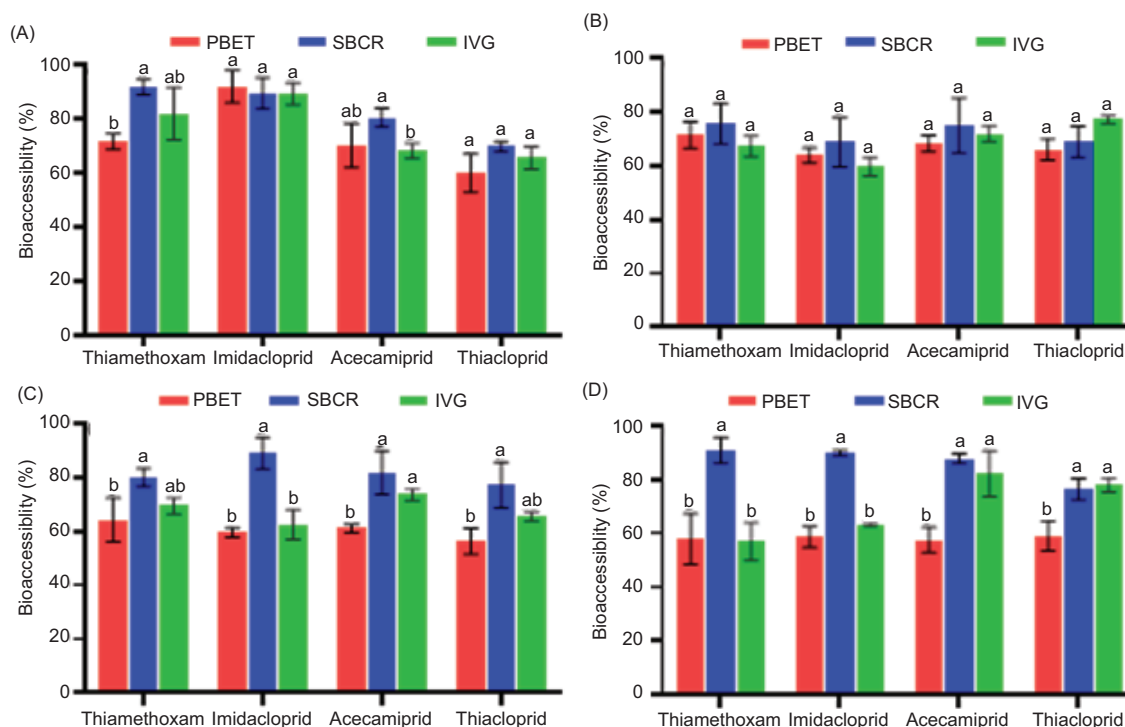

Figure 1. Comparison of neonicotinoids bioaccessibility in apple (A) and pear (B) samples based on the gastric phases, as well as in apple (C) and pear (D) samples based on the intestinal phases among different *in vitro* methods. Error bars represent the standard deviation of three replicates. Bars marked with different lowercase letters indicate significant differences with respect to bioaccessibility (P < 0.05).

incubation can have a positive effect on bioaccessibility decreases of neonicotinoids. In addition, a similar inhibition effect was observed for neonicotinoids bioaccessibility in pear with the addition of Cr(III) and Cr(VI) in a simulated digestive system. The presence of Cr(III) and Cr(VI) decreased the bioaccessibility of neonicotinoids significantly in the gastrointestinal digests by 17.21–81.21% and 11.61–73.70%, respectively, compared with the case where Cr was absent. The formation of insoluble chromium-pesticide complexes may explain this reduction. Kang *et al*. (2016) also reported that the compound can be precipitated with heavy metal in the intestine via surface complexation or ligand exchange when the pH was increased from the gastric to the intestinal phase. In comparison, the addition of Cr(VI) to the system showed relative higher bioaccessibility than that with Cr(III), but the differences in bioaccessibility was not statistically significant. It is also possible that neonicotinoids show higher affinity for Cr(III) than Cr(VI).

Health risk assessment

For the model, two subpopulation groups, adults (as the general population) and children (as a sensitive group) were calculated, respectively. To assume a worst-case scenario, the maximum residue limit (MRL, mg/kg) and the corresponding acceptable daily intake (ADI) values for neonicotinoids in selected fruits were obtained. The

upper boundary bioaccessibility of thiamethoxam, imidacloprid, acetamiprid, and thiacloprid in apple was measured by the SBRC method with values of 86.74, 78.57, 88.21, and 64.18%, respectively, and in pear with values of 78.47, 79.26, 89.16, and 77.45%, respectively. The consumption data of apples (84,646 mg/day) and pears (32,798 mg/day) in China were obtained from a market forecast in 2019 by INDEXBOX (https://www.indexbox.io/). The EF was assumed to be 365 days/year; ED of 70 and 6 years were considered for adults and children, respectively; the body weights of 65 kg and 15 kg for an average Chinese adult and child were used, respectively.

Table 3 shows HQ values calculated for apple and pear, revealing an exposure range of 4.24×10^{-3} –2.54×10^{-1} and 1.48×10^{-3} –1.19×10^{-1}, respectively, and were therefore well below 1, and within the acceptable level. Pesticides with the highest HQ values were thiacloprid (2.74×10^{-2} –2.54×10^{-1}), while thiamethoxam (1.48×10^{-3} –1.84×10^{-2}) displayed the lowest HQ values. Based on these HQ values, dietary safety was ordered as pear > apple. And, all of the values about HQ and risk on children were higher than that on adults, which indicated that there existed a bigger exposure risk in children. In addition, the bioaccessibility of neonicotinoids determined by the SBRC method was used to assess the health risk of exposure, resulting in lower risk values (10.84–35.82% reduction).
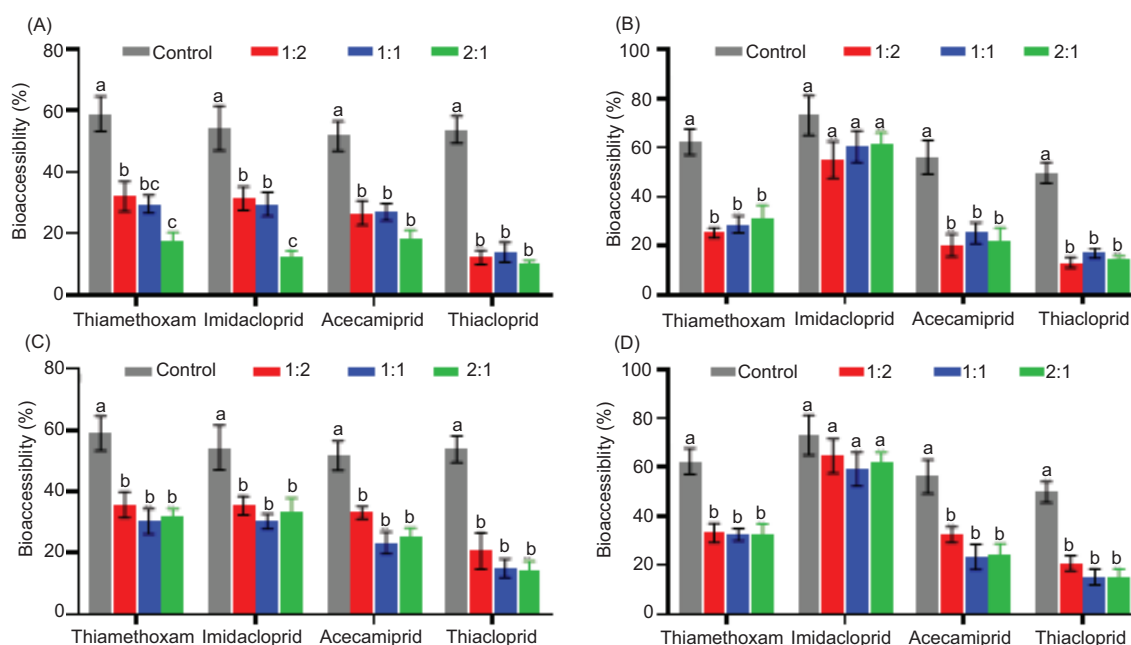
Figure 2. Bioaccessibility values of neonicotinoids in apple (A) and pear (B) samples with or without the addition of Cr(III), and in apple (C) and pear (D) samples with or without the addition of Cr(VI). The initial ratios of Cr and neonicotinoids were 1:2, 1:1, and 2:1, respectively. Error bars represent the standard deviation of three replicates. Bars marked with different lowercase letters indicate significant differences with respect to the bioaccessibility (P < 0.05).

Table 3.   Hazard quotient of thiamethoxam, imidacloprid, acetamiprid, and thiacloprid in apple and pear for adult and children via ingestion exposure.

Pesticides	Matrix	MRLs (mg/kg)	ADI (mg/kg·bw)	Bioaccessibility (%)	ADD values (mg/kg·bw)		HQ values	
					Adult	Children	Adult	Children
Thiamethoxam	Apple	0.3	0.8	86.74	3.39E-04	1.47E-03	4.24E-03	1.84E-02
	Pear	0.3		78.47	1.19E-04	5.15E-04	1.48E-03	6.43E-03
Imidacloprid	Apple	0.5	0.6	78.57	5.12E-04	2.22E-03	8.53E-03	3.69E-02
	Pear	0.5		79.26	2.00E-04	8.67E-04	3.33E-03	1.44E-02
Acetamiprid	Apple	0.8	0.7	88.21	9.19E-04	3.98E-03	1.31E-02	5.69E-02
	Pear	2		89.16	9.00E-04	3.90E-03	1.29E-02	5.57E-02
Thiacloprid	Apple	0.7	0.01	64.18	5.85E-04	2.54E-03	5.85E-02	2.54E-01
	Pear	0.7		77.45	2.74E-04	1.19E-03	2.74E-02	1.19E-01

HQ, Hazard quotient.

Conclusion

This study clearly demonstrated that neonicotinoids' (thiamethoxam, imidacloprid, acetamiprid, and thiacloprid) bioaccessibility in apple and pear samples varied between *in vitro* methods, which may be in part reflective of the differences in assay parameters (i.e., pH values, incubation time, and constituents) for the *in vitro* methods. The conservative bioaccessibility of the four neonicotinoids was measured by PBET with values of 60.00–92.17% (except for imidacloprid in apple) and 56.41–64.29% in gastric phase and intestinal phase, respectively. In contrast, the addition of Cr to the system significantly decreased the *in vitro* bioaccessibility (11.61–81.21%) of neonicotinoids, and the decreases were statistically significant. Our risk assessment based on a worst-case scenario calculated using the HQ approach revealed that exposure to pesticide residues in the tested fruits were all below levels that might pose a health risk.

References

Ayala-Bribiesca, E., Lussier, M., Chabot, D., Turgeon, S. and Britten, M., 2016. Effect of calcium enrichment of Cheddar cheese on its structure, in vitro digestion and lipid bioaccessibility. International Dairy Journal 53: 1–9. https://doi.org/10.1016/j.idairyj.2015.09.002

Bempah, C., Agyekum, A., Akuamoa, F., Frimpong, S. and Buah-Kwofie, A., 2016. Dietary exposure to chlorinated pesticide residues in fruits and vegetables from Ghanaian markets. Journal of Food Composition and Analysis 46: 103–113. https://doi.org/10.1016/j.jfca.2015.12.001

Bruzzoniti, M., Abollino, O., Pazzi, M., Rivoira, L., Giacomino, A. and Vincenti, M., 2017. Chromium, nickel, and cobalt in cosmetic matrices: an integrated bioanalytical characterization through total content, bioaccessibility, and Cr(III)/Cr(VI)

speciation. Analytical and Bioanalytical Chemistry 409(29): 6831–6841. https://doi.org/10.1007/s00216-017-0644-8

Chang, C.H., Yu, C.J., Du, J.C., Chiou, H.C., Chen, H.C., Yang, W., Chung, M.Y., Chen, Y.S., Hwang, B., Mao, I.F. and Chen, M.L., 2018. The interactions among organophosphate pesticide exposure, oxidative stress, and genetic polymorphisms of dopamine receptor D4 increase the risk of attention deficit/hyperactivity disorder in children. Environmental Research 160: 339–346. https://doi.org/10.1016/j.envres.2017.10.011

Cui, X., Xiang, P., He, R., Juhasz, A. and Ma, L., 2016. Advances in in vitro methods to evaluate oral bioaccessibility of PAHs and PBDEs in environmental matrices. Chemosphere 150: 378–389. https://doi.org/10.1016/j.chemosphere.2016.02.041

Diacomanolis, V., Noller, B. and Ng, J., 2014. Bioavailability and pharmacokinetics of arsenic are influenced by the presence of cadmium. Chemosphere 112: 203–209. https://doi.org/10.1016/j.chemosphere.2014.04.013

Dong, Z., Yan, K., Liu, Y., Naidu, R., Duan, L. and Wijayawardena, A., 2016. A meta-analysis to correlate lead bioavailability and bioaccessibility and predict lead bioavailability. Environment International 92–93: 139–145. https://doi.org/10.1016/j.envint.2016.04.009

Fujimori, T., Taniguchi, M., Agusa, T., Shiota, K., Takaoka, M., Yoshida, A., Terazono, A., Ballesteros, F. and Takigami, H., 2018. Effect of lead speciation on its oral bioaccessibility in surface dust and soil of electronic-wastes recycling sites. Journal of Hazardous Materials 341: 365–372. https://doi.org/10.1016/j.jhazmat.2017.07.066

Garau, M., Garau, G., Diquattro, S., Roggero, P. and Castaldi, P., 2019. Mobility, bioaccessibility and toxicity of potentially toxic elements in a contaminated soil treated with municipal solid waste compost. Ecotoxicology and Environmental Safety 186: 109766. https://doi.org/10.1016/j.ecoenv.2019.109766

Hlihor, R., Pogăcean, M., Rosca, M., Cozma, P. and Gavrilescu, M., 2019. Modelling the behavior of pesticide residues in tomatoes and their associated long-term exposure risks. Journal of Environmental Management 233: 523–529. https://doi.org/10.1016/j.jenvman.2018.11.045

Kang, Y., Pan, W., Liang, S., Li, N., Zeng, L. and Zhang, Q., 2016. Assessment of relative bioavailability of heavy metals in soil using in vivo mouse model and its implication for risk assessment compared with bioaccessibility using in vitro assay. Environmental Geochemistry and Health 38(5): 1183–1191. https://doi.org/10.1007/s10653-015-9782-0

Laird, B., Weiseth, B., Packull-Mccormick, S, Peak, D., Dodd, M. and Siciliano, S., 2015. Solid–liquid separation method governs the in vitro bioaccessibility of metals in contaminated soil-like test materials. Chemosphere 134: 544–549. https://doi.org/10.1016/j.chemosphere.2014.12.019

Li, A.J. and Kannan, K., 2020. Profiles of urinary neonicotinoids and dialkylphosphates in populations in nine countries. Environment International 145: 106120. https://doi.org/10.1016/j.envint.2020.106120

Li, J., Li, K., Cave, M., Li, H. and Ma, L., 2015b. Lead bioaccessibility in 12 contaminated soils from China: Correlation to lead relative bioavailability and lead in different fractions. Journal of Hazardous Materials 295: 55–62. https://doi.org/10.1016/j.jhazmat.2015.03.061

Li, S., Li, J., Li, H., Naidu, R. and Ma, L., 2015a. Arsenic bioaccessibility in contaminated soils: coupling in vitro assays with sequential and HNO3 extraction. Journal of Hazardous Materials 295: 145–152. https://doi.org/10.1016/j.jhazmat.2015.04.011

Liu, Y., Ma, J., Yan, H., Ren, Y., Wang, B. and Lin, C., 2016. Bioaccessibility and health risk assessment of arsenic in soil and indoor dust in rural and urban areas of Hubei province, China. Ecotoxicology and Environmental Safety 126: 14–22. https://doi.org/10.1016/j.ecoenv.2015.11.037

Lundqvist, J., Hellman, B. and Oskarsson, A., 2016. Fungicide prochloraz induces oxidative stress and DNA damage in vitro. Food and Chemical Toxicology 91: 36–41. https://doi.org/10.1016/j.fct.2016.03.002

Ning, Z., Liu, E., Yao, D., Xiao, T., Ma, L., Liu, Y. and Liu, C., 2021. Contamination, oral bioaccessibility and human health risk assessment of thallium and other metal(loid)s in farmland soils around a historic Tl-Hg mining area. Science of the Total Environment 758: 143577. https://doi.org/10.1016/j.scitotenv.2020.143577

Obuekwe, I. and Semple, K., 2013. Impact of Zn, Cu, Al and Fe on the partitioning and bioaccessibility of 14C-phenanthrene in soil. Environmental Pollution 180: 180–189. https://doi.org/10.1016/j.envpol.2013.05.020

Rahman, E., Momin, A., Zhao, L., Guo, X., Xu, D. and Zhou, F., 2018. Bioactive, nutritional composition, heavy metal and pesticide residue of four Chinese jujube cultivars. Food Science and Biotechnology 27(2): 323–331. https://doi.org/10.1007/s10068-017-0256-2

Ruby, M., Lowney, Y., Bunge, A., Roberts, S., Gomez-Eyles, J., Ghosh, U., Kissel, J., Tomlinson, P. and Menzie, C., 2016. Oral bioavailability, bioaccessibility, and dermal absorption of PAHs from soil—state of the science. Environmental Science & Technology 50(5): 2151–2164. https://doi.org/10.1021/acs.est.5b04110

Schroder, L., Basta, N., Casteel, S., Evans, T. and Si, J., 2004. Validation of the in vitro gastrointestinal (IVG) method to estimate relative bioavailable lead in contaminated soils. Journal of Environmental Quality 33(2): 513–521. https://doi.org/10.2134/jeq2004.5130

Shi, Y., Xiao, J., Liu, Y., Fu, Y., Ye, Z., Liao, M. and Cao, H., 2019. Interactions of food matrix and dietary components on neonicotinoid bioaccessibility in raw fruit and vegetables. Food & Function 10(1): 289–295. https://doi.org/10.1039/c8fo02142b

Szpyrka, E., Kurdziel, A., Matyaszek, A., Podbielska, M., Rupar, J. and Słowik-Borowiec, M., 2015. Evaluation of pesticide residues in fruits and vegetables from the region of south-eastern Poland. Food Control 48: 137–142. https://doi.org/10.1016/j.foodcont.2014.05.039

Wang, J., Li, S., Cui, X., Li, H., Qian, X. and Wang, C., 2016. Bioaccessibility, sources and health risk assessment of trace metals in urban park dust in Nanjing, Southeast China. Ecotoxicology and Environmental Safety 128: 161–170. https://doi.org/10.1016/j.ecoenv.2016.02.020

Xia, Q., Peng, C., Lamb, D., Mallavarapu, M., Naidu, R. and Ng, J., 2016. Bioaccessibility of arsenic and cadmium assessed for in vitro bioaccessibility in spiked soils and their interaction during the Unified BARGE Method (UBM) extraction. Chemosphere 147: 444–450. https://doi.org/10.1016/j.chemosphere.2015.12.091

Xing, G., Rui, X., Wang, D., Liu, M., Chen, X. and Dong, M., 2017. Effect of fermentation pH on protein bioaccessibility of soymilk curd with added tea polyphenols as assessed by in vitro gastrointestinal digestion. Journal of Agricultural and Food Chemistry 65(50): 11125–11132. https://doi.org/10.1021/acs.jafc.7b04456

Yager, J., Greene, T. and Schoof, R., 2015. Arsenic relative bioavailability from diet and airborne exposures: implications for risk assessment. Science of The Total Environment 536: 368–381. https://doi.org/10.1016/j.scitotenv.2015.05.141

Yin, N., Du, H., Zhang, Z., Cai, X., Li, Z. and Sun, G., 2016. Variability of arsenic bioaccessibility and metabolism in soils by human gut microbiota using different in vitro methods combined with SHIME. Science of the Total Environment 566–567: 1670–1677. https://doi.org/10.1016/j.scitotenv.2016.06.071

Yu, R., Liu, Q., Liu, J., Wang, Q. and Wang, Y., 2016. Concentrations of organophosphorus pesticides in fresh vegetables and related human health risk assessment in Changchun, Northeast China. Food Control 60: 353–360. https://doi.org/10.1016/j.foodcont.2015.08.013

Zhao, X., Shi, C., Zhou, X., Lin, T. and Fang, J., 2019. Preparation of a nanoscale dihydromyricetin-phospholipid complex to improve the bioavailability: in vitro and in vivo evaluations. European Journal of Pharmaceutical Sciences 138: 104994. https://doi.org/10.1016/j.ejps.2019.104994

Zhuang, P., Zhang, C., Li, Y., Zou, B., Mo, H. and Wu, K., 2016. ssessment of influences of cooking on cadmium and arsenic bioaccessibility in rice, using an in vitro physiologically-based extraction test. Food Chemistry 213: 206–214. https://doi.org/10.1016/j.foodchem.2016.06.066