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Development of a High-Throughput Screening Analysis for 195 Pesticides in Raw Milk by Modified QuEChERS Sample Preparation and Liquid Chromatography Quadrupole Time-of-Flight Mass Spectrometry

Xingqiang Wu [1], Kaixuan Tong [1], Changyou Yu [2], Shuang Hou [2], Yujie Xie [1], Chunlin Fan [1], Hui Chen [1,*], Meiling Lu [3] and Wenwen Wang [3]

[1] Key Laboratory of Food Quality and Safety for State Market Regulation, Chinese Academy of Inspection & Quarantine, No. 11, Ronghua South Road, Beijing 100176, China; xingqiangheda@163.com (X.W.); tongkx@caiq.org.cn (K.T.); xieyj@caiq.org.cn (Y.X.); caiqfcl@163.com (C.F.)
[2] Laboratory of Heilongjiang Feihe Dairy Co., Ltd., Qiqihar 164800, China; yuchangyou@feihe.com (C.Y.); houshuang@feihe.com (S.H.)
[3] Agilent Technologies (China) Limited, Beijing 100102, China; mei-ling.lu@agilent.com (M.L.); wen-wen_wang@agilent.com (W.W.)
* Correspondence: chenh@caiq.org.cn

Abstract: This study aimed to develop a simple, high-throughput method based on modified QuEChERS (quick, easy, cheap, effective, rugged, and safe) followed by liquid chromatography quadrupole time-of-flight mass spectrometry (LC-Q-TOF/MS) for the rapid determination of multi-class pesticide residues in raw milk. With acidified acetonitrile as the extraction solvent, the raw milk samples were pretreated with the modified QuEChERS method, including extraction, salting-out, freezing, and clean-up processes. The target pesticides were acquired in a positive ion electrospray ionization mode and an All ions MS/MS mode. The developed method was validated, and good performing characteristics were achieved. The screening detection limits (SDL) and limits of quantitation (LOQ) for all the pesticides ranged within 0.1–20 and 0.1–50 μg/kg, respectively. The recoveries of all analytes ranged from 70.0% to 120.0% at three spiked levels (1 × LOQ, 2 × LOQ, and 10 × LOQ), with relative standard deviations less than 20.0%. The coefficient of determination was greater than 0.99 within the calibration linearity range for the detected 195 pesticides. The method proved the simple, rapid, high throughput screening and quantitative analysis of pesticide residues in raw milk.

Keywords: raw milk 1; pesticides 2; screening 3; QuEChERS 4; high-throughput 5

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1. Introduction

Milk is considered an important part of a healthy diet, providing essential nutrients and energy. High-quality raw milk is required by dairy factories to make dairy products, such as cheese, yogurt, and cream [1]. Once the raw milk is defective, it cannot be improved in the subsequent processing, which may have far-reaching effects. Currently, China is one of the world's largest producing and consuming countries of milk and dairy products, with the per capita consumption of milk in China increasing from 4.89 kg in 1997 to 19.2 kg in 2019 [2]. The quality and safety of milk and its products are of a great concern to both the government and consumers [3]. Meanwhile, the contamination of milk with pesticide residues is a severe concern in many countries [4–6]. Pesticide residues in milk may come from direct or indirect sources such as feeding animals from contaminated forage grass, feeding and drinking water, and various pesticides used to treat pests, pathogens, and fungal diseases [7]. Through the above pathways, these pesticide residues inevitably accumulate in animals. They are transferred to secreted milk, with serious health hazards

likely to occur as humans consume contaminated milk or dairy products [8,9]. Hence, it is necessary to ascertain pesticide residues in milk to ensure safe dietary intake.

To ensure food safety, several organizations and countries, such as the European Commission [10] and China [11], have established maximum residue limits (MRL) for various pesticides in milk. Therefore, to meet these requirements, there is an increasing need for an effective analytical method for simultaneous qualitative and quantitative screening of pesticide residues in milk. The current reported methods for the analysis of multi-residue pesticides in milk use different detection techniques, such as high-performance liquid chromatography with diode-array detection (HPLC-DAD) [12], gas chromatography–electron capture detection (GC-ECD) [13], gas chromatography–mass spectrometry (GC-MS) [14], gas chromatography–tandem mass spectrometry (GC-MS/MS) [15,16], and liquid chromatography–tandem mass spectrometry (LC-MS/MS) [17–19]. Recently, liquid chromatography coupled with high-resolution mass spectrometry techniques (LC-HRMS) had been applied to determine pesticide residues in milk matrices [20,21]. LC-HRMS offered the ability to collect full scan spectra and accurate masses while acquiring and reprocessing data without prior compound-specific adjustments, enabling retrospective data analysis [22]. Hence, LC-HRMS has a strong competitive advantage compared with low-resolution mass spectrometry in the multi-residue analysis of compounds and has demonstrated great potential for non-targeted detection.

Although LC-HRMS demonstrates high sensitivity and accuracy in developing analytical methods, selecting a suitable sample preparation method is an important prerequisite for achieving multi-residue analysis. Milk is a complex matrix in which interfering components (e.g., proteins, fatty acids, and pigments) may play a role in suppressing the signal of pesticide residues. Therefore, effectively reducing matrix interference is crucial for determining pesticide residues in milk [23]. Different sample preparation methods for extracting pesticides from milk have been explored. These methods mainly include liquid–liquid extraction (LLE) [19,24], gel permeation chromatography (GPC) [15], solid-phase extraction (SPE) [5,25], dispersive solid-phase extraction (d-SPE) [21], and the QuEChERS (quick, easy, cheap, effective, rugged, and safe) method [13,14,16,18]. Among them, GPC and SPE are tedious and time-consuming to operate, which do not facilitate the processing of a large number of samples. Meanwhile, LE and d-SPE methods have a large background interference of the sample matrix after pretreatment, which causes a decrease in detection sensitivity of the analytical instrument [26]. QuEChERS is fast, safe, and low-cost in the aforementioned techniques, including extraction and purification steps. Compared to other sample preparation techniques, QuEChERS is simple to use and has efficiency improvement with good reproducibility and stability. The QuEChERS method has been widely used for the high-throughput analysis of chemical contaminants in various food products [27].

This work aimed to establish a simple and efficient pretreatment method for the simultaneous detection of multi-pesticide residues in raw milk using an advanced LC-Q-TOF/MS technique. The pretreatment procedure was optimized, including different extraction salts, purification sorbents, and freezing times. Meanwhile, this method's linearity, sensitivity, accuracy, precision, and matrix effect were fully evaluated. Finally, a simple and effective sample preparation procedure was established to determine 195 pesticide residues in raw milk combined with LC-Q-TOF/MS. Moreover, the validated method was employed to screen pesticide residues in actual raw milk samples from dairy farms.

2. Materials and Methods

2.1. Instrumentation

The liquid chromatography quadrupole time-of-flight mass spectrometry (1290–6550) was from Agilent Technologies (Santa Clara, CA, USA). Chromatographic separation was achieved on a chromatographic condition: equipped with a reversed-phase chromatography column (ZORBAX SB-C18 column 2.1 mm × 100 mm, 3.5 µm; Agilent Technologies, Santa Clara, CA, USA); mobile phase A is 5 mM ammonium acetate-0.1% formic acid-water;

mobile phase B is acetonitrile; gradient elution program, 0 min: 1%B, 3 min: 30%B, 6 min: 40%B, 9 min: 40%B, 15 min: 60%B, 19 min: 90%B, 23 min: 90%B, 23.01 min: 1%B, run after 4 min. The flow rate was set at 0.4 mL/min. The column temperature was 40 °C. The injection volume was 5 μL.

An Agilent Dual Jet Stream electrospray source was used on the Q-TOF in positive ionization mode. The conditions for mass spectrometry were set as follows: Scan mode: All ions MS/MS; capillary voltage was 4 kV; nebulizer gas was 0.14 MPa; drying gas temperature was at 325 °C with a flow rate of 12.0 L/min; sheath gas temperature was set at 375 °C with a flow rate of 11.0 L/min; Fragmentation voltage at 145 v. All Ions MS/MS mode parameter settings: acquisition range was m/z 50–1000, data acquisition rate is four spectra/s; collision energy was 0 eV at 0 min, and collision energy was set to 0, 15, and 35 eV in consecutive order after 0.5 min.

The mass spectrum information of 195 pesticide databases is shown in Table 1. PL602-L electronic balance was purchased from Mettler-Toledo Co., Ltd. (Zurich, Switzerland); N-112 Nitrogen evaporator concentrator was obtained from Organomation Associates (EVAP 112, Worcester, MA, USA); SR-2DS oscillator was obtained from Taitec company (Saitama, Japan); KDC-40 Low-speed centrifuge was obtained from Zonkia Group Corp., Ltd. (Hefei, China); Milli-Q ultrapure water machine was obtained from Millipore Co., Ltd. (Milford, MA, USA).

2.2. Reagents and Materials

Raw milk samples were collected from local dairy farms. All pesticide standards (purity grade, >98%) were obtained from Alta Company (Tianjin, China). Formic acid, ammonium acetate, acetonitrile, methanol (all LC-MS grade), and toluene (HPLC grade) were obtained from Fisher Scientific, Inc. (Fair Lawn, NJ, USA). Analytical grade forms of acetic acid, sodium chloride, anhydrous Na_2SO_4, trisodium citrate, disodium citrate, and anhydrous $MgSO_4$ were obtained from Shanghai Anpu Experimental Technology (Shanghai, China). The cleanup absorbents as octadecylsilane (C18) and primary secondary amine (PSA) were obtained from Tianjin Agela Technology (Tianjin, China).

2.3. Preparation of Standard Solutions

Standard stock solutions of individual pesticides were prepared in acetonitrile, methanol, or water to a concentration of 500–1000 mg/L. All stock solutions were stable for 6 months in a closed tea-colored volumetric flask at −20 °C. The 10 mg/L intermediate working solution and the working internal standard solution (Atrazine-D5) were prepared by diluting the stock solution with methanol. Working solutions were prepared daily by diluting a stock solution with all pesticides and used immediately after preparation.

2.4. Sample Preparation

The QuEChERS procedure entailed the following steps: 2.0 g of raw milk sample were weighed into the 50 mL tube. 16 mL of 1% acetic acid acetonitrile (v/v) was added, followed by EN salt (4 g $MgSO_4$, 1 g NaCl, 0.5 g disodium citrate, and 1 g trisodium citrate), vortexed for 1 min, and shaken for 2 min. After that, the sample tubes were frozen at −20 °C for 0.5 h and then centrifuged (4200 rpm) for 5 min. 5 mL of supernatant was again pipetted into a 15 mL clean-up tube (containing 500 mg $MgSO_4$ and 200 mg C18). The clean-up tube was vortexed for 5 s and then shaken for 2 min, followed by centrifugation at 4200 rpm for 5 min. Subsequently, 2 mL of the supernatant from the clean-up tube was pipetted into a 10 mL glass tube and evaporated to dryness in a 40 °C water bath with a gentle stream of nitrogen. Finally, 1 mL of acetonitrile/water (3:2, v/v) solution was used to redissolve the solution and pass it over the membrane for LC-Q-TOF/MS analysis.

Table 1. LC-Q-TOF/MS parameters and validation parameters for all target analytes in raw milk.

NO.	Compound	Formula	RT/Min	Quantitative Ion (*m*/*z*)	Production (*m*/*z*)	SDL (mg/kg)	LOQ (mg/kg)	MRL (mg/kg; European Union, China)	R^2	1 × LOQ		2 × LOQ		10 × LOQ	
										Rec. (%)	RSD (%)	Rec. (%)	RSD (%)	Rec. (%)	RSD (%)
1	1-(2-chloro-4-(4-chlorophenoxy)phenyl)-2-(1H-1,2,4-triazol-1-yl)ethanol	$C_{16}H_{13}Cl_2N_3O_2$	10.16	350.0458	70.0400	20.0	20.0	—, —	0.9988	100.2	1.0	98.1	0.9	86.2	1.1
2	1-(2-Chloro-pyridin-5-yl-methyl)-2-imino-imidazolidine hydrochloride	$C_9H_{12}Cl_2N_4$	2.28	211.0745	90.0338	0.5	1.0	—, —	0.9990	94.4	18.7	82.2	6.7	101.0	16.8
3	1-methyl-3-(tetrahydro-3-furylmethyl) urea	$C_7H_{14}N_2O_2$	1.87	159.1128	58.0287	0.2	1.0	—, —	0.9926	96.2	7.6	98.7	14.3	104.2	11.7
4	3-(Trifluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide	$C_6H_6F_3N_3O$	2.63	194.0536	134.0349	10.0	10.0	—, —	0.9932	94.8	14.7	106.4	8.5	85.8	6.6
5	5-hydroxy Imidacloprid	$C_9H_{10}ClN_5O_3$	3.05	272.0545	225.0538	2.0	5.0	—, —	0.9992	109.6	11.3	112.9	18.0	101.4	18.0
6	Acetamiprid	$C_{10}H_{11}ClN_4$	3.97	223.0745	126.0105	0.5	0.5	0.2, —	0.9994	77.9	5.8	84.6	10.4	103.9	7.5
7	Acetamiprid-N-desmethyl	$C_9H_9ClN_4$	3.62	209.0589	126.0105	0.2	1.0	—, —	0.9976	119.0	12.3	94.6	15.3	97.1	15.7
8	Acetochlor	$C_{14}H_{20}ClNO_2$	12.62	270.1255	133.0886	1.0	1.0	0.01, —	0.9989	83.4	18.5	119.8	6.8	101.7	10.5
9	Alachlor	$C_{14}H_{20}ClNO_2$	12.58	270.1255	238.0993	1.0	2.0	0.01, —	0.9989	118.6	7.4	98.4	3.2	94.7	2.2
10	Aldicarb-sulfone	$C_7H_{14}N_2O_4S$	2.66	223.0747	62.9899	10.0	20.0	—, —	0.9980	99.3	7.5	95.7	3.6	87.6	2.4
11	Allidochlor	$C_8H_{12}ClNO$	5.00	174.0680	98.0964	10.0	10.0	—, —	0.9968	71.4	16.8	85.9	6.5	72.1	17.6
12	Ametryn	$C_9H_{17}N_5S$	6.71	228.1277	68.0243	0.1	0.5	—, —	0.9973	96.2	2.8	98.0	1.7	100.2	1.4
13	Aminocyclopyrachlor	$C_8H_8ClN_3O_2$	0.76	214.0378	68.0495	10.0	10.0	—, —	0.9976	72.9	9.9	75.7	8.8	86.4	11.6
14	Aminopyralid	$C_6H_4Cl_2N_2O_2$	1.70	206.9723	160.9668	20.0	50.0	0.02, —	0.9973	70.0	8.9	76.0	6.7	83.0	5.3
15	Atrazine	$C_8H_{14}ClN_5$	6.44	216.1010	174.0541	0.1	0.1	—, —	0.9976	87.3	13.6	105.9	3.9	101.7	4.4
16	Avermectin	$C_{48}H_{72}O_{14}$	18.72	895.4814	751.4052	0.5	0.5	—, —	0.9993	87.4	7.4	108.6	3.8	92.7	4.7
17	Azoxystrobin	$C_{22}H_{17}N_3O_5$	11.17	404.1241	329.0795	0.1	0.1	0.01, —	0.9973	86.8	19.3	97.2	12.6	100.7	3.9
18	Benalaxyl	$C_{20}H_{23}NO_3$	14.11	326.1751	91.0542	0.2	0.5	0.02, —	0.9981	110.5	9.8	92.5	2.7	101.2	1.5
19	Benzovindiflupyr	$C_{18}H_{15}Cl_2F_2N_3O$	14.43	398.0640	159.0364	0.5	0.5	0.01, —	0.9985	93.6	7.0	107.6	4.2	100.7	2.0
20	Bioresmethrin	$C_{22}H_{26}O_3$	19.09	339.1955	143.0855	10.0	20.0	—, —	0.9905	103.3	17.6	80.5	11.7	82.1	9.8
21	Bitertanol	$C_{20}H_{23}N_3O_2$	12.77	338.1863	70.0400	10.0	10.0	0.01, —	0.9964	101.6	16.1	83.5	5.8	90.0	3.5
22	Boscalid	$C_{18}H_{12}Cl_2N_2O$	11.30	343.0399	271.0866	1.0	1.0	0.02, —	0.9989	116.4	8.3	105.6	8.9	104.1	13.6
23	Bromobutide	$C_{15}H_{22}BrNO$	13.80	312.0958	119.0855	1.0	2.0	—, —	0.9999	90.9	18.1	104.3	8.5	101.0	3.4
24	Bupirimate	$C_{13}H_{24}N_4O_3S$	12.61	317.1642	44.0495	0.5	0.5	0.01, —	0.9993	110.5	5.7	103.8	4.6	100.0	1.1
25	Buprofezin	$C_{16}H_{23}N_3OS$	17.42	306.1635	57.0699	0.5	0.5	0.01, —	0.9978	104.4	12.1	106.6	18.6	102.4	3.7
26	Butachlor	$C_{17}H_{26}ClNO_2$	17.52	312.1725	57.0699	0.5	1.0	—, —	0.9988	86.8	17.0	84.9	9.8	102.8	12.1
27	Butamifos	$C_{13}H_{21}N_2O_4PS$	16.50	333.1035	95.9668	0.5	1.0	—, —	0.9984	107.1	10.5	86.0	14.5	106.0	8.8

Table 1. *Cont.*

NO.	Compound	Formula	RT/Min	Quantitative Ion (*m*/*z*)	Production (*m*/*z*)	SDL (mg/kg)	LOQ (mg/kg)	MRL (mg/kg; European Union, China)	R^2	1 × LOQ		2 × LOQ		10 × LOQ	
										Rec. (%)	RSD (%)	Rec. (%)	RSD (%)	Rec. (%)	RSD (%)
28	Butylate	$C_{11}H_{23}NOS$	16.72	218.1573	57.0699	10.0	20.0	0.01, —	0.9985	92.2	14.2	72.3	17.8	77.0	6.7
29	Cadusafos	$C_{10}H_{23}O_2PS_2$	14.78	271.0950	96.9508	0.2	0.5	0.01, —	0.9995	73.5	17.7	75.0	11.5	96.0	2.9
30	Carbaryl	$C_{12}H_{11}NO_2$	6.29	202.0863	127.0542	20.0	50.0	0.05, —	0.9952	72.0	13.5	83.0	7.2	88.0	6.2
31	Carbendazim	$C_9H_9N_3O_2$	2.65	192.0768	160.0505	0.1	0.2	0.05, —	0.9992	70.9	12.6	102.9	3.9	107.6	4.6
32	Carbofuran	$C_{12}H_{15}NO_3$	5.87	222.1125	123.0441	0.5	1.0	0.001, —	0.9974	102.3	12.3	115.8	6.1	96.7	11.2
33	Carbofuran-3-Hydroxy	$C_{12}H_{15}NO_4$	3.60	238.1074	107.0491	1.0	1.0	—, —	0.9924	71.0	13.5	99.2	8.5	110.0	13.8
34	Carfentrazone-ethyl	$C_{15}H_{14}Cl_2F_3N_3O_3$	14.29	412.0435	345.9956	1.0	1.0	0.01, —	0.9997	115.7	12.5	92.1	4.0	107.4	15.5
35	Chlorantraniliprole	$C_{18}H_{14}BrCl_2N_5O_2$	8.36	481.9781	283.9216	1.0	1.0	0.05, —	0.9987	97.3	14.9	76.1	11.5	103.3	15.7
36	Chlorfenvinphos	$C_{12}H_{14}Cl_3O_4P$	13.78	358.9768	98.9843	0.5	0.5	0.01, —	0.9990	74.3	19.6	97.8	11.4	90.1	5.0
37	Chloridazon	$C_{10}H_8ClN_3O$	3.67	222.0429	77.0386	0.5	5.0	0.3, —	0.9951	112.5	5.7	105.6	13.2	92.2	13.2
38	Chlormequat	$C_5H_{12}ClN$	0.75	122.0731	58.0651	0.1	0.1	0.5, 0.5	0.9990	118.2	4.9	108.0	3.0	119.3	6.0
39	Chlorotoluron	$C_{10}H_{13}ClN_2O$	6.15	213.0789	72.0449	0.5	0.5	0.01, —	0.9995	98.0	9.7	104.7	5.0	100.2	3.6
40	Chlorpyrifos	$C_9H_{11}Cl_3NO_3PS$	17.76	349.9336	96.9508	5.0	5.0	0.01, —	0.9924	115.4	8.8	95.2	19.9	90.9	19.9
41	Clodinafop-propargyl	$C_{17}H_{13}ClFNO_4$	15.12	350.0590	91.0542	0.5	0.5	—, —	0.9998	116.4	15.1	117.3	8.3	104.1	2.8
42	Clofentezine	$C_{14}H_8Cl_2N_4$	15.40	303.0199	102.0338	10.0	10.0	0.05, —	0.9955	91.8	11.1	83.5	2.5	93.0	4.4
43	Clomazone	$C_{12}H_{14}ClNO_2$	8.00	240.0786	125.0153	2.0	5.0	0.01, —	0.9979	96.6	8.9	94.6	8.7	92.7	8.7
44	Clothianidin	$C_6H_8ClN_5O_2S$	3.54	250.0160	131.9669	2.0	5.0	0.02, —	0.9917	109.8	8.8	101.4	17.2	103.2	17.2
45	Cyanazine	$C_9H_{13}ClN_6$	5.22	241.0963	214.0854	0.5	5.0	—, —	0.9976	106.2	2.6	106.7	16.4	99.2	16.4
46	Cycloate	$C_{11}H_{21}NOS$	15.41	216.1417	55.0542	10.0	20.0	—, —	0.9981	89.2	7.9	84.5	4.0	75.3	4.7
47	Cycloxydim	$C_{17}H_{27}NO_3S$	16.37	326.1784	107.0491	1.0	1.0	0.05, —	0.9994	87.1	15.0	84.6	20.0	91.6	9.6
48	Cyprodinil	$C_{14}H_{15}N_3$	11.76	226.1339	93.0573	0.1	0.5	0.02, —	0.9982	103.3	9.2	104.9	1.7	96.7	2.6
49	Cyromazine	$C_6H_{10}N_6$	0.80	167.1040	85.0509	2.0	2.0	0.01, —	0.9989	73.5	10.6	74.0	9.8	93.1	6.7
50	Desmetryn	$C_8H_{15}N_5S$	5.23	214.1121	172.0651	0.2	0.2	—, —	0.9978	99.7	13.3	90.8	8.9	101.0	3.7
51	Diallate	$C_{10}H_{17}Cl_2NOS$	16.72	270.0481	86.0600	10.0	20.0	—, —	0.9972	93.4	12.7	74.5	3.8	78.1	2.3
52	Diazinon	$C_{12}H_{21}N_2O_3PS$	15.09	305.1083	96.9508	0.2	0.5	0.02, —	0.9984	94.0	7.9	94.0	6.5	94.7	0.9
53	Dichlorvos	$C_4H_7Cl_2O_4P$	5.24	220.9532	109.0049	20.0	20.0	—, —	0.9908	110.3	20.0	81.5	12.2	71.5	14.0
54	Difenoconazole	$C_{19}H_{17}Cl_2N_3O_3$	14.63	406.0720	251.0025	0.5	1.0	0.005, —	0.9979	98.4	6.4	100.1	6.0	101.4	14.3
55	Diflubenzuron	$C_{14}H_9ClF_2N_2O_2$	12.19	311.0393	141.0146	20.0	20.0	0.01, —	0.9954	116.1	14.9	91.0	10.4	90.9	2.1
56	Dimethenamid	$C_{12}H_{18}ClNO_2S$	9.77	276.0820	244.0557	0.2	0.5	0.01, —	0.9970	114.3	13.4	96.9	11.9	91.2	12.7
57	Dimethoate	$C_5H_{12}NO_3PS_2$	3.83	230.0069	198.9647	5.0	5.0	0.01, 0.05	0.9924	94.3	15.2	100.4	18.1	88.1	18.1

Table 1. *Cont.*

NO.	Compound	Formula	RT/Min	Quantitative Ion (*m*/*z*)	Production (*m*/*z*)	SDL (mg/kg)	LOQ (mg/kg)	MRL (mg/kg; European Union, China)	R^2	1 × LOQ		2 × LOQ		10 × LOQ	
										Rec. (%)	RSD (%)	Rec. (%)	RSD (%)	Rec. (%)	RSD (%)
58	Dimethylvinphos (E)	$C_{10}H_{10}Cl_3O_4P$	11.58	330.9455	127.0155	10.0	20.0	—, —	0.9918	105.9	18.9	93.3	15.0	89.5	4.5
59	Dimethylvinphos (Z)	$C_{10}H_{10}Cl_3O_4P$	10.59	330.9455	127.0155	5.0	5.0	—, —	0.9984	98.8	10.6	94.3	13.4	93.5	13.4
60	Diniconazole	$C_{15}H_{17}Cl_2N_3O$	13.05	326.0821	70.0400	5.0	5.0	0.01, —	0.9980	100.7	3.3	104.6	14.7	94.8	14.7
61	Dinotefuran	$C_7H_{14}N_4O_3$	2.33	203.1139	58.0526	5.0	10.0	0.1, —	0.9975	81.0	19.3	106.5	3.5	96.2	6.5
62	Dioxabenzofos	$C_8H_9O_3PS$	9.19	217.0083	77.0386	2.0	5.0	—, —	0.9990	101.7	2.7	98.2	11.8	97.2	11.8
63	Dipropetryn	$C_{11}H_{21}N_5S$	11.42	256.1590	102.0120	0.1	0.5	—, —	0.9995	96.0	5.6	103.4	2.8	98.0	0.5
64	Diuron	$C_9H_{10}Cl_2N_2O$	6.72	233.0243	72.0449	0.5	0.5	0.05, —	1.0000	97.4	8.8	92.4	5.3	103.3	2.2
65	Edifenphos	$C_{14}H_{15}O_2PS_2$	13.54	311.0324	109.0107	0.5	0.5	—, —	0.9981	104.8	7.0	101.9	1.9	104.4	1.4
66	Emamectin B1a	$C_{49}H_{75}NO_{13}$	15.63	886.5311	158.1176	0.2	0.5	0.01, —	0.9980	92.6	9.3	113.7	14.2	93.9	3.5
67	Ethion	$C_9H_{22}O_4P_2S_4$	17.97	384.9949	199.0011	1.0	1.0	0.01, —	0.9970	111.4	14.9	107.3	16.2	101.1	11.7
68	Ethoprophos	$C_8H_{19}O_2PS_2$	10.96	243.0637	96.9508	0.5	0.5	0.01, —	0.9991	91.6	17.4	88.0	6.0	93.4	2.8
69	Etrimfos	$C_{10}H_{17}N_2O_4PS$	14.61	293.0719	124.9821	0.5	1.0	—, —	0.9986	114.6	5.3	107.6	7.6	96.4	7.7
70	Fenamidone	$C_{17}H_{17}N_3OS$	10.94	312.1165	92.0495	0.5	0.5	0.01, —	0.9957	82.7	16.2	110.9	8.1	103.7	3.2
71	Fenamiphos	$C_{13}H_{22}NO_3PS$	10.60	304.1131	201.9848	0.5	0.5	0.005, —	0.9979	100.2	7.4	91.1	5.7	100.2	2.2
72	Fenamiphos-sulfone	$C_{13}H_{22}NO_5PS$	5.65	336.1029	266.0247	0.2	0.5	—, —	0.9988	111.4	5.2	93.3	5.6	100.8	3.5
73	Fenamiphos-sulfoxide	$C_{13}H_{22}NO_4PS$	4.65	320.1080	108.0573	0.1	0.5	—, —	0.9988	94.9	7.4	97.4	2.5	101.0	1.4
74	Fenarimol	$C_{17}H_{12}Cl_2N_2O$	10.69	331.0399	81.0447	1.0	5.0	0.02, —	0.9980	97.2	2.0	104.1	11.9	101.2	11.9
75	Fenbuconazole	$C_{19}H_{17}ClN_4$	12.50	337.1215	70.0400	1.0	1.0	0.05, —	0.9992	77.7	4.9	86.2	11.5	107.7	10.3
76	Fenobucarb	$C_{12}H_{17}NO_2$	8.91	208.1332	77.0386	20.0	20.0	—, —	0.9906	88.2	16.7	87.5	11.2	89.9	1.0
77	Fensulfothion	$C_{11}H_{17}O_4PS_2$	7.53	309.0379	140.0290	0.5	0.5	—, —	0.9986	99.8	4.1	115.2	6.9	101.1	1.6
78	Fenthion-sulfoxide	$C_{10}H_{15}O_4PS_2$	6.06	295.0222	109.0049	0.2	0.5	—, —	0.9982	103.6	8.1	100.5	4.3	98.5	1.6
79	Fluacrypyrim	$C_{20}H_{21}F_3N_2O_5$	16.71	427.1475	145.0648	0.5	0.5	—, —	0.9992	92.6	15.9	104.3	6.9	101.5	3.1
80	Fluazifop-butyl	$C_{19}H_{20}F_3NO_4$	17.73	384.1417	91.0542	0.1	0.1	—, —	0.9974	113.1	11.1	107.3	9.5	117.5	16.4
81	Flubendiamide	$C_{23}H_{22}F_7IN_2O_4S$	14.68	705.0125	530.9799	0.2	0.5	0.1, —	0.9987	106.8	2.8	97.7	5.6	99.6	2.8
82	Flumiclorac-pentyl	$C_{21}H_{23}ClFNO_5$	17.51	441.1593	308.0484	0.5	1.0	—, —	0.9963	109.9	11.3	97.6	13.7	81.7	16.8
83	Fluopicolide	$C_{14}H_8Cl_3F_3N_2O$	11.97	382.9727	172.9556	1.0	1.0	0.02, —	0.9991	90.2	10.1	101.6	4.8	104.8	12.3
84	Fluquinconazole	$C_{16}H_8Cl_2FN_5O$	11.52	376.0163	306.9836	10.0	10.0	0.01, —	0.9988	94.2	14.9	95.3	4.5	95.0	1.8
85	Fluridone	$C_{19}H_{14}F_3NO$	9.35	330.1100	309.0960	0.1	0.1	—, —	0.9988	114.7	11.4	95.3	5.9	102.1	1.9
86	Flusilazole	$C_{16}H_{15}F_2N_3Si$	12.45	316.1076	247.0749	0.5	1.0	0.02, —	0.9974	114.7	7.7	93.4	2.6	102.6	12.7
87	Flutriafol	$C_{16}H_{13}F_2N_3O$	6.46	302.1099	70.0400	0.5	1.0	0.01, —	0.9979	99.2	3.9	100.4	3.2	102.6	15.4

Table 1. *Cont.*

NO.	Compound	Formula	RT/Min	Quantitative Ion (*m*/*z*)	Production (*m*/*z*)	SDL (mg/kg)	LOQ (mg/kg)	MRL (mg/kg; European Union, China)	R^2	1 × LOQ		2 × LOQ		10 × LOQ	
										Rec. (%)	RSD (%)	Rec. (%)	RSD (%)	Rec. (%)	RSD (%)
88	Fluxapyroxad	$C_{18}H_{12}F_5N_3O$	11.58	382.0973	342.0849	0.5	0.5	0.02, —	0.9995	119.7	11.5	110.1	3.3	95.5	2.5
89	Fonofos	$C_{10}H_{15}OPS_2$	15.40	247.0375	80.9558	5.0	10.0	—, —	0.9960	116.8	7.3	103.8	6.7	89.9	3.7
90	Fosthiazate	$C_9H_{18}NO_3PS_2$	6.44	284.0538	104.0165	0.5	0.5	—, —	0.9992	118.5	6.3	98.8	7.1	94.4	4.1
91	Furathiocarb	$C_{18}H_{26}N_2O_5S$	17.31	383.1635	195.0474	0.1	0.5	0.001, —	0.9987	95.2	9.1	100.6	4.1	103.9	2.1
92	Haloxyfop	$C_{15}H_{11}ClF_3NO_4$	12.37	362.0401	316.0347	20.0	20.0	0.015, —	0.9972	79.2	10.0	103.2	4.5	86.8	3.3
93	Haloxyfop-2-ethoxyethyl	$C_{19}H_{19}ClF_3NO_5$	17.12	434.0977	91.0542	0.5	0.5	—, —	0.9986	116.0	12.2	117.6	8.1	101.0	2.1
94	Haloxyfop-methyl	$C_{16}H_{13}ClF_3NO_4$	16.30	376.0546	272.0085	0.5	0.5	—, —	0.9993	93.1	17.6	111.8	8.1	100.4	2.5
95	Hexaconazole	$C_{14}H_{17}Cl_2N_3O$	12.29	314.0825	70.0400	1.0	5.0	—, —	0.9972	91.6	3.3	103.8	12.3	97.3	12.3
96	Hexythiazox	$C_{17}H_{21}ClN_2O_2S$	17.76	353.1085	168.0570	5.0	5.0	0.05, —	0.9987	117.6	8.2	99.6	10.3	90.7	10.3
97	Imazalil	$C_{14}H_{14}Cl_2N_2O$	5.78	297.0550	69.0447	0.2	0.5	0.02, —	0.9979	98.6	15.5	112.1	11.9	99.2	1.8
98	Imazapyr	$C_{13}H_{15}N_3O_3$	3.11	262.1186	69.0699	1.0	5.0	0.01, —	0.9987	102.0	2.4	98.6	17.2	93.2	17.2
99	Imidacloprid	$C_9H_{10}ClN_5O_2$	3.73	256.0596	209.0589	10.0	10.0	0.01, —	0.9908	105.4	17.2	101.5	7.9	88.4	7.5
100	Imidacloprid-Olefin	$C_9H_8ClN_5O_2$	3.07	254.0439	171.0665	5.0	5.0	—, —	0.9948	115.6	10.6	113.0	12.9	98.7	12.9
101	Iprobenfos	$C_{13}H_{21}O_3PS$	12.40	289.1022	91.0542	5.0	5.0	—, —	0.9985	108.2	16.2	100.3	11.6	88.9	11.6
102	Iprovalicarb	$C_{18}H_{28}N_2O_3$	10.60	321.2173	119.0855	1.0	1.0	0.01, —	0.9987	118.7	12.8	95.6	7.4	101.5	13.5
103	Isazofos	$C_9H_{17}ClN_3O_3PS$	13.69	314.0490	119.9957	0.1	0.5	—, —	0.9976	108.4	5.5	106.6	3.9	99.3	2.8
104	Isofenphos	$C_{15}H_{24}NO_4PS$	16.54	346.1236	121.0287	20.0	20.0	—, —	0.9973	113.5	10.4	107.3	15.7	94.7	5.0
105	Isoproturon	$C_{12}H_{18}N_2O$	6.73	207.1492	72.0444	0.2	0.5	0.01, —	0.9995	100.0	9.3	100.4	3.5	103.2	1.5
106	Isopyrazam	$C_{20}H_{23}F_2N_3O$	15.74	360.1895	320.1758	0.5	0.5	0.01, —	0.9979	105.6	9.5	105.0	3.4	97.9	0.9
107	Kresoxim-methyl	$C_{18}H_{19}NO_4$	14.39	314.1387	116.0495	5.0	5.0	0.02, —	0.9991	82.8	12.7	105.8	7.1	98.1	7.1
108	Linuron	$C_9H_{10}Cl_2N_2O_2$	9.22	249.0192	132.9606	5.0	5.0	0.01, —	0.9986	102.3	14.3	97.5	11.1	95.0	11.1
109	Malaoxon	$C_{10}H_{19}O_7PS$	5.77	315.0662	99.0077	0.1	0.5	0.02, —	0.9984	116.8	7.6	97.2	4.6	97.9	1.8
110	Malathion	$C_{10}H_{19}O_6PS_2$	12.60	331.0433	99.0077	1.0	1.0	0.02, —	0.9995	119.3	16.3	104.4	7.1	103.0	12.0
111	Mepanipyrim	$C_{14}H_{13}N_3$	11.59	224.1182	77.0386	0.5	5.0	0.01, —	0.9984	98.6	4.1	109.0	11.9	98.1	11.9
112	Metaflumizone	$C_{24}H_{16}F_6N_4O_2$	17.44	507.1250	178.0463	10.0	10.0	0.01, —	0.9973	105.7	18.1	95.4	15.6	91.9	6.6
113	Metalaxyl	$C_{15}H_{21}NO_4$	6.76	280.1543	45.0335	0.1	0.2	0.01, —	0.9995	105.1	10.5	118.3	12.0	103.6	3.3
114	Metconazole	$C_{17}H_{22}ClN_3O$	12.54	320.1524	70.0400	5.0	5.0	0.02, —	0.9974	102.2	2.1	101.4	15.0	98.7	15.0
115	Methiocarb	$C_{11}H_{15}NO_2S$	8.96	226.0896	121.0648	10.0	50.0	0.03, —	0.9943	72.0	6.6	78.0	5.8	89.0	5.1
116	Methiocarb-sulfoxide	$C_{11}H_{15}NO_3S$	3.51	242.0845	122.0726	0.5	0.5	0.03, —	0.9945	98.8	13.7	94.0	6.3	114.4	6.4
117	Metolachlor	$C_{15}H_{22}ClNO_2$	12.41	284.1412	252.1150	0.2	0.5	0.01, —	0.9987	87.7	10.6	116.9	7.4	97.4	3.0

Table 1. *Cont.*

NO.	Compound	Formula	RT/Min	Quantitative Ion (*m*/*z*)	Production (*m*/*z*)	SDL (mg/kg)	LOQ (mg/kg)	MRL (mg/kg; European Union, China)	R^2	1 × LOQ		2 × LOQ		10 × LOQ	
										Rec. (%)	RSD (%)	Rec. (%)	RSD (%)	Rec. (%)	RSD (%)
118	Metrafenone	$C_{19}H_{21}BrO_5$	16.32	409.0645	209.0808	0.2	0.5	0.01, —	0.9989	111.0	13.2	112.2	13.5	99.1	2.7
119	Metribuzin	$C_8H_{14}N_4OS$	5.33	215.0961	49.0106	1.0	5.0	0.1, —	0.9975	99.4	2.4	99.0	11.9	98.8	11.9
120	Mevinphos	$C_7H_{13}O_6P$	3.43	225.0523	127.0155	2.0	5.0	—, —	0.9919	74.4	19.6	112.2	16.5	74.5	16.5
121	Monocrotophos	$C_7H_{14}NO_5P$	2.81	224.0682	58.0287	0.5	0.5	—, —	0.9986	74.0	17.7	80.6	18.3	105.2	8.3
122	Myclobutanil	$C_{15}H_{17}ClN_4$	10.67	289.1215	70.0400	5.0	5.0	0.01, —	0.9993	103.9	7.8	105.0	14.4	94.1	14.4
123	Napropamide	$C_{17}H_{21}NO_2$	11.72	272.1645	171.0804	0.2	0.5	0.01, —	0.9985	105.3	12.7	113.0	5.5	98.0	1.2
124	Norflurazon	$C_{12}H_9ClF_3N_3O$	7.15	304.0459	140.0306	0.1	0.2	—, —	0.9977	92.7	8.1	94.2	4.7	96.4	1.1
125	Omethoate	$C_5H_{12}NO_4PS$	2.10	214.0297	182.9875	0.5	0.5	0.01, —	0.9993	101.0	8.6	104.0	5.1	99.1	3.2
126	Oxadixyl	$C_{14}H_{18}N_2O_4$	5.06	279.1339	132.0808	1.0	1.0	0.01, —	0.9968	101.5	12.7	98.6	8.7	103.1	12.9
127	Paclobutrazol	$C_{15}H_{20}ClN_3O$	8.77	294.1368	70.0400	1.0	1.0	0.01, —	0.9993	94.4	7.4	93.5	3.4	106.5	13.8
128	Pendimethalin	$C_{13}H_{19}N_3O_4$	17.75	282.1448	92.0495	10.0	20.0	0.02, —	0.9963	102.6	10.8	108.9	9.2	81.1	5.6
129	Penthiopyrad	$C_{16}H_{20}F_3N_3OS$	14.57	360.1362	256.0351	0.2	0.5	0.01, —	0.9979	113.8	9.1	101.5	5.7	100.2	3.0
130	Phenthoate	$C_{12}H_{17}O_4PS_2$	15.02	321.0379	79.0542	5.0	20.0	—, —	0.9938	97.1	11.2	88.6	4.9	82.2	2.8
131	Phorate-Sulfone	$C_7H_{17}O_4PS_3$	8.65	293.0097	96.9508	20.0	20.0	0.01, —	0.9982	96.0	13.2	113.8	5.7	82.5	4.0
132	Phorate-sulfoxide	$C_7H_{17}O_3PS_3$	6.37	277.0150	96.9508	0.5	0.5	0.01, —	0.9992	105.4	9.4	97.6	6.5	109.1	3.4
133	Phosalone	$C_{12}H_{15}ClNO_4PS_2$	16.04	367.9941	110.9996	20.0	20.0	0.01, —	0.9990	119.9	15.3	109.9	5.7	86.9	5.6
134	Phosphamidon	$C_{10}H_{19}ClNO_5P$	4.73	300.0762	127.0155	0.2	0.5	—, —	0.9978	95.1	4.2	95.5	4.3	104.1	2.2
135	Phoxim	$C_{12}H_{15}N_2O_3PS$	16.05	299.0614	77.0389	10.0	20.0	0.02, —	0.9933	90.9	19.6	97.3	4.5	108.2	13.4
136	Picoxystrobin	$C_{18}H_{16}F_3NO_4$	14.80	368.1104	145.0648	0.5	1.0	0.01, —	0.9995	114.8	19.0	71.2	10.8	99.1	16.5
137	Piperonyl Butoxide	$C_{19}H_{30}O_5$	17.12	356.2423	119.0855	0.2	0.5	—, —	0.9993	115.1	16.2	108.4	8.6	100.4	4.6
138	Pirimicarb	$C_{11}H_{18}N_4O_2$	4.42	239.1503	72.0444	0.5	1.0	0.05, —	0.9982	105.8	12.0	95.1	6.5	102.7	14.5
139	Pirimiphos-methyl	$C_{11}H_{20}N_3O_3PS$	15.91	306.1036	164.1182	0.5	0.5	0.01, —	0.9971	104.2	9.3	101.5	5.6	99.7	2.4
140	Pretilachlor	$C_{17}H_{26}ClNO_2$	16.25	312.1725	252.1150	0.2	0.5	—, —	0.9977	98.8	10.0	116.7	6.6	101.2	3.3
141	Prochloraz	$C_{15}H_{16}Cl_3N_3O_2$	13.12	376.0381	70.0287	0.5	0.5	0.03, —	0.9977	115.1	8.7	101.3	8.8	93.7	2.4
142	Profenofos	$C_{11}H_{15}BrClO_3PS$	16.19	372.9424	96.9509	5.0	5.0	0.01, —	0.9989	105.5	13.6	106.3	7.5	97.9	7.5
143	Prometryn	$C_{10}H_{19}N_5S$	8.68	242.1434	68.0243	0.2	0.5	—, —	0.9975	104.2	2.3	101.0	4.1	100.0	1.2
144	Propamocarb	$C_9H_{20}N_2O_2$	2.16	189.1598	74.0237	1.0	1.0	0.01, —	0.9990	88.6	6.1	72.3	6.3	98.0	13.7
145	Propanil	$C_9H_9Cl_2NO$	8.21	218.0134	127.0178	5.0	5.0	0.01, —	0.9954	95.9	13.0	116.3	10.5	91.6	10.5
146	Propaphos	$C_{13}H_{21}O_4PS$	13.19	305.0971	221.0032	0.2	0.5	—, —	0.9987	108.8	9.1	102.8	8.4	96.2	3.4
147	Propargite	$C_{19}H_{26}O_4S$	18.36	368.1886	57.0699	20.0	20.0	0.01, —	0.9906	99.4	10.7	91.2	4.1	82.9	2.8
148	Propazine	$C_9H_{16}ClN_5$	8.22	230.1167	146.0228	0.1	0.1	—, —	0.9972	111.4	6.6	114.9	3.9	96.8	7.4

Table 1. *Cont.*

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										Rec. (%)	RSD (%)	Rec. (%)	RSD (%)	Rec. (%)	RSD (%)
149	Propiconazole	$C_{15}H_{17}Cl_2N_3O_2$	13.16	342.0771	69.0699	0.1	1.0	0.01, —	0.9982	102.8	6.3	100.0	4.2	102.0	11.7
150	Propyzamide	$C_{12}H_{11}Cl_2NO$	11.12	256.0290	189.9821	5.0	5.0	0.01, —	0.9953	115.0	14.2	98.2	12.5	94.8	12.5
151	Prothioconazole-desthio	$C_{14}H_{15}Cl_2N_3O$	10.55	312.0664	70.0400	0.5	0.5	0.01, —	0.9994	119.4	3.9	108.1	11.1	111.4	1.8
152	Prothiofos	$C_{11}H_{15}Cl_2O_2PS_2$	19.11	344.9701	240.9041	20.0	20.0	—, —	0.9917	118.6	10.6	83.6	10.1	82.0	9.6
153	Pyraclostrobin	$C_{19}H_{18}ClN_3O_4$	15.47	388.1059	194.0812	0.5	0.5	0.01, —	0.9981	119.8	4.3	108.5	6.0	103.0	0.5
154	Pyridaben	$C_{19}H_{25}ClN_2OS$	18.85	365.1449	147.1168	0.5	0.5	0.01, —	0.9969	86.6	3.9	118.6	18.3	104.4	11.6
155	Pyridaphenthion	$C_{14}H_{17}N_2O_4PS$	11.69	341.0719	92.0498	0.5	0.5	—, —	0.9992	100.6	13.8	98.8	19.7	103.5	4.0
156	Pyrimethanil	$C_{12}H_{13}N_3$	7.56	200.1182	77.0386	0.5	0.5	0.05, —	0.9972	102.4	7.0	96.2	4.2	100.1	2.8
157	Pyriproxyfen	$C_{20}H_{19}NO_3$	17.56	322.1438	96.0444	0.5	0.5	0.05, —	0.9977	114.8	13.3	118.8	19.0	108.9	8.2
158	Quinalphos	$C_{12}H_{15}N_2O_3PS$	14.06	299.0614	96.9508	0.5	0.5	—, —	0.9986	113.0	8.7	110.8	3.6	99.1	3.3
159	Quinoxyfen	$C_{15}H_8Cl_2FNO$	16.82	308.0040	196.9789	1.0	1.0	0.05, —	0.9963	117.7	14.5	104.5	15.3	92.9	7.8
160	Quizalofop-ethyl	$C_{19}H_{17}ClN_2O_4$	16.68	373.0950	91.0542	0.5	1.0	—, —	0.9995	99.8	12.5	98.2	11.7	102.0	11.7
161	Saflufenacil	$C_{17}H_{17}ClF_4N_4O_5S$	11.03	501.0617	348.9998	2.0	5.0	0.01, —	0.9982	109.8	8.8	101.4	17.2	103.2	17.2
162	Simazine	$C_7H_{12}ClN_5$	5.04	202.0854	132.0323	0.5	0.5	0.01, —	0.9974	100.8	2.2	99.3	1.7	101.7	1.4
163	Spinosyn A	$C_{41}H_{65}NO_{10}$	12.82	732.4681	142.1226	0.2	0.5	0.2, —	0.9990	100.9	3.5	110.2	6.3	97.6	1.0
164	Spinosyn D	$C_{42}H_{67}NO_{10}$	14.44	746.4838	142.1226	1.0	1.0	0.2, —	0.9991	110.3	13.1	94.1	5.5	99.7	16.4
165	Spirodiclofen	$C_{21}H_{24}Cl_2O_4$	19.01	411.1124	71.0855	1.0	5.0	0.004, —	0.9997	87.0	13.1	106.5	16.8	92.2	16.8
166	Spirotetramat	$C_{21}H_{27}NO_5$	10.19	374.1962	302.1751	5.0	5.0	0.01, —	0.9981	73.0	14.5	96.1	13.1	79.3	13.1
167	Spirotetramat-enol	$C_{18}H_{23}NO_3$	5.33	302.1758	216.1019	0.5	0.5	0.01, —	0.9943	95.1	7.6	118.6	2.5	91.9	5.6
168	Spirotetramat-enol-glucoside	$C_{24}H_{33}NO_8$	2.89	464.2279	302.1751	2.0	5.0	—, —	0.9979	109.8	8.8	101.4	17.2	103.2	17.2
169	Spiroxamine	$C_{18}H_{35}NO_2$	8.31	298.2741	100.1121	0.5	0.5	0.015, —	0.9959	95.4	10.1	105.7	10.5	97.5	2.9
170	Sulfentrazone	$C_{11}H_{10}Cl_2F_2N_4O_3S$	6.43	386.9891	306.9944	5.0	10.0	—, —	0.9987	112.7	15.1	96.7	5.9	96.8	2.0
171	Sulfotep	$C_8H_{20}O_5P_2S_2$	15.80	323.0300	96.9508	1.0	1.0	—, —	0.9970	92.1	4.5	96.0	2.6	92.5	12.0
172	Sulfoxaflor	$C_{10}H_{10}F_3N_3OS$	4.57	278.0569	154.0463	1.0	10.0	0.2, —	0.9989	99.0	7.2	101.5	3.6	92.9	1.3
173	Sulprofos	$C_{12}H_{19}O_2PS_3$	18.03	323.0358	218.9698	5.0	5.0	—, —	0.9990	102.9	18.6	94.4	7.5	91.0	7.5
174	Tebuconazole	$C_{16}H_{22}ClN_3O$	11.84	308.1524	70.0400	1.0	5.0	0.02, —	0.9990	91.7	2.8	103.7	12.9	97.0	12.9
175	Tebufenozide	$C_{22}H_{28}N_2O_2$	14.05	353.2224	133.0648	1.0	10.0	0.01, —	0.9908	118.8	9.3	93.0	10.0	94.9	7.7
176	Terbufos-Sulfone	$C_9H_{21}O_4PS_3$	11.80	321.0412	275.0535	5.0	5.0	0.01, —	0.9992	102.3	9.4	100.0	12.0	101.7	12.0
177	Terbufos-Sulfoxide	$C_9H_{21}O_3PS_3$	8.40	305.0465	130.9385	0.5	1.0	0.01, —	0.9983	109.5	14.5	115.5	8.7	101.4	13.8
178	Terbumeton	$C_{10}H_{19}N_5O$	5.61	226.1662	170.1036	0.2	0.5	—, —	0.9982	92.2	2.2	100.5	3.5	101.9	1.5
179	Terbuthylazine	$C_9H_{16}ClN_5$	8.90	230.1167	174.0541	0.5	0.5	0.02, —	0.9972	111.0	10.5	106.3	11.4	96.4	4.5

Table 1. *Cont.*

NO.	Compound	Formula	RT/Min	Quantitative Ion (*m*/*z*)	Production (*m*/*z*)	SDL (mg/kg)	LOQ (mg/kg)	MRL (mg/kg; European Union, China)	R^2	1 × LOQ		2 × LOQ		10 × LOQ	
										Rec. (%)	RSD (%)	Rec. (%)	RSD (%)	Rec. (%)	RSD (%)
180	Terbutryn	$C_{10}H_{19}N_5S$	9.09	242.1434	186.0808	0.2	0.5	—, —	0.9983	99.3	9.0	94.3	6.2	101.9	2.2
181	Tetramethrin	$C_{19}H_{25}NO_4$	17.09	332.1856	164.0706	20.0	20.0	—, —	0.9934	90.9	5.2	89.8	9.4	84.7	4.0
182	Thiabendazole	$C_{10}H_7N_3S$	2.90	202.0433	131.0604	0.2	0.2	0.2, 0.2	0.9996	81.2	16.6	107.1	16.1	72.9	4.3
183	Thiacloprid	$C_{10}H_9ClN_4S$	4.55	253.0309	126.0087	0.2	0.5	0.05, —	0.9999	106.3	5.7	89.5	7.0	104.8	2.0
184	Thiamethoxam	$C_8H_{10}ClN_5O_3S$	3.17	292.0266	131.9664	0.5	1.0	0.05, —	0.9994	100.8	16.1	91.4	9.6	103.4	17.3
185	Thiobencarb	$C_{12}H_{16}ClNOS$	15.23	258.0714	125.0153	1.0	5.0	0.01, —	0.9985	100.0	5.2	99.4	8.2	92.6	8.2
186	Thiophanate-methyl	$C_{12}H_{14}N_4O_4S_2$	5.50	343.0529	151.0324	2.0	20.0	0.05, —	0.9995	78.2	13.8	81.7	4.4	77.7	14.2
187	Tolfenpyrad	$C_{21}H_{22}ClN_3O_2$	16.96	384.1477	197.0961	0.5	0.5	—, —	0.9994	108.7	16.7	118.0	12.1	102.2	7.5
188	Triadimefon	$C_{14}H_{16}ClN_3O_2$	11.26	294.1004	57.0699	1.0	5.0	0.01, —	0.9993	101.6	3.5	102.4	14.5	97.1	14.5
189	Trichlorfon	$C_4H_8Cl_3O_4P$	3.36	256.9299	78.9945	10.0	10.0	0.01, —	0.9981	105.9	17.6	102.6	13.3	95.8	3.4
190	Trifloxystrobin	$C_{20}H_{19}F_3N_2O_4$	16.78	409.1370	145.0260	0.2	0.5	0.02, —	0.9982	106.0	19.8	109.7	9.2	102.3	1.3
191	Triflumizole	$C_{15}H_{15}ClF_3N_3O$	15.00	346.0929	69.0447	0.5	0.5	0.01, —	0.9980	96.7	11.1	119.4	6.5	99.8	3.1
192	Trinexapac-ethyl	$C_{13}H_{16}O_5$	7.60	253.1071	69.0335	10.0	20.0	—, —	0.9976	73.1	12.7	100.9	4.9	83.2	0.7
193	Uniconazole	$C_{15}H_{18}ClN_3O$	10.67	292.1213	70.0400	0.5	0.5	—, —	0.9980	108.2	11.8	107.6	4.9	101.6	1.3
194	Warfarin	$C_{19}H_{16}O_4$	9.15	309.1121	163.0390	0.5	0.5	0.01, —	0.9991	79.4	19.0	76.6	10.5	92.6	2.3
195	Zoxamide	$C_{14}H_{16}Cl_3NO_2$	15.00	336.0319	186.9712	0.5	0.5	0.01, —	0.9994	95.5	17.6	96.2	6.3	99.8	4.5

RT: retention time; SDL: screening detection limit; LOQ: the limit of quantification; MRL: maximum residue limits; R^2: coefficient of determination. "—" means no MRL value.

2.5. Validation of the Method

The method was validated in the raw milk matrix by evaluating the following parameters: screening detection limit (SDL), the limit of quantification (LOQ), linearity, matrix effect, accuracy, and precision. To define the SDL, refer to the European SANTE/12682/2019 guidelines [28]. LOQs were assessed by determining the lowest concentration of spiked samples where recovery and precision were satisfactory (70–120% and less than 20%, respectively). Calibration curves were investigated by determining the results of a series of standard addition recovery experiments (1–200 μg/kg) of blank matrix extract solutions before injection. Matrix effects were evaluated by comparing the slope of the matrix-matched calibration curve with the solvent calibration curve. To validate the accuracy and precision of the established method, recovery studies were performed for each substrate in six replicates for three spiked levels at 1 × LOQ, 2 × LOQ, and 10 × LOQ.

Agilent Mass Hunter (version B. 08.00) software was used to analyze the data based on the self-built database. To ensure the accuracy of target pesticide identifications, the specific settings of the corresponding screening parameters included the retention time offset threshold (≤ 0.15 min), the co-exist score (≥15), the signal-to-noise ratio (≥3), the mass deviation (≤10 ppm), and the number of characteristic ions in the qualitative identification of compounds (5:2). The data results were analyzed and summarized by Microsoft Excel 2016 (Seattle, WA, USA) software, and the analysis of graphs was drawn by Origin 2018 software.

3. Results

3.1. Optimization of the QuEChERS Procedure

The QuEChERS procedure was evaluated due to the possibility of matrix interferences influencing the identification of compounds, which are the most challenging situations in high-throughput screening and are also required to validate quantitative determination. For this reason, different procedures based on the QuEChERS method have been evaluated as follows.

3.1.1. Optimization of the Extraction Solvent Volume

This study used acetonitrile with 1% acetate as an extraction solvent because it can extract various compounds with different polarity ranges and is the most effective organic solvent in multi-residue methods [17,18,20]. The volumes of extraction solution, such as 10 mL, 16 mL, and 20 mL of acetonitrile with 1% acetate, were compared to improve the extraction efficiency. In the spiked level of 100 μg/kg, the detected pesticides were 170, 173, and 166, respectively, using 10 mL, 16 mL, and 20 mL of acetonitrile with 1% acetate for raw milk. By 10 mL of the extraction solution, the final sample solution contains a high matrix background interference, affecting the definitive identification of compounds under the same purification conditions. Moreover, when the extraction solution volume was 20 mL, the sample solution was diluted by a factor of five, which noticeably reduced the sensitivity of the compound detection. Ultimately, the relatively good experimental results could be found when the volume of the extraction solution was 16 mL. Considering the response of the target pesticide and background interference, 16 mL acetonitrile with 1% acetate was selected for the extraction solvent.

3.1.2. Optimization of the Type of Extraction Salt

The matrix environment, especially pH, may play an essential role in extracting some pesticides during the extraction process. Therefore, the effect of pH on pesticide recovery has been frequently investigated in many studies [27]. Extraction salts could adjust the pH of the matrix and affect the extraction efficiency by reducing the solubility of the target pesticides in an aqueous solution and enhancing their transfer into the extraction solution. To assess the extraction salt, the various compositions of salt pocket from the initial method (4 g anhydrous $MgSO_4$ and 1 g sodium chloride), the AOAC method (6 g anhydrous $MgSO_4$ and 1.5 g sodium acetate), and the EN method (4 g anhydrous $MgSO_4$, 1 g anhydrous NaCl,

1 g dihydrate trisodium citrate, and 0.5 g disodium citrate) [29] were compared. As shown in Figure 1, the number of pesticides with the recovery in 70–120% by the EN method was slightly higher than the other two methods. This is because citrate buffering (EN) gently adjusts the pH of the matrix to between 5.0 and 5.5, enabling the satisfactory recovery of some sensitive pesticides under acidic or basic conditions. The results also verified that pH-sensitive pesticides, such as carbofuran and carbofuran-3-hydroxy (carbamate pesticides), had good performance and stability effects through EN buffer salts. Therefore, the EN method salt pocket was selected.

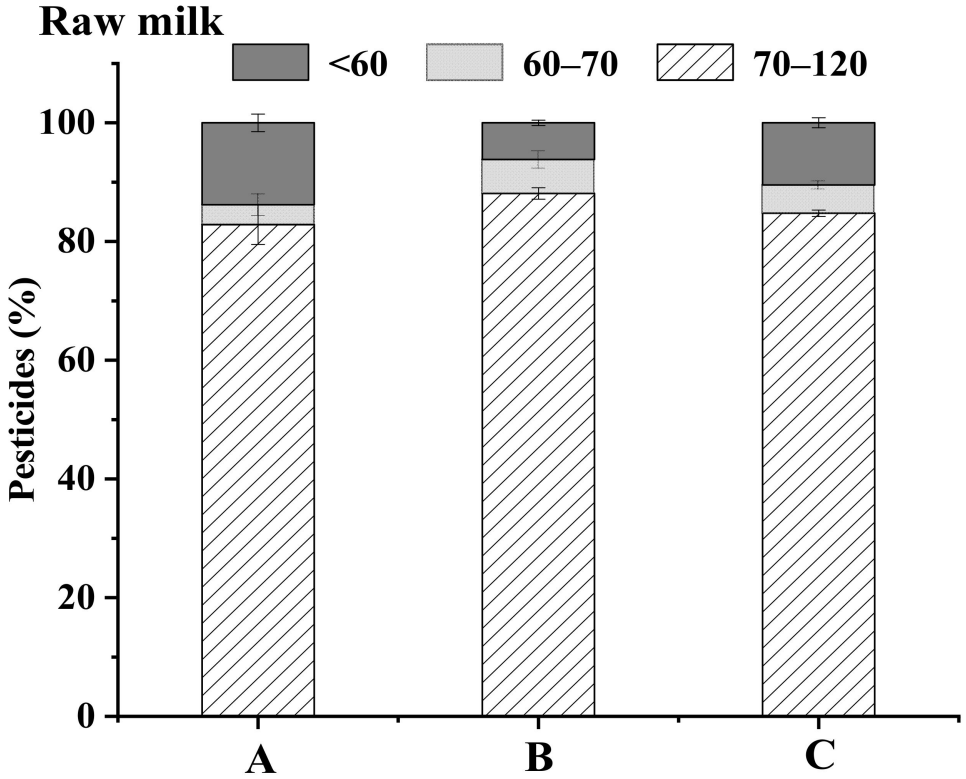

Figure 1. Recoveries (%) obtained for various salt pockets methods; (**A**) 4 g anhydrous $MgSO_4$, 1 g sodium chloride, (**B**) 4 g anhydrous $MgSO_4$, 1 g anhydrous NaCl, 1 g dihydrate trisodium citrate and 0.5 g disodium citrate, and (**C**) 6 g anhydrous $MgSO_4$, 1.5 g sodium acetate.

3.1.3. Optimization of the Freezing Temperature

The low-temperature precipitation step enables the removal of a large proportion of interfering substances, such as lipids, fats, and proteins that may be extracted along with the target pesticide residues. The significant advantage of this purification technology is that it is simple to operate and does not require specialized equipment [30]. The main components of milk are protein and animal oil esters. Therefore, it was necessary to use a low-temperature precipitation method for the raw milk to reduce the co-extracts in the extracts. As shown in Figure 2, the TIC chromatograms of different experimental groups overlapped, indicating a significant reduction in the signal intensity of co-extractives and matrix-derived interferences under low-temperature conditions. Meanwhile, the results showed that the recovery and precision of pesticides frozen at −20 °C for 0.5 h were better than those of the experimental group without freezing. Still, the results were similar to those of the experimental group frozen for 1.0 h. Thus, a freezing time of 0.5 h was chosen in the final method.

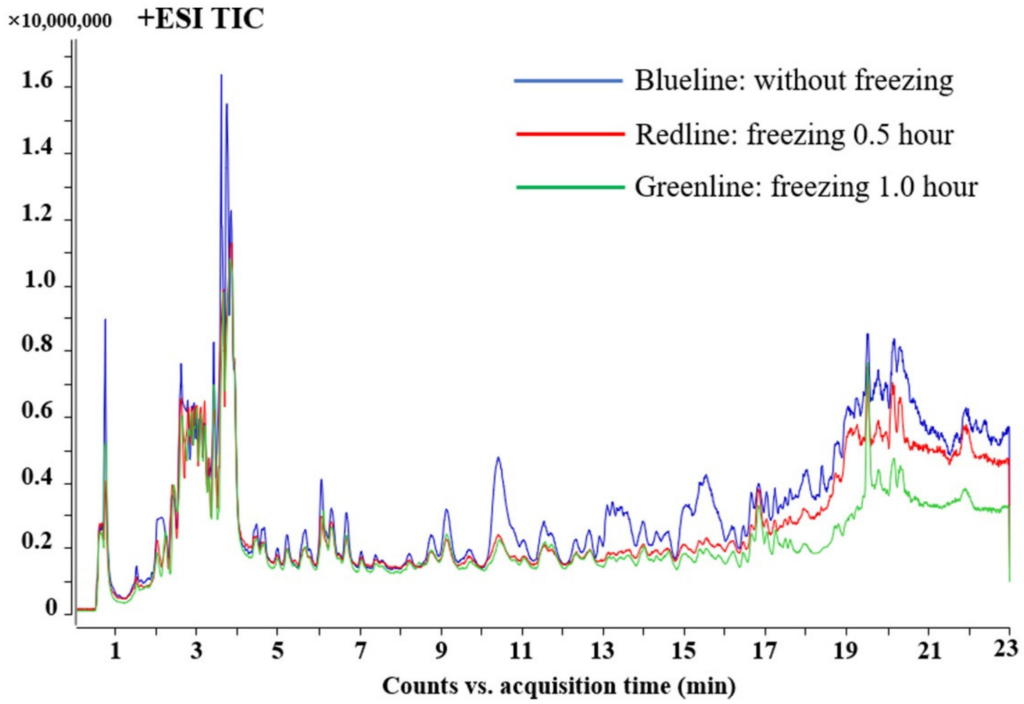

Figure 2. LC-Q-TOF/MS Total ion chromatogram overlap showing the effect of freezing (Blueline: without freezing; Redline: freezing 0.5 h; Greenline: freezing 1.0 h).

3.1.4. Optimization of the Purification Adsorbent

Despite the sample solution being frozen-out to remove most of the interfering substances, the remaining matrix components may still interfere with the determination and contaminate the LC-Q-TOF/MS system, so it is necessary to develop an additional efficient clean-up step. Sorbents play a crucial role in the QuEChERS method. Various sorbents such as primary secondary amines (PSA) and octadecyl (C18) are often used for sample clean-up in pesticide residue analysis. C18 is a reversed-phase adsorption material that removes non-polar impurities such as lipids, cholesterol, and lipophilic compounds. PSA is a weak anion exchange sorbent that could adsorb polar molecules and effectively remove co-extracted components from the matrix, such as organic acids and sugars [27].

Raw milk is a complicated matrix with high lipid, fat, and protein intensities. Thus, the optimization of the purification step is achieved by different adsorbent combinations and dosage variables. In the present experiment, 500 mg of anhydrous magnesium sulfate was applied to remove the residual water. In addition, five different types of sorbents (100 mg of C18, 200 mg of C18, 300 mg of C18, 50 mg of PSA, and 50 mg of PSA + 200 mg of C18) were tested to investigate the influences on recoveries in raw milk.

According to SANTE/12682/2019 guidelines, the acceptable recovery interval is 70–120%, with an RSD less than or equal to 20% for multi-residue methods. As shown in Figure 3, the most significant number of pesticides with satisfactory recoveries and RSDs were found when 200 mg of C18 was used, along with better peak shapes and less matrix interference for some drugs, such as thiophanate-methyl. It may be that 200 mg of C18 can remove more interfering substances without affecting the pesticide detection, but excessive use of C18 will adsorb pesticides to reduce the recovery. Meanwhile, PSA adsorbent alone could not effectively remove lipids and proteins, which affected the detection of target pesticides. Finally, based on these results, 200 mg of C18 was selected as the sorbent to clean-up raw milk samples in this study.

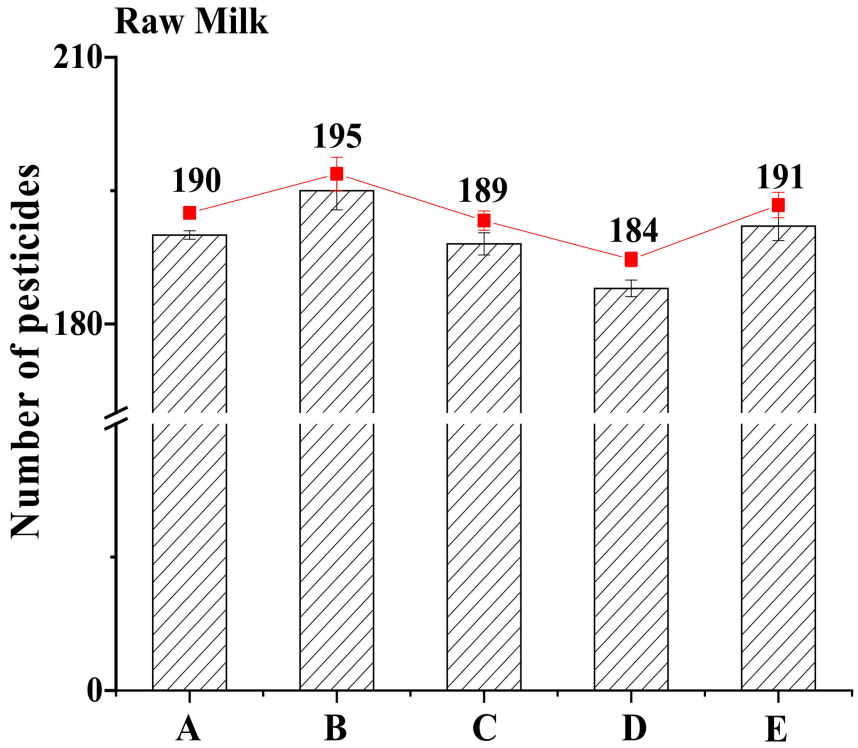

Figure 3. Comparison of different sorbents for dispersive-SPE clean-up of analytes in raw milk. (**A**): 100 mg C18; (**B**): 200 mg C18; (**C**): 300 mg C18; (**D**): 50 mg PSA; and (**E**): 50 mg PSA+ 200 mg C18.

3.2. Matrix Effect

The co-eluting components, such as lipids, fats, and proteins in raw milk interfere with the ionization of pesticides with the suppression or the enhancement of the response. The formula evaluated the matrix effect in raw milk: the matrix effect (ME, %) = (slope of the matrix standard curve/slope of the solvent standard curve $-$ 1) $\times$ 100. Matrix effects can be classified into three categories based on the results of the calculated data (Strong matrix effect: $|ME| \geq 50$; Medium matrix effect: $20 < |ME| < 50$; and Weak matrix effect: $|ME| \leq 20$) [23]. As shown in Figure 4, more than 89.2% of the pesticides had a weak matrix effect in raw milk. The data results indicate that the method accurately analyzes trace pesticide residues in milk.

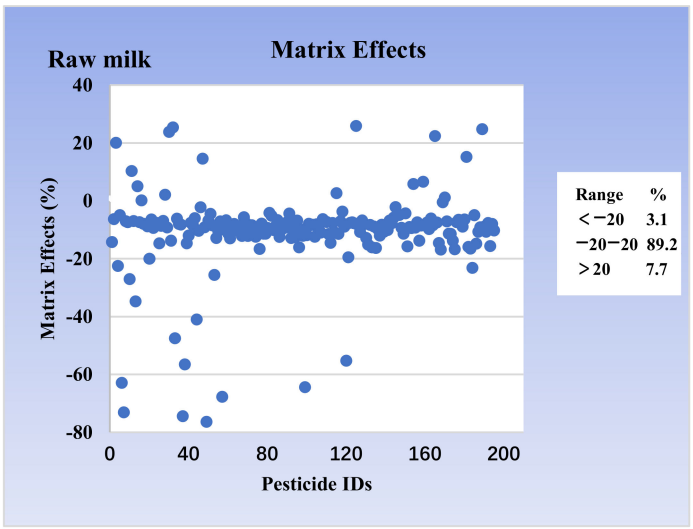

Figure 4. Matrix effect distribution of pesticides in raw milk analysis methods.

3.3. Method Validation

The linearity, SDL, LOQ, accuracy, and precision were determined to evaluate the performance of the modified QuEChERS method. The linearity was selected in the 1–200 μg/kg concentration range. As presented in Table 1, the coefficients of determination (R^2) were higher than 0.99 for the pesticides in different linear ranges.

The sensitivity of the method was performed by SDL according to SANTE/12682/2019. SDLs were determined by spiking a series of mixed standard solutions in 20 blank samples and the lowest level at which pesticides had been screened in at least 95% of the samples [28]. As shown in Figure 5A, the percentage of pesticides with SDLs no more than 10 μg/kg was 93.3% for raw milk. LOQs were determined as the lowest validated spike level based on the recovery results by spiking a series of mixed standard solutions in blank samples. For raw milk, the LOQs were in the range of 0.5–50 μg/kg, and more than 87.2% of pesticides were less than or equal to 10 μg/kg, as shown in Figure 5B. The details of the SDLs and LOQs are listed in Table 1.

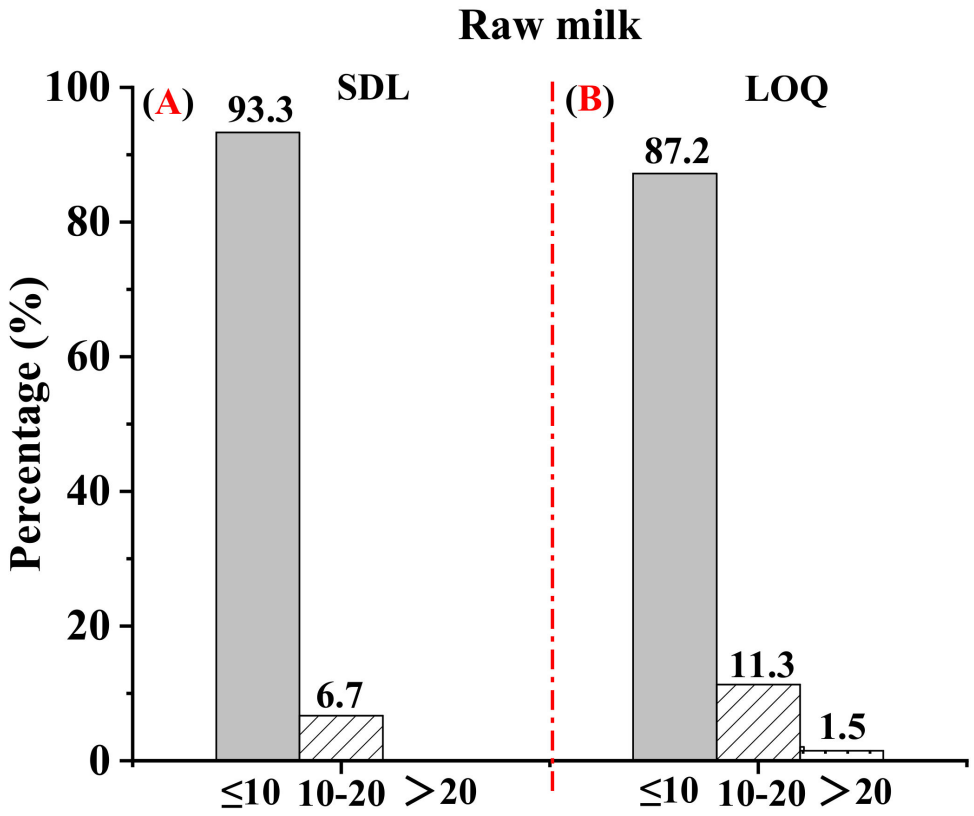

Figure 5. The distribution of the screening and quantification limits of pesticides in raw milk: (**A**) SDL distribution of pesticides in raw milk; (**B**) LOQ distribution of pesticides in raw milk.

For the accuracy and precision assessment, six replicates at three spiked levels were used, including 1 × LOQ, 2 × LOQ, and 10 × LOQ. The overall accuracy values for quantifying target pesticides in raw milk through recovery experiments ranged between 70.0% and 119.8%. The lowest accuracy value was relative to aminopyralid (70.0%). Thus, the method's precision can be considered appropriate (SANTE/12682/2019). For 195 pesticide residues, the RSD values ranged from 0.5 to 20.0% under in-laboratory conditions in all recovery experiments, indicating that the method's precision was acceptable. Therefore, it could be concluded that the modified QuEChERS method was sufficiently sensitive to determine the residues of the investigated pesticides in raw milk samples. The experimental results of the method performance evaluation, including recovery values (Rec, %) and RSD (%), are shown in Table 1.

3.4. Analysis of Real Samples

The established method was applied to 21 actual raw milk samples collected from local dairy farms in China (six batches from the Inner Mongolia Autonomous Region, six batches from Shaanxi Province, six batches from Shandong Province, and three batches from Hebei Province). Raw milk samples were collected at the dairy farm, transported to the laboratory using the cold chain, and stored at −20 °C. Samples need to be thawed to room temperature before analysis. To guarantee the accuracy and reliability of the experimental results, the spiked samples were tested simultaneously. The samples were pretreated according to the preparation section and then analyzed by LC-Q-TOF/MS. The results obtained showed that no pesticides were detected in the actual samples. The recovery results of the quality control samples met the analytical requirements, indicating that the values were accurate and reliable.

4. Conclusions

A high-throughput screening method based on modified QuEChERS and LC-Q-TOF/MS was established to analyze multi-residue pesticides in raw milk rapidly. The modified QuEChERS sample preparation method used an EN salting agent, followed by a freezing treatment, and then a purification treatment with C18 adsorbent, which effectively removed interference and reduced the matrix effect of multiple pesticide residues in raw milk. Overall, 195 pesticides passed the validation with satisfactory recoveries (70−120%) and an RSD of ≤20%. The method exhibited a good sensitivity to milk matrices, and the percentage of pesticides with SDL and LOQ values not exceeding 10 μg/kg for the established method were 93.3% and 87.2%, respectively. These results show that the method is cost-effective, convenient, and reliable for the routine screening of pesticide residues in raw milk and fully complies with the requirements of relevant regulations.

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