Application of Ultrahigh-Performance Liquid Chromatography and Electrospray Ionization Quadrupole Orbitrap High-Resolution Mass Spectrometry for Determination of 166 Pesticides in Fruits and Vegetables

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ABSTRACT: This paper presents an application of ultrahigh-performance liquid chromatography and electrospray ionization quadrupole Orbitrap high-resolution mass spectrometry (UHPLC/ESI Q-Orbitrap) for determination of 166 pesticide residues in fruits and vegetables. Pesticides were extracted from the samples using the QuEChERS (quick, easy, cheap, effective, rugged, and safe) procedure. UHPLC/ESI Q-Orbitrap MS (i.e., full MS scan) acquired full MS data for quantification, and UHPLC/ESI Q-Orbitrap dd-MS^2 (i.e., data-dependent scan) obtained product-ion spectra for confirmation. UHPLC/ESI Q-Orbitrap MS quantification was achieved using matrix-matched standard calibration curves with isotopically labeled standards or chemical analogues as internal standards. The method performance characteristics that included overall recovery, intermediate precision, and measurement uncertainty were evaluated according to a nested experimental design. For the matrices studied, about 90.3−91.5% of the pesticides had recoveries between 81 and 110%, 92.1−97.6% had intermediate precision ≤20%, and 89.7−95.2% had measurement uncertainty ≤40%. Confirmation was based on mass accuracy ≤5 ppm and LC retention time tolerance within ±2.5%. Overall, the UHPLC/ESI Q-Orbitrap has demonstrated great performance for quantification and confirmation of pesticide residues in fresh fruits and vegetables.

KEYWORDS: UHPLC/ESI Q-Orbitrap, high-resolution mass spectrometer, pesticides, fruits and vegetables

■ INTRODUCTION

Pesticides have been widely used in various combinations and at different stages of cultivation and during postharvest storage to protect crops against a range of pests and fungi and/or to provide quality preservation. Pesticide residues, which might pose a potential risk for human health due to their subacute and chronic toxicity, could possibly remain in crops such as fruits and vegetables. It is important to control or regulate the uses of pesticides in crop production and to monitor their levels for compliance so as to ensure the safety of the food supply. Therefore, national or international bodies have set regulations for monitoring programs and health risk assessment of pesticide residues in food. For example, there are 1289 active substances or pesticides that are controlled in EU Regulation (EC) No. 1107/2009; 514 pesticides have been given maximum residue limits (MRLs) in various food commodities under Regulation (EC) No. 396/2005; and, for those with no MRLs, a default limit of 0.01 mg/kg was set.[1−3]

In Canada, as part of the assessment process prior to the registration of a pesticide, Health Canada determines whether the consumption of the maximum amount of residues remaining in food will be a concern to human health and sets science-based MRLs to ensure the Canadian food supply is safe.[4] Many food commodities such as fruits and vegetables, infant food, tea, grains, pulses, etc., have been tested for pesticide residues under the Canadian National Chemical Residues Monitoring Program and Food Safety Action Plan by the Canadian Food Inspection Agency.[5] To determine the levels of pesticide residues and to screen for a large number of

pesticides in various food commodities consistently remain as challenges for analytical chemists. Improved multiclass or multiresidue methodologies with high sensitivity and expanded scopes, which include as many pesticides and commodities as possible in a single method, are always required for checking compliance and/or for studying risk assessment of consumer exposure to pesticides.

Pesticides in foods are traditionally determined using gas chromatography (GC) coupled with selective detectors, for example, electron capture or mass spectrometer (MS). GC-MS continues to be a key tool to analyze pesticides because it is inexpensive and easy to operate and satisfies the required sensitivity and selectivity for both quantification and confirmation. However, some pesticides, such as N-methyl carbamates or newer ones, are not amenable to GC because of their thermal instability and polarity;[6] therefore, liquid chromatography (LC) has been used as an alternative technique to analyze these compounds. Although LC coupled to ultraviolet, diode array, fluorescence (nondestructive detection techniques), etc., is feasible, these techniques may not provide sufficient selectivity or sensitivity, especially for pesticides in complex matrices. Recently, LC-MS has been widely used as a very practical technique to quantify LC-amenable pesticides and confirm their identities in fruits and

Table 1. Pesticides, Exact Masses, and UHPLC Retention Times for Data Processing and Quantification

compound 1[c]	retention time (min) 2	molecular formula 3	precursor[a,b] exact mass [M + H]+ 4	[M + NH₄]+ 5	[M + Na]+ 6	fragment[a,b] elemental composition 7	exact mass 8
abamectin B$_{1a}$	9.38	C$_{48}$H$_{72}$O$_{14}$	873.49949	890.52604	**895.48143**		
acetochlor	7.07	C$_{14}$H$_{20}$ClNO$_2$	270.12553	287.15208	292.10748	C$_{12}$H$_{15}$ClNO$^+$	**224.08367**
aldicarb	4.13	C$_7$H$_{14}$N$_2$O$_2$S	191.08488	208.11143	213.06682	C$_5$H$_{10}$NS$^+$	**116.05285**
aldicarb sulfone	2.15	C$_7$H$_{14}$N$_2$O$_4$S	**223.07471**	240.10126	245.05665		
aldicarb sulfoxide	1.63	C$_7$H$_{14}$N$_2$O$_3$S	207.07979	224.10634	229.06174	C$_5$H$_{10}$NOS$^+$	**132.04776**
anilofos	7.61	C$_{13}$H$_{19}$ClNO$_3$PS$_2$	**368.03053**	385.05708	390.01247		
azaconazole	5.40	C$_{12}$H$_{11}$C$_{12}$N$_3$O$_2$	**300.03011**	317.05666	322.01205		
benoxacor	6.36	C$_{11}$H$_{11}$Cl$_2$NO$_2$	**260.02396**	277.05051	282.00591		
bitertanol	7.02	C$_{20}$H$_{23}$N$_3$O$_2$	**338.18630**	355.21285	360.16825		
bromuconazole	6.40	C$_{13}$H$_{12}$BrCl$_2$N$_3$O	**375.96136**	392.98790	397.94330		
butafenacil	7.25	C$_{20}$H$_{18}$ClF$_3$N$_2$O$_6$	475.08783	**492.11438**	497.06977		
butocarboxim	3.97	C$_7$H$_{14}$N$_2$O$_2$S	191.08488	208.11143	**213.06682**		
butocarboxim sulfoxide	1.42	C$_7$H$_{14}$N$_2$O$_3$S	207.07979	224.10634	229.06174	C$_5$H$_{10}$NOS$^+$	**132.04776**
cadusafos	7.72	C$_{10}$H$_{23}$O$_2$PS$_2$	**271.09499**	288.12154	293.07693		
carbaryl	5.13	C$_{12}$H$_{11}$NO$_2$	202.08626	219.11280	224.06820	C$_{10}$H$_9$O$^+$	**145.06479**
carbendazim	3.26	C$_9$H$_9$N$_3$O$_2$	**192.07675**	209.10330	214.05870		
carbendazim-d_4 (IS)	3.26	C$_9$H$_5$D$_4$N$_3$O$_2$	**196.10186**	213.12841	218.08381		
carbetamide	4.21	C$_{12}$H$_{16}$N$_2$O$_3$	**237.12337**	254.14992	259.10531		
carbofuran	4.92	C$_{12}$H$_{15}$NO$_3$	**222.11247**	239.13902	244.09441		
carbofuran-d_3 (IS)	4.92	C$_{12}$H$_{12}$D$_3$NO$_3$	**225.13130**	242.15785	247.11325		
carfentrazone-ethyl	7.37	C$_{15}$H$_{14}$C$_{12}$F$_3$N$_3$O$_3$	**412.04371**	429.07026	434.02565		
chlorantraniliprole	5.92	C$_{18}$H$_{14}$BrCl$_2$N$_5$O$_2$	**481.97807**	499.00462	503.96001		
chlorbromuron	6.39	C$_9$H$_{10}$BrClN$_2$O$_2$	**292.96869**	309.99524	314.95064		
chloridazon	3.28	C$_{10}$H$_8$ClN$_3$O	**222.04287**	239.06942	244.02481		
chlorimuron-ethyl	3.94	C$_{15}$H$_{15}$ClN$_4$O$_6$S	**415.04736**	432.07391	437.02931		
chloroxuron	6.39	C$_{15}$H$_{15}$ClN$_2$O$_2$	**291.08948**	308.11603	313.07143		
chlorthiamid	4.30	C$_7$H$_5$Cl$_2$NS	**205.95925**	222.98580	227.94120		
chlortoluron	5.07	C$_{10}$H$_{13}$ClN$_2$O	**213.07892**	230.10547	235.06086		
clodinafop-propargyl	7.58	C$_{17}$H$_{13}$ClFNO$_4$	**350.05899**	367.08554	372.04094		
cloquintocet-mexyl	8.34	C$_{18}$H$_{22}$ClNO$_3$	**336.13610**	353.16265	358.11804		
clothianidin	3.15	C$_6$H$_8$ClN$_5$O$_2$S	**250.01600**	267.04255	271.99795		
cyanofenphos	7.79	C$_{15}$H$_{14}$NO$_2$PS	304.05557	321.08211	326.03751	C$_7$H$_6$NO$^+$	**120.04439**
cyazofamid	7.37	C$_{13}$H$_{13}$ClN$_4$O$_2$S	**325.05205**	342.07860	347.03400		
cycloxydim	5.70	C$_{17}$H$_{27}$NO$_3$S	**326.17844**	343.20499	348.16039		
cycluron	5.15	C$_{11}$H$_{22}$N$_2$O	**199.18049**	216.20704	221.16243		
cyromazin	1.17	C$_6$H$_{10}$N$_6$	**167.10397**	184.13052	189.08592		
demeton-S-methyl sulfone	2.66	C$_6$H$_{15}$O$_5$PS$_2$	**263.01713**	280.04368	284.99908		
demeton-S-methyl sulfoxide	2.21	C$_6$H$_{15}$O$_4$PS$_2$	**247.02222**	264.04877	269.00416		
desmedipham	6.11	C$_{16}$H$_{16}$N$_2$O$_4$	**301.11828**	318.14483	323.10023		
dialifor	8.10	C$_{14}$H$_{17}$ClNO$_4$PS$_2$	394.00980	411.03634	415.99174	C$_{10}$H$_7$ClNO$_2$$^+$	**208.01598**
diethofencarb	6.27	C$_{14}$H$_{21}$NO$_4$	268.15434	285.18088	290.13628	C$_{11}$H$_{16}$NO$_4$$^+$	**226.10739**
difenoconazole	7.54	C$_{19}$H$_{17}$Cl$_2$N$_3$O$_3$	**406.07197**	423.09852	428.05392		
dimethametryn	7.04	C$_{11}$H$_{21}$N$_5$S	**256.15904**	273.18559	278.14099		
dimethomorph	6.14	C$_{21}$H$_{22}$ClNO$_4$	**388.13101**	405.15756	410.11296		
dimetilan	3.52	C$_{10}$H$_{16}$N$_4$O$_3$	**241.12952**	258.15607	263.11146		
dimoxystrobin	7.13	C$_{19}$H$_{22}$N$_2$O$_3$	327.17032	344.19687	349.15226	C$_{11}$H$_{13}$N$_2$O$_2$$^+$	**205.09715**
diniconazole	7.16	C$_{15}$H$_{17}$Cl$_2$N$_3$O	**326.08214**	343.10869	348.06409		
dioxacarb	3.47	C$_{11}$H$_{13}$NO$_4$	224.09174	241.11828	246.07368	C$_9$H$_{11}$O$_3$$^+$	**167.07027**
dipropetryn	7.22	C$_{11}$H$_{21}$N$_5$S	**256.15904**	273.18559	278.14099		
diuron	5.36	C$_9$H$_{10}$Cl$_2$N$_2$O	**233.02430**	250.05084	255.00624		
dodemorph	10.53	C$_{18}$H$_{35}$NO	**282.27914**	299.30569	304.26109		
emamectin B$_{1a}$	8.67	C$_{49}$H$_{75}$NO$_{13}$	**886.53112**	903.55767	908.51307		
epoxiconazole	6.56	C$_{17}$H$_{13}$ClFN$_3$O	**330.08039**	347.10694	352.06234		
ethiofencarb	5.30	C$_{11}$H$_{15}$NO$_2$S	226.08963	243.11618	248.07157	C$_7$H$_7$O$^+$	**107.04914**
ethiofencarb sulfone	3.18	C$_{11}$H$_{15}$NO$_4$S	**258.07946**	275.10601	280.06140		
ethiofencarb sulfoxide	2.85	C$_{11}$H$_{15}$NO$_3$S	**242.08454**	259.11109	264.06649	C$_9$H$_{13}$O$_2$S$^+$	185.06308
ethiprole	6.21	C$_{13}$H$_9$Cl$_2$F$_3$N$_4$OS	**396.98990**	414.01645	418.97184		

Table 1. continued

compound 1[c]	retention time (min) 2	molecular formula 3	[M + H]+ 4	[M + NH₄]+ 5	[M + Na]+ 6	elemental composition 7	exact mass 8
			precursor[a,b] — exact mass			fragment[a,b]	
ethirimol	4.43	$C_{11}H_{19}N_3O$	**210.16009**	227.18664	232.14203		
ethoprop	6.67	$C_8H_{19}O_2PS_2$	**243.06369**	260.09024	265.04563		
etoxazole	9.03	$C_{21}H_{23}F_2NO_2$	**360.17696**	377.20351	382.15891		
fenamidone	6.55	$C_{17}H_{17}N_3OS$	**312.11651**	329.14306	334.09846		
fenazaquin	8.84	$C_{20}H_{22}N_2O$	**307.18049**	324.20704	329.16243		
fenhexamid	6.63	$C_{14}H_{17}Cl_2NO_2$	**302.07091**	319.09746	324.05286		
fenoxanil	7.41	$C_{15}H_{18}Cl_2N_2O_2$	**329.08181**	346.10836	351.06375		
fenpropidin	6.98	$C_{19}H_{31}N$	**274.25293**	291.27947	296.23487		
fenpropimorph	10.00	$C_{20}H_{33}NO$	**304.26349**	321.29004	326.24544		
fenpyroximate	8.91	$C_{24}H_{27}N_3O_4$	**422.20743**	439.23398	444.18938		
fentrazamide	7.74	$C_{16}H_{20}ClN_5O_2$	350.13783	367.16438	372.11977	$C_{10}H_{17}N_2O_2^+$	**197.12845**
fluazifop-butyl	8.64	$C_{19}H_{20}F_3NO_4$	**384.14172**	401.16827	406.12366		
flubendiamide	7.37	$C_{23}H_{22}F_7IN_2O_4S$	683.03060	700.05715	705.01255	$C_{13}H_{15}INO_4S^+$	**407.97611**
flucarbazone	3.09	$C_{12}H_{11}F_3N_4O_6S$	**397.04242**	414.06897	419.02436		
fluoxastrobin	7.11	$C_{21}H_{16}ClFN_4O_5$	**459.08660**	476.11315	481.06855		
flutolanil	6.99	$C_{17}H_{16}F_3NO_2$	**324.12059**	341.14714	346.10253		
flutriafol	5.22	$C_{16}H_{13}F_2N_3O$	**302.10994**	319.13649	324.09189		
forchlorfenuron	5.17	$C_{12}H_{10}ClN_3O$	**248.05852**	265.08507	270.04046		
fosthiazate	5.23	$C_9H_{18}NO_3PS_2$	**284.05385**	301.08040	306.03580		
fuberidazole	3.78	$C_{11}H_8N_2O$	**185.07094**	202.09749	207.05288		
furathiocarb	8.52	$C_{18}H_{26}N_2O_5S$	**383.16352**	400.19007	405.14547		
griseofulvin	5.46	$C_{17}H_{17}ClO_6$	**353.07864**	370.10519	375.06059		
haloxyfop	4.75	$C_{15}H_{11}ClF_3NO_4$	**362.04015**	379.06670	384.02209		
hydroxycarbofuran (3-OH)	3.25	$C_{12}H_{15}NO_4$	238.10739	255.13393	260.08933	$C_{12}H_{14}NO_3^+$	**220.09682**
imazamethabenz-methyl	4.50	$C_{16}H_{20}N_2O_3$	**289.15467**	306.18122	311.13661		
imidacloprid	3.31	$C_9H_{10}ClN_5O_2$	**256.05958**	273.08613	278.04152		
indoxacarb	8.12	$C_{22}H_{17}ClF_3N_3O_7$	**528.07799**	545.10454	550.05994		
ipconazole	7.54	$C_{18}H_{24}ClN_3O$	**334.16807**	351.19462	356.15001		
iprovalicarb	6.42	$C_{18}H_{28}N_2O_3$	**321.21727**	338.24382	343.19921		
isocarbamide	3.24	$C_8H_{15}N_3O_2$	**186.12370**	203.15025	208.10565		
isoprocarb	5.56	$C_{11}H_{15}NO_2$	194.11756	211.14410	216.09950	$C_9H_{13}O^+$	**137.09609**
isoxadifen-ethyl	7.49	$C_{18}H_{17}NO_3$	**296.12812**	313.15467	318.11007		
isoxathion	8.03	$C_{13}H_{16}NO_4PS$	**314.06105**	331.08759	336.04299		
linuron	6.24	$C_9H_{10}Cl_2N_2O_2$	**249.01921**	266.04576	271.00116		
mandipropamid	6.61	$C_{23}H_{22}ClNO_4$	**412.13101**	429.15756	434.11296		
mepanipyrim	6.76	$C_{14}H_{13}N_3$	**224.11822**	241.14477	246.10017		
mephosfolan	4.42	$C_8H_{16}NO_3PS_2$	**270.03820**	287.06475	292.02015		
methabenzthiazuron	4.98	$C_{10}H_{11}N_3OS$	**222.06956**	239.09611	244.05151		
methidathion	6.16	$C_6H_{11}N_2O_4PS_3$	302.96914	319.99569	324.95108	$C_4H_5N_2O_2S^+$	**145.00663**
methiocarb	6.17	$C_{11}H_{15}NO_2S$	226.08963	243.11618	248.07157	$C_9H_{13}OS^+$	**169.06816**
methiocarb sulfone	3.84	$C_{11}H_{15}NO_4S$	**258.07946**	275.10601	280.06140		
methiocarb sulfoxide	3.06	$C_{11}H_{15}NO_3S$	**242.08454**	259.11109	264.06649		
methomyl	2.40	$C_5H_{10}N_2O_2S$	163.05358	180.08013	185.03552	$C_3H_6NS^+$	**88.02155**
methoxyfenozide	6.84	$C_{22}H_{28}N_2O_3$	369.21727	386.24382	391.19921	$C_{18}H_{21}N_2O_3^+$	**313.15467**
metolcarb	4.46	$C_9H_{11}NO_2$	166.08626	183.11280	188.06820	$C_7H_9O^+$	**109.06479**
metosulam	3.90	$C_{14}H_{13}Cl_2N_5O_4S$	**418.01381**	435.04036	439.99575		
metoxuron	4.14	$C_{10}H_{13}ClN_2O_2$	**229.07383**	246.10038	251.05578		
mexacarbate	6.51	$C_{12}H_{18}N_2O_2$	**223.14410**	240.17065	245.12605		
molinate	6.51	$C_9H_{17}NOS$	**188.11036**	205.13691	210.09231		
monocrotophos	2.41	$C_7H_{14}NO_5P$	224.06824	241.09479	246.05018	$C_6H_{10}O_5P^+$	193.02604
napropamide	6.77	$C_{17}H_{21}NO_2$	**272.16451**	289.19105	294.14645		
naptalam	3.37	$C_{18}H_{13}NO_3$	292.09682	309.12337	314.07877	$C_{10}H_{10}N^+$	**144.08078**
neburon	7.16	$C_{12}H_{16}Cl_2N_2O$	**275.07125**	292.09779	297.05319		
ofurace	5.33	$C_{14}H_{16}ClNO_3$	**282.08915**	299.11570	304.07109		
oxadixyl	4.48	$C_{14}H_{18}N_2O_4$	**279.13393**	296.16048	301.11588		
oxamyl-oxime	1.61	$C_5H_{10}N_2O_2S$	**163.05358**	180.08013	185.03552		
oxycarboxine	4.04	$C_{12}H_{13}NO_4S$	**268.06381**	285.09036	290.04575		

Table 1. continued

compound 1[c]	retention time (min) 2	molecular formula 3	[M + H]+ 4	[M + NH4]+ 5	[M + Na]+ 6	elemental composition 7	exact mass 8
				precursor[a,b] exact mass		fragment[a,b]	
paclobutrazol	6.05	$C_{15}H_{20}ClN_3O$	**294.13677**	311.16332	316.11871		
pencycuron	7.90	$C_{19}H_{21}ClN_2O$	**329.14152**	346.16807	351.12346		
penoxsulam	4.00	$C_{16}H_{14}F_5N_5O_5S$	**484.07086**	501.09741	506.05280		
picolinafen	8.36	$C_{19}H_{12}F_4N_2O_2$	**377.09077**	394.11732	399.07271		
picoxystrobin	7.49	$C_{18}H_{16}F_3NO_4$	368.11042	385.13697	390.09236	$C_{12}H_{13}O_3{}^+$	**205.08592**
piperophos	8.09	$C_{14}H_{28}NO_3PS_2$	**354.13210**	371.15865	376.11405		
pretilachlor	8.18	$C_{17}H_{26}ClNO_2$	**312.17248**	329.19903	334.15443		
primisulfuron-methyl	4.73	$C_{15}H_{12}F_4N_4O_7S$	**469.04356**	486.07011	491.02551		
prodiamine	8.48	$C_{13}H_{17}F_3N_4O_4$	**351.12747**	368.15402	373.10941		
propamocarb	1.95	$C_9H_{20}N_2O_2$	**189.15975**	206.18630	211.14170		
propoxur	4.84	$C_{11}H_{15}NO_3$	210.11247	227.13902	232.09441	$C_8H_{10}NO_3{}^+$	**168.06552**
pymetrozine	2.15	$C_{10}H_{11}N_5O$	**218.10364**	235.13019	240.08558		
pyraclostrobin	7.75	$C_{19}H_{18}ClN_3O_4$	**388.10586**	405.13241	410.08781		
pyraflufen-ethyl	7.58	$C_{15}H_{13}Cl_2F_3N_2O_4$	**413.02772**	430.05427	435.00967		
pyridaphenthion	6.67	$C_{14}H_{17}N_2O_4PS$	**341.07194**	358.09849	363.05389		
pyridate	10.00	$C_{19}H_{23}ClN_2O_2S$	**379.12415**	396.15070	401.10610		
pyrifenox	6.85	$C_{14}H_{12}Cl_2N_2O$	**295.03995**	312.06649	317.02189		
pyrimethanil	6.09	$C_{12}H_{13}N_3$	**200.11822**	217.14477	222.10017		
pyriproxyfen	8.65	$C_{20}H_{19}NO_3$	**322.14377**	339.17032	344.12571		
pyriquilon	4.14	$C_{11}H_{11}NO$	**174.09134**	191.11789	196.07329		
pyroxsulam	3.19	$C_{14}H_{13}F_3N_6O_5S$	**435.06930**	452.09585	457.05125		
quinoxyfen	8.39	$C_{15}H_8Cl_2FNO$	**308.00397**	325.03052	329.98592		
quizalofop	4.36	$C_{17}H_{13}ClN_2O_4$	**345.06366**	362.09021	367.04561		
quizalofop-ethyl	8.21	$C_{19}H_{17}ClN_2O_4$	**373.09496**	390.12151	395.07691		
schradan	3.18	$C_8H_{24}N_4O_3P_2$	**287.13964**	304.16619	309.12159		
simeconazole	6.49	$C_{14}H_{20}FN_3OSi$	**294.14324**	311.16979	316.12519		
spinosyn A	9.65	$C_{41}H_{65}NO_{10}$	**732.46813**	749.49467	754.45007		
spinosyn D	10.12	$C_{42}H_{67}NO_{10}$	**746.48378**	763.51032	768.46572		
spirodiclofen	9.51	$C_{21}H_{24}Cl_2O_4$	**411.11244**	428.13899	433.09439		
spiromesifen	9.39	$C_{23}H_{30}O_4$	371.22169	388.24824	393.20363	$C_{17}H_{21}O_3{}^+$	**273.14852**
spirotetramat	6.36	$C_{21}H_{27}NO_5$	**374.19620**	391.22275	396.17815		
sulfentrazone	4.70	$C_{11}H_{10}Cl_2F_2N_4O_3S$	386.98915	**404.01570**	408.97110		
tebufenozide	7.29	$C_{22}H_{28}N_2O_2$	**353.22235**	370.24890	375.20430		
tebufenpyrad	8.27	$C_{18}H_{24}ClN_3O$	**334.16807**	351.19462	356.15001		
tebupirimfos	8.76	$C_{13}H_{23}N_2O_3PS$	**319.12398**	336.15053	341.10592		
tepraloxydim	3.71	$C_{17}H_{24}ClNO_4$	**342.14666**	359.17321	364.12861		
tetraconazole	6.72	$C_{13}H_{11}Cl_2F_4N_3O$	**372.02881**	389.05536	394.01075		
thiabendazole	3.58	$C_{10}H_7N_3S$	**202.04335**	219.06989	224.02529		
thiabendazole-d_4 (IS)	3.58	$C_{10}H_3D_4N_3S$	**206.06845**	223.09500	228.05040		
thiacloprid	4.04	$C_{10}H_9ClN_4S$	**253.03092**	270.05747	275.01287		
thiamethoxam	2.79	$C_8H_{10}ClN_5O_3S$	**292.02657**	309.05312	314.00851		
thiazopyr	7.76	$C_{16}H_{17}F_5N_2O_2S$	**397.10037**	414.12691	419.08231		
thiodicarb	4.86	$C_{10}H_{18}N_4O_4S_3$	**355.05630**	372.08285	377.03824		
thiofanox	5.23	$C_9H_{18}N_2O_2S$	**219.11618**	236.14273	241.09812		
thiofanox sulfone	3.54	$C_9H_{18}N_2O_4S$	**251.10601**	268.13256	273.08795		
thiofanox sulfoxide	2.93	$C_9H_{18}N_2O_3S$	235.11109	252.13764	257.09304	$C_3H_6NOS{}^+$	**104.01646**
tolfenpyrad	8.34	$C_{21}H_{22}ClN_3O_2$	**384.14733**	401.17388	406.12928		
tralkoxydim	6.28	$C_{20}H_{27}NO_3$	**330.20637**	347.23292	352.18832		
trichlorfon	3.03	$C_4H_8Cl_3O_4P$	**256.92986**	273.95641	278.91180		
tricyclazole	3.65	$C_9H_7N_3S$	**190.04335**	207.06989	212.02529		
trietazine	6.81	$C_9H_{16}ClN_5$	**230.11670**	247.14325	252.09864		
trifloxysulfuron	3.68	$C_{14}H_{14}F_3N_5O_6S$	**438.06897**	455.09552	460.05091		
triforine	5.48	$C_{10}H_{14}Cl_6N_4O_2$	**432.93207**	449.95862	454.91402		
trimethacarb	5.56	$C_{11}H_{15}NO_2$	194.11756	211.14410	216.09950	$C_9H_{13}O{}^+$	**137.09609**
zinophos	5.88	$C_8H_{13}N_2O_3PS$	**249.04573**	266.07228	271.02767		
zoxamide	7.67	$C_{14}H_{16}Cl_3NO_2$	**336.03194**	353.05849	358.01388		

Table 1. continued

[a]Number or text in bold font indicates ionization form or charge state for data processing or quantification. [b]The electron mass (0.000549 amu) is subtracted when calculating exact mass. [c]Column number.

vegetables at low parts-per-billion (ppb) concentration levels.[7,8] LC−triple-quadrupole tandem mass spectrometry (LC-MS/MS) is the most commonly used LC-MS technique for this purpose as a result of its high selectivity and sensitivity. LC-MS/MS is based on multiple-reaction monitoring (MRM) and is practical to determine hundreds of targeted pesticides in a single analysis. However, LC-MS/MS requires extensive compound-dependent parameter optimization, which is time-consuming and tedious. Alternatively, LC can be coupled to full scan mass spectrometers such as Orbitrap and TOF, which have been increasingly used for quantification, identification, characterization, and structural elucidation of pharmaceuticals, pesticides, unknown contaminants, and their transformation or degradation products in foods and environmental samples.[9−12] Orbitrap and TOF mass spectrometers (recent advanced models) offer high resolution (>20000 FWHM), accurate mass measurement (<5 ppm), excellent full MS scan sensitivity, and complete mass spectral information. The full MS scan data allow for screening of targeted analytes, quantifying selected compounds, confirming positive findings, identifying unknowns or metabolites, and retrospective analysis even when appropriate standards are not available. Currently, the quadrupole Orbitrap can achieve a superior resolving power of 17000, 35000, 70000 or 140000 FWHM, which ensures highly accurate mass measurements and enables confident discrimination of coeluting, isobaric compounds in complex matrices. Moreover, Q-Orbitrap MS/MS and QqTOF MS/MS provide product-ion spectra with accurate mass measurement that permit unequivocal confirmation of compounds of interest. In routine practice, Orbitrap and TOF mass spectrometers in full MS scan mode have been favored for multiresidue screening purpose, and any incurred analytes will be confirmed using Q-Orbitrap MS/MS and QqTOF MS/MS.

In this paper, we demonstrate rapid quantification and accurate mass confirmation of 166 pesticides in fruits and vegetables at low ppb concentration levels using an UHPLC/ESI Q-Orbitrap along with the QuECHERs (quick, easy, cheap, effective, rugged, and safe) extraction procedure. The UHPLC/ESI Q-Orbitrap MS (i.e., full MS scan) for quantification was evaluated and the UHPLC/ESI Q-Orbitrap dd-MS[2] (i.e., data-dependent scan) for confirmation was demonstrated. UHPLC/ESI Q-Orbitrap mass spectrometer proved to be a very promising and powerful tool for the determination of pesticide residues in fruits and vegetables.

■ MATERIALS AND METHODS

Materials and Reagents. Five fruit and five vegetable blank samples were obtained from either local markets or previous year's sample monitoring program. Fruits included apple, banana, grape, orange, and strawberry. Vegetables included carrot, potato, tomato, cucumber, and lettuce. All samples were homogenized using a food processor, and 2 kg of each sample was prepared and kept in −20 °C. Pierce LTQ ESI positive ion calibration solution (10 mL) was purchased from ThermoFisher Scientific (Rockford, IL, USA). The calibration solution, which includes *n*-butylamine (m/z 74), caffeine (m/z 195 and its fragment m/z 138), Ultramark 1621 (m/z 1022, 1122, 1222, 1322, 1422, 1522, 1622, 1722, 1822), and MRFA (m/z 524), was used to tune and calibrate the Q-Orbitrap. Ammonium acetate (reagent grade or LC-MS grade) and LC-MS acetonitrile

(Chromasolv, 2.5 L) were purchased from Sigma-Aldrich Corp. (Canada). ENVIRO CLEAN extraction columns (6.0 g of anhydrous magnesium sulfate ($MgSO_4$) and 1.5 g of anhydrous sodium acetate, 50 mL centrifuge tubes) and ENVIRO CLEAN extraction columns [(900 mg of $MgSO_4$, 150 mg C_{18}, and 300 mg primary−secondary amine (PSA), 15 mL centrifuge tubes) or (900 mg of $MgSO_4$, 150 mg of ChloroFiltr, and 300 mg of PSA, 15 mL centrifuge tubes)] were from United Chemical Technologies, Inc. (Bristol, PA, USA). Acetic acid (glacial acetic acid, reagent grade, 99.7%), acetonitrile (distilled in glass), and methanol (distilled in glass) were obtained from Caledon Laboratories Ltd. (Canada). Water (18.2 MΩ·cm) used for reagent and sample preparation was from a Burnstead Nanopure system (Thermo Scientific, USA). Pesticide standards (Table 1, column 1) were obtained from EQ Laboratories Inc. (USA), Riedel-de Haen AG (Germany), or Chem Service (USA). Internal standards carbendazim-d_4 and carbofuran-d_3 were purchased from EQ Laboratories Inc. (USA), and thiabendazole-d_4 was from Chemical Synthesis Services (Northern Ireland). LC vials were Mini-UniPrep syringeless filter devices with polypropylene housing and PVDF 0.45 μm membrane (Whatman Inc., USA).

Preparation of Standard Solutions. Individual pesticide standard stock solutions were generally prepared at a concentration of 4000.0 μg/mL in methanol. Due to their poor solubility in methanol, carbendazim was prepared at 200.0 μg/mL and a few of pesticides were prepared at 1000.0 or 2000.0 μg/mL (Table 2, column 1). Intermediate pesticide standard mix working solutions were prepared at two levels, that is, 10.0 and 15.0 μg/mL, from stock solutions. Stock and intermediate solutions were stored at −20 °C. A six-level pesticide standard mix working solution was prepared by transferring 0.1, 0.5, 2.0, 4.0, 6.0, and 10.0 mL of 10.0 μg/mL intermediate working solution into six separate 50 mL volumetric flasks and making up to volume with methanol to prepare 0.02, 0.1, 0.4, 0.8, 1.2, and 2.0 μg/mL standard solutions for constructing matrix-matched standard calibration curves. Four-level sample spike pesticide standard working solutions were prepared by transferring 1.0, 9.0, 24.0, and 40.0 mL of 15.0 μg/mL intermediate working solution into separate 50 mL volumetric flasks and making up to volume with methanol to prepare 0.3, 2.7, 7.2, and 12.0 μg/mL standard solutions for sample fortification. Internal standard working solutions (2.0 and 100.0 μg/mL) including carbofuran-d_3, carbendazim-d_4, and thiabendazole-d_4 were prepared in a mixture of acetonitrile and methanol (50:50, v/v). All working solutions were stored at 4 °C.

Preparation of Reagent Solutions. Acetonitrile/acetic acid (99 + 1, v/v) was prepared by mixing 990 mL of acetonitrile with 10 mL of acetic acid. Ammonium acetate (0.1 M) was prepared by weighing 7.7 g of ammonium acetate and dissolving in 800 mL of water. After transfer into a 1000 mL volumetric flask, the solution was made up to the volume with water. Solvent buffer was a mixture of 0.1 M ammonium acetate and methanol (50 + 50, v/v).

UHPLC/ESI Q-Orbitrap Parameters. The UHPLC/ESI Q-Orbitrap system consisted of an Accela 1250 LC pump and an Accela open autosampler coupled with a Q Exactive mass spectrometer (ThermoFisher Scientific, Germany). The system was controlled by Xcalibur 2.2 software.

Ultrahigh-Pressure Liquid Chromatography. UHPLC mobile phase B was acetonitrile, and mobile phase A was 10 mM ammonium acetate in water. The UHPLC column utilized was an Acquity UPLC BEH C_{18} 100 mm × 2.1 mm, 1.7 μm column (Waters, USA). Gradient profile and flow rate are shown in Table 3. Column oven temperature was set at 45 °C, and autosampler temperature was set at 5 °C. Injection volume was 5 μL, and total run time was 14 min.

Q-Orbitrap Parameters. Q-Exactive ion source was equipped with a heated electrospray ionization (HESI) probe and was tuned and calibrated using the calibration solution once a week. Q-Exactive was

Table 2. UHPLC/ESI Q-Orbitrap MS Method Perofmance Results

pesticide[l] 1	fruits				green vegetables				vegetables			
	overall recovery[a] (%) 2	intermediate precision[b] (%) 3	measurement uncertainty[c] (%) 4	peak height at LCL[d] (μg/kg) 5	overall recovery[a] (%) 6	intermediate precision[b] (%) 7	measurement uncertainty[c] (%) 8	peak height at LCL[d] (μg/kg) 9	overall recovery[a] (%) 10	intermediate precision[b] (%) 11	measurement uncertainty[c] (%) 12	peak height at LCL[d] (μg/kg) 13
abamectin B$_{1a}$[g]	102.4	12.2	28.6	77169 (S)	98.8	11.5	24.2	122524 (S)	102.8	8.9	18.0	236591 (S)
acetochlor	102.8	5.8	12.7	117570 (S)	103.2	8.6	17.7	115579 (S)	103.2	8.0	16.0	276643 (S)
aldicarb	103.1	5.7	11.5	158670 (S)	104.3	7.5	15.2	147629 (S)	101.4	8.9	18.0	180760 (S)
aldicarb sulfone	102.1	6.2	12.4	107380 (S)	105.0	8.2	16.7	110215 (S)	99.7	7.0	14.2	67527 (S)
aldicarb sulfoxide	99.5	5.5	11.1	61927 (S)	103.8	8.7	17.5	61641 (S)	103.9	12.2	24.5	982089 (S)
anilofos	103.5	7.0	15.1	830310 (S)	102.8	9.0	18.2	792003 (S)	101.1	9.0	18.2	711993 (S)
azaconazole	101.9	5.9	12.7	270064 (S)	102.6	7.1	15.0	422527 (S)				
benoxacor	101.8	18.6	37.6	36525 (100)	108.4	11.6	25.0	27982 (100)	105.1	11.8	24.2	54447 (100)
bitertanol	101.3	7.0	14.6	47532 (S)	98.1	8.2	16.9	49076 (S)	101.0	9.6	19.7	45347 (S)
bromuconazole	100.8	5.6	12.8	81640 (S)	99.4	8.3	18.0	84217 (S)	101.2	11.5	23.1	98470 (S)
butafenacil	103.9	10.6	21.3	131769 (S)	101.6	11.6	23.5	151301 (S)	103.3	15.5	31.2	270987 (S)
butocarboxim	102.7	4.8	9.7	52087 (25)	104.4	7.5	15.1	32790 (25)	101.1	9.8	19.8	230645 (25)
butocarboxim sulfoxide	97.8	5.7	11.8	42091 (S)	102.9	8.6	18.0	54208 (S)	98.1	7.2	14.5	46363 (S)
cadusafos	100.9	6.2	13.5	305964 (S)	99.8	8.4	17.8	309082 (S)	100.6	9.8	20.1	431577 (S)
carbaryl	104.9	5.2	10.7	280629 (S)	102.7	7.2	16.0	245204 (S)	103.0	7.7	15.4	1067225 (S)
carbendazim	101.6	5.3	10.7	2400869 (S)	102.3	6.0	13.1	2430336 (S)	99.5	6.3	12.7	2062283 (S)
carbetamide	103.6	6.3	12.6	410622 (S)	104.5	7.4	14.9	420283 (S)	102.8	6.8	13.7	453789 (S)
carbofuran	105.1	5.8	11.6	490562 (S)	105.5	6.8	14.2	583386 (S)	102.9	7.2	14.5	1026050 (S)
carfentrazone-ethyl	105.2	8.4	17.0	56503 (S)	105.0	11.0	22.2	55386 (S)	105.1	13.2	26.6	227544 (S)
chlorantraniliprole	101.9	6.2	13.6	148827 (S)	100.2	8.5	18.3	153770 (S)	102.7	9.2	18.7	151527 (S)
chlorbromuron	105.1	11.1	22.4	91031 (100)	98.1	18.8	38.2	21056 (25)	102.4	10.3	20.9	97824 (25)
chloridazon[f]	102.4	6.6	13.5	1697481 (S)	103.4	8.7	18.0	1737405 (S)	102.6	7.7	15.5	1616952 (S)
chlorimuron-ethyl	100.3	6.0	19.0	367037 (S)	96.5	8.2	19.3	371322 (S)	101.2	11.8	25.8	492066 (S)
chloroxuron	101.2	5.6	13.5	1247098 (S)	99.6	8.9	18.6	1058385 (S)	101.9	8.9	18.0	1629989 (S)
chlorthiamid	67.5	12.2	47.1	25249 (100)					71.3	18.6	42.7	134787 (100)
chlortoluron	103.3	5.4	11.1	1467087 (S)	103.2	7.3	15.0	1508484 (S)	103.0	8.4	16.9	2045472 (S)
clodinafop-propargyl	99.3	19.6	42.9	102203 (S)	98.7	18.0	36.4	90360 (S)	80.8	58.1	116.9	293725 (S)
cloquintocet-mexyl	102.6	11.7	24.3	1160758 (S)	98.3	11.9	24.9	1274275 (S)	104.0	14.8	30.3	1361812 (S)
clothianidin	100.8	5.9	12.9	26924 (S)	102.8	8.1	16.8	36675 (S)	101.3	9.5	19.3	105247 (S)
cyanofenphos	106.3	10.9	22.4	138714 (100)	102.5	10.7	21.8	38429 (25)	107.3	12.4	25.2	53420 (25)
cyazofamid	115.5	12.3	25.9	28591 (25)	118.0	12.7	27.7	22365 (25)	116.3	17.0	34.4	147954 (25)
cycloxydim	115.9	5.6	13.7	1811290 (25)	99.5	13.1	28.3	378211 (S)	114.0	12.2	24.6	515240 (S)
cycluron	100.9	5.6	11.6	2136075 (S)	103.4	6.7	14.9	2278888 (S)	101.2	8.5	17.0	2896257 (S)
cyromazin	72.8	7.1	19.8	650507 (S)	84.3	8.2	18.5	940217 (S)	78.2	8.3	20.6	572810 (S)
demeton-S-methyl sulfone[j]	103.6	5.6	11.2	692125 (S)	107.6	7.5	15.3	713712 (S)	104.0	7.5	15.1	1032205 (S)
demeton-S-methyl sulfoxide[f]	98.7	5.8	11.6	842266 (S)	103.1	7.9	15.9	701352 (S)	99.9	7.4	14.9	559045 (S)
desmedipham	101.9	5.5	12.0	188183 (S)	98.5	8.5	17.2	162876 (S)	102.5	9.8	19.8	392677 (S)

Table 2. continued

pesticide [1]	fruits				green vegetables				vegetables			
	overall recovery[a] (%) 2	intermediate precision[b] (%) 3	measurement uncertainty[c] (%) 4	peak height at LCL[d] (μg/kg) 5	overall recovery[a] (%) 6	intermediate precision[b] (%) 7	measurement uncertainty[c] (%) 8	peak height at LCL[d] (μg/kg) 9	overall recovery[a] (%) 10	intermediate precision[b] (%) 11	measurement uncertainty[c] (%) 12	peak height at LCL[d] (μg/kg) 13
dialifor	_123.8_	10.6	21.4	44238 (100)					_128.7_	16.1	32.5	70467 (25)
diethofencarb	103.8	5.4	10.9	331245 (S)	103.3	7.9	15.9	320941 (S)	103.7	8.0	16.1	845575 (S)
difenoconazole	101.4	5.9	13.3	255320 (S)	99.5	8.9	18.5	264197 (S)	102.2	10.7	21.6	261857 (S)
dimethametryn	102.2	6.1	13.4	2152996 (S)	98.5	9.0	18.5	2235562 (S)	101.4	9.4	19.0	2397179 (S)
dimethomorph	99.2	7.0	14.8	286728 (S)	99.2	8.5	17.4	450178 (S)	101.0	9.6	19.3	392189 (S)
dimetilan	103.3	6.1	12.2	1346466 (S)	106.3	8.0	16.2	1383267 (S)	103.8	7.6	15.2	1346204 (S)
dimoxystrobin	102.7	5.8	13.3	584555 (S)	101.5	8.3	17.6	580139 (S)	101.8	8.8	18.6	605917 (S)
diniconazole	101.1	5.1	11.9	193741 (S)	97.1	9.6	19.4	218270 (S)	100.9	10.2	20.4	429160 (S)
dioxacarb	102.4	6.0	12.8	442894 (S)	105.3	7.5	15.1	416213 (S)	102.3	8.8	17.7	591113 (S)
dipropetryn	102.3	6.0	13.4	2052584 (S)	98.6	9.0	18.2	2190186 (S)	101.6	9.6	19.7	2482095 (S)
diuron	104.2	5.0	10.7	191468 (S)	102.5	7.1	14.6	209233 (S)	100.8	6.5	13.9	737677 (S)
dodemorph	85.0	15.1	31.9	2575937 (S)	100.1	12.6	27.5	2502570 (S)	87.8	_20.7_	41.7	3583328 (S)
emamectin B$_{1a}$	92.8	9.2	20.6	165999 (S)	100.5	12.5	26.3	267392 (S)	92.5	16.2	33.1	212660 (S)
epoxiconazole	102.5	5.5	12.0	322321 (S)	101.4	8.7	17.7	339948 (S)	101.4	10.3	20.8	667902 (S)
ethiofencarb	102.7	5.8	12.2	177308 (S)	96.4	7.4	14.9	193250 (S)	103.3	9.2	18.5	425612 (S)
ethiofencarb sulfone	104.1	6.6	13.2	154269 (S)	104.5	7.6	16.9	153311 (S)	102.6	8.3	16.7	255253 (S)
ethiofencarb sulfoxide	103.1	6.7	13.5	656337 (S)	_111.5_	9.5	21.7	588968 (S)	103.3	7.5	15.1	374449 (S)
ethiprole	103.8	4.5	9.5	115709 (25)	104.9	9.2	18.8	15477 (S)	104.0	9.8	19.8	73121 (S)
ethirimol[f]	94.7	5.3	12.2	3670174 (S)	93.5	8.4	16.9	3420488 (S)	95.6	10.1	20.3	3842637 (S)
ethoprop	101.8	5.3	11.3	649444 (S)	102.2	7.5	15.5	535760 (S)	102.2	8.2	16.4	993505 (S)
etoxazole	103.8	15.5	31.1	1853351 (S)	100.2	13.7	27.7	2265949 (S)	103.6	15.3	30.9	2104452 (S)
fenamidone	102.3	5.6	12.1	1035814 (S)	101.0	8.0	16.3	1072374 (S)	102.1	9.1	18.3	1518883 (S)
fenazaquin	99.7	18.1	36.6	1781751 (S)	95.0	17.8	35.9	2107934 (S)	101.9	16.3	33.6	2042785 (S)
fenhexamid	100.0	5.4	12.5	124275 (25)	90.5	9.2	21.2	15245 (S)	98.1	14.1	28.3	61368 (S)
fenoxanil	103.6	6.0	12.2	31219 (S)	100.6	8.4	18.2	41841 (S)	103.0	9.3	18.7	132696 (S)
fenpropidin	96.6	_24.5_	49.5	1259172 (S)	103.3	15.6	31.5	1088563 (S)	96.3	_24.3_	49.0	1447735 (S)
fenpropimorph	92.7	15.2	32.1	1371247 (S)	100.0	12.6	25.8	1391719 (S)	95.8	_20.3_	40.9	2386923 (S)
fenpyroximate[f]	103.2	16.5	33.2	662245 (S)	98.9	14.4	29.4	841154 (S)	105.2	15.5	31.8	858374 (S)
fentrazamide	103.0	8.2	17.0	377393 (S)	100.9	10.4	21.1	405932 (S)	103.6	13.1	26.4	572303 (S)
fluazifop-butyl	104.9	16.4	33.3	699130 (S)	101.1	13.8	28.4	771149 (S)	105.8	17.8	35.9	1173503 (S)
flubendiamide	103.6	5.3	11.3	226217 (S)	103.5	8.5	17.1	307896 (S)	103.0	8.9	18.0	422656 (S)
flucarbazone	_66.5_	16.5	37.5	66085 (S)	_69.7_	18.6	37.6	67033 (S)	_71.8_	_23.2_	46.8	127232 (S)
fluoxastrobin	103.1	5.9	13.3	730047 (S)	102.8	8.7	19.0	682878 (S)	102.3	9.6	19.8	787518 (S)
flutolanil	103.8	4.9	11.1	395516 (S)	102.7	8.6	17.4	368231 (S)	103.3	10.5	21.2	944295 (S)
flutriafol	102.7	5.3	11.4	482971 (S)	101.5	7.2	15.6	555662 (S)	100.5	8.2	18.4	1120549 (S)
forchlorfenuron	99.9	5.2	11.5	770122 (S)	89.4	8.6	18.4	960341 (S)	99.8	10.4	20.9	1416743 (S)
fosthiazate	102.9	5.8	12.2	513100 (S)	104.2	6.4	13.9	474582 (S)	103.3	8.0	16.1	511408 (S)
fuberidazole	100.5	5.7	11.4	2643773 (S)	92.1	7.8	16.1	2869503 (S)	101.2	7.9	15.8	2467493 (S)
furathiocarb	102.8	8.5	17.7	703046 (S)	100.6	10.6	21.6	832850 (S)	104.0	12.2	24.5	1004478 (S)

Table 2. continued

pesticide [1]	fruits				green vegetables				vegetables			
	overall recovery[a] (%) 2	intermediate precision[b] (%) 3	measurement uncertainty[c] (%) 4	peak height at LCL[d] (µg/kg) 5	overall recovery[a] (%) 6	intermediate precision[b] (%) 7	measurement uncertainty[c] (%) 8	peak height at LCL[d] (µg/kg) 9	overall recovery[a] (%) 10	intermediate precision[b] (%) 11	measurement uncertainty[c] (%) 12	peak height at LCL[d] (µg/kg) 13
griseofulvin	103.2	5.6	12.0	520936 (5)	104.1	7.5	15.2	596841 (5)	103.3	9.1	18.3	908077 (5)
haloxyfop	**65.1**	13.5	29.7	30544 (25)	**55.0**	**22.7**	46.0	30788 (25)	**63.5**	**23.5**	47.5	147055 (25)
hydroxycarbofuran (3-OH)	103.3	5.6	11.5	267791 (5)	102.9	8.2	17.7	220672 (5)	102.3	8.4	16.9	382130 (5)
imazamethabenz-methyl	102.4	5.3	10.6	1598036 (5)	102.0	7.9	15.9	1721670 (5)	102.7	8.2	16.4	1348992 (5)
imidacloprid	102.7	6.4	14.0	351651 (5)	106.0	8.0	17.1	405996 (5)	104.4	7.8	15.7	355907 (5)
indoxacarb[e]	104.1	14.3	29.3	123943 (5)	104.0	12.8	25.9	120567 (5)	106.0	18.7	37.6	201010 (5)
ipconazole	101.6	5.3	12.2	415532 (5)	98.0	9.0	18.2	431282 (5)	101.9	9.8	19.6	620035 (5)
iprovalicarb	102.2	5.9	12.9	636873 (5)	103.1	7.9	16.0	524719 (5)	102.7	8.0	16.2	620765 (5)
isocarbamide	102.3	9.2	19.6	416075 (5)	105.7	10.9	22.7	480110 (5)	101.6	10.9	22.0	956683 (5)
isoprocarb	103.9	5.5	11.1	399869 (5)	103.3	6.9	14.0	409009 (5)	103.5	7.6	15.2	1072553 (5)
isoxadifen-ethyl	**116.4**	9.8	23.0	16919 (5)	**113.9**	11.4	23.2	61288 (25)	**115.6**	16.2	33.7	138430 (5)
isoxathion	**116.3**	11.8	45.7	23511 (5)	**114.7**	10.5	48.7	16624 (5)	**117.8**	16.3	48.3	144276 (5)
linuron[f]	102.9	6.1	12.3	35571 (25)	103.9	8.6	19.2	15055 (5)	103.9	8.4	16.9	27525 (5)
mandipropamid	103.0	6.0	12.2	484704 (5)	103.9	8.8	17.8	318093 (5)	102.8	9.9	19.9	432351 (5)
mepanipyrim	103.2	6.5	14.0	2095153 (5)	96.7	8.9	18.8	2161962 (5)	102.5	8.5	17.4	2468413 (5)
mephosfolan	102.9	5.5	11.9	2600460 (5)	104.5	8.1	16.4	2240453 (5)	102.8	8.1	16.4	2244791 (5)
methabenzthiazuron	102.7	5.2	10.5	969133 (5)	98.3	7.2	15.8	935748 (5)	102.2	7.8	15.7	1500952 (5)
methidathion[f]	103.5	5.8	11.7	89948 (25)	106.2	9.1	21.6	30372 (5)	107.0	9.7	21.1	132092 (5)
methiocarb	103.7	4.9	10.3	154581 (25)	101.8	7.6	16.0	30468 (5)	103.3	8.9	17.9	240363 (5)
methiocarb sulfone	**117.8**	4.3	15.8	45637 (25)	**120.8**	7.8	21.2	31530 (25)	**114.0**	11.7	24.9	268770 (25)
methiocarb sulfoxide[f]	105.4	5.7	11.7	1267904 (5)	107.8	6.8	14.9	1166443 (5)	105.5	8.7	17.8	1202150 (5)
methomyl	105.5	6.1	12.3	693395 (25)	108.8	10.0	20.1	123675 (5)	104.6	6.3	12.7	504222 (25)
methoxyfenozide	102.5	5.5	12.6	443502 (5)	101.3	8.7	17.8	447342 (5)	102.0	9.2	19.3	517866 (5)
metolcarb	103.4	6.1	12.8	127386 (25)	104.4	6.3	15.6	329199 (100)	102.0	7.8	15.7	438644 (25)
metosulam	99.3	5.8	12.7	552432 (5)	98.2	9.1	18.4	798806 (5)	102.2	12.9	25.9	830882 (5)
metoxuron	102.8	6.3	12.6	1926642 (5)	104.4	7.3	14.8	1794754 (5)	102.9	7.7	15.4	1859150 (5)
mexacarbate[f]	101.2	6.0	12.5	1719433 (5)	100.7	8.6	17.4	1660771 (5)	101.6	9.4	18.9	2251321 (5)
molinate	98.7	6.6	15.2	36868 (5)	96.6	8.2	17.8	23928 (5)	100.1	8.6	17.5	36538 (5)
monocrotophos[f,h]	101.4	6.3	12.6	3008898 (5)	103.5	8.1	16.6	475045 (5)	100.7	7.7	15.5	343860 (5)
napropamide	102.5	5.7	12.8	1894592 (5)	101.3	8.7	17.7	1954392 (5)	103.3	9.0	18.2	1827299 (5)
naptalam	**42.9**	**21.1**	**62.1**	762564 (5)	**32.1**	**32.3**	65.2	963277 (5)	**44.2**	**33.9**	68.2	595161 (5)
neburon	102.7	5.2	11.5	296329 (5)	98.5	9.4	19.0	389970 (5)	102.0	9.7	19.5	815083 (5)
ofurace	104.2	6.0	12.0	604415 (5)	106.2	6.9	13.9	513166 (5)	104.0	8.4	16.9	1323644 (5)
oxadixyl[f]	103.1	5.8	11.9	299559 (5)	104.3	7.8	15.9	224891 (5)	102.9	8.6	17.3	224292 (5)
oxamyl-oxime	99.4	6.7	13.4	72126 (5)	99.7	7.9	17.6	87355 (5)	98.1	7.7	15.5	100687 (5)
oxycarboxine[f]	101.9	5.4	11.0	326392 (5)	102.7	7.6	15.4	355644 (5)	101.2	8.8	17.7	599861 (5)
paclobutrazol	102.0	6.0	12.9	581234 (5)	101.2	8.7	18.7	624107 (5)	102.2	9.0	18.2	1098399 (5)
pencycuron	102.6	6.3	13.6	1137106 (5)	97.7	10.0	20.3	1289799 (5)	103.2	11.5	23.2	1475228 (5)

Table 2. continued

pesticide[1] 1	fruits				green vegetables				vegetables			
	overall recovery[a] (%) 2	intermediate precision[b] (%) 3	measurement uncertainty[c] (%) 4	peak height at LCL[d] (μg/kg) 5	overall recovery[a] (%) 6	intermediate precision[b] (%) 7	measurement uncertainty[c] (%) 8	peak height at LCL[d] (μg/kg) 9	overall recovery[a] (%) 10	intermediate precision[b] (%) 11	measurement uncertainty[c] (%) 12	peak height at LCL[d] (μg/kg) 13
penoxsulam	100.5	6.3	15.1	626500 (5)	98.1	9.2	18.7	753909 (5)	101.5	10.4	21.0	557905 (5)
picolinafen	105.4	20.2	40.9	25948 (5)	102.2	15.5	32.0	23622 (5)	107.6	21.6	43.5	91280 (5)
picoxystrobin	104.0	8.1	16.4	708698 (5)	103.4	9.3	18.8	706360 (5)	104.7	13.0	26.2	1083935 (5)
piperophos	102.8	7.1	14.7	1244048 (5)	102.5	9.7	19.6	1349847 (5)	103.7	11.8	24.1	1539034 (5)
pretilachlor	102.9	6.3	13.5	435270 (5)	103.3	9.7	19.7	570436 (5)	103.7	10.2	20.6	551730 (5)
primisulfuron-methyl[e]	88.2	8.2	24.4	171848 (5)	80.1	10.7	26.6	181500 (5)	89.9	12.9	29.2	132970 (5)
prodiamine	106.5	11.3	23.8	29570 (25)	104.4	12.4	25.1	7061 (5)	109.3	16.6	33.6	61158 (25)
propamocarb	85.7	6.1	16.1	679056 (5)	99.5	8.1	16.4	639611 (5)	88.2	13.2	26.6	528393 (5)
propoxur	104.4	6.0	12.1	313990 (5)	105.3	7.9	15.9	241832 (5)	103.4	7.7	15.5	505582 (5)
pymetrozine	87.1	6.8	17.7	829188 (5)	94.7	9.6	24.8	1354741 (5)	94.3	7.6	15.4	677420 (5)
pyraclostrobin	103.3	9.0	19.4	684631 (5)	98.9	10.2	20.8	688556 (5)	103.8	13.4	27.4	677261 (5)
pyraflufen-ethyl	104.5	8.4	18.3	63499 (5)	100.3	11.6	23.8	69261 (5)	98.7	15.9	40.2	179387 (5)
pyridaphenthion	114.5	5.6	36.5	115148 (5)	116.6	7.0	41.6	73872 (5)	114.5	11.1	39.2	424889 (5)
pyridate	96.1	28.3	83.7	44519 (5)	58.5	23.9	114.3	23134 (5)	96.1	31.9	88.2	139705 (5)
pyrifenox	97.5	9.7	22.7	495997 (5)	94.1	13.1	33.2	547843 (5)	98.7	11.8	24.1	719940 (5)
pyrimethanil	100.9	5.7	12.9	542711 (5)	97.1	8.5	17.2	504824 (5)	102.0	8.3	16.8	731461 (5)
pyriproxyfen	104.3	19.1	38.9	1078008 (5)	93.4	15.1	31.0	1004136 (5)	106.5	17.5	35.7	1366270 (5)
pyroquilon	101.0	5.6	11.4	663957 (5)	103.6	7.9	16.2	717122 (5)	100.8	8.1	16.3	1651090 (5)
pyroxsulam	97.6	7.0	15.2	828322 (5)	93.5	7.2	18.1	951716 (5)	97.2	11.9	24.3	730526 (5)
quinoxyfen	101.0	14.6	29.4	399394 (5)	90.4	14.7	30.4	382075 (5)	102.6	14.8	29.9	759480 (5)
quizalofop	56.9	14.0	37.6	147934 (25)	43.9	26.0	52.5	36701 (5)	56.7	26.7	53.7	72192 (5)
quizalofop-ethyl	102.7	11.2	24.1	216459 (5)	100.9	12.3	25.0	227652 (5)	98.7	22.7	45.8	490394 (5)
schradan[e]	94.5	5.4	11.6	1425047 (5)	100.1	7.7	17.5	1750622 (5)	95.7	9.0	18.1	1496147 (5)
simeconazole	102.1	5.2	11.5	535746 (5)	102.4	8.8	17.7	570036 (5)	101.4	8.9	17.9	1257285 (5)
spinosyn A	92.7	11.9	24.1	567958 (5)	102.2	11.6	25.2	618642 (5)	92.9	27.9	56.4	291746 (5)
spinosyn D	91.3	11.9	24.6	284289 (5)	102.2	23.6	47.7	331481 (5)				
spirodiclofen	102.1	15.1	31.7	87013 (25)	96.8	16.2	32.7	22083 (5)	105.7	20.1	40.4	107255 (5)
spiromesifen	88.8	16.8	48.4	1545476 (5)	70.2	16.4	57.0	1565366 (5)	88.9	16.6	42.7	2435638 (5)
spirotetramat	98.4	5.3	12.1	1344257 (5)	96.0	9.3	18.9	1151623 (5)	97.8	10.7	21.6	1173217 (5)
sulfentrazone	104.5	6.9	13.8	23408 (5)	102.3	7.5	17.3	25127 (5)	103.2	10.5	21.5	69703 (5)
tebufenozide	102.9	6.3	14.5	112445 (5)	100.5	7.6	16.8	117195 (5)	101.2	10.0	21.6	52607 (5)
tebufenpyrad	102.7	7.3	15.1	275640 (5)	99.6	10.6	21.3	357091 (5)	103.9	10.4	20.9	526551 (5)
tebupirimfos	103.6	10.9	22.1	304403 (5)	102.7	12.7	25.7	448945 (5)	104.6	11.9	24.4	425337 (5)
tepraloxydim	138.3	7.4	15.1	70750 (5)	142.7	11.5	23.3	104356 (5)	136.4	8.4	16.9	162896 (5)
tetraconazole	103.3	5.3	11.8	172422 (5)	104.2	9.2	18.8	168151 (5)	103.3	9.6	19.3	373439 (5)
thiabendazole	105.9	5.6	11.8	1855915 (5)	107.8	6.9	14.6	2064229 (5)	103.8	7.6	15.8	1577775 (5)
thiacloprid	103.0	5.8	11.9	703725 (5)	104.9	7.7	15.5	832479 (5)	102.3	7.5	15.0	1074920 (5)
thiamethoxam	101.3	5.9	12.1	412331 (5)	103.8	7.3	15.2	467792 (5)	102.6	7.5	15.0	325795 (5)
thiazopyr	103.5	7.7	15.9	365536 (5)	103.4	10.6	21.4	410410 (5)	103.5	13.6	27.4	662516 (5)

Table 2. continued

pesticide[i] 1	fruits				green vegetables				vegetables			
	overall recovery[a] (%) 2	intermediate precision[b] (%) 3	measurement uncertainty[c] (%) 4	peak height at LCL[d] (µg/kg) 5	overall recovery[a] (%) 6	intermediate precision[b] (%) 7	measurement uncertainty[c] (%) 8	peak height at LCL[d] (µg/kg) 9	overall recovery[a] (%) 10	intermediate precision[b] (%) 11	measurement uncertainty[c] (%) 12	peak height at LCL[d] (µg/kg) 13
thiodicarb[f]	99.7	7.8	18.0	299431 (5)	99.1	10.1	23.5	320863 (5)	100.0	13.0	27.4	280499 (5)
thiofanox	104.6	6.9	14.7	118901 (100)	103.1	7.3	16.5	79155 (100)	104.9	9.8	19.9	48170 (100)
thiofanox sulfone	103.6	6.5	13.0	124591 (5)	102.2	9.3	23.9	120317 (5)	103.2	7.1	14.3	99497 (5)
thiofanox sulfoxide	101.5	6.4	12.9	179472 (5)	109.3	11.7	23.9	163072 (5)	102.1	7.0	14.0	187045 (5)
tolfenpyrad	102.1	10.0	20.7	99710 (5)	95.4	11.1	22.9	156333 (5)	104.0	11.3	23.4	230429 (5)
tralkoxydim	**113.6**	7.7	18.7	596236 (5)	**113.5**	11.4	23.0	488206 (5)	**113.4**	8.2	16.9	706532 (5)
trichlorfon	106.3	7.4	16.7	7786 (5)	105.4	8.8	17.9	80673 (25)	103.6	11.3	23.5	90431 (5)
tricyclazole[f]	99.3	5.8	11.7	2549785 (5)	102.3	7.7	16.3	2509138 (5)	100.4	7.1	14.3	2403812 (5)
trietazine	102.0	5.5	12.2	856299 (5)	100.5	8.1	16.6	870888 (5)	101.3	8.6	17.7	1117259 (5)
trifloxysulfuron	97.5	6.6	22.8	661420 (5)	97.0	8.2	26.7	778158 (5)	100.5	10.9	24.0	513570 (5)
triforine[e]					100.2	9.9	28.8	13238 (25)	98.8	12.5	26.9	30496 (25)
trimethacarb[f]	103.9	5.5	11.1	400345 (5)	103.3	6.9	14.0	409009 (5)	103.6	7.5	15.1	1060121 (5)
zinophos	103.8	5.7	13.0	1309190 (100)	106.5	7.8	15.7	150773 (25)	**113.0**	7.5	34.1	28303 (5)
zoxamide	102.7	5.5	11.9	118200 (5)	100.6	9.2	18.6	153328 (5)	102.5	11.3	22.8	328980 (5)

[a] Underlined entries in bold font are pesticides with recoveries not in the range of 81–110%. [b] Underlined entries in bold font are pesticides with intermediate precision >20%. [c] Underlined entries in bold font are pesticides with MU >50%. [d] Peak height (NL) was determined at the lowest concentration level (LCL; µg/kg, in bracket) in orange, carrot, and lettuce, respectively. When LCL 5 µg/kg, the method performance is evaluated on the basis of four spike levels. When LCL is 25 µg/kg, method performance was based on three spike levels, i.e, 90.0, 240.0, and 400.0 µg/kg, due to its poor sensitivity. When LCL is 100 µg/kg, method performance was based on two spike levels, i.e, 240.0 and 400.0 µg/kg, due to its poor sensitivity. [e] Pesticides have a relatively low solubility in methanol. Stock solution was prepared in 1000.0 µg/mL. [f] Pesticides have a relatively low solubility in methanol. Stock solution was prepared in 2000.0 µg/mL. [g] Method performance was evaluated from matices of apple, orange, and strawberry. [h] Method performance was evaluated from apple, banana, grape, and strawberry. [i] Column number.

Table 3. Ultrahigh-Performance Liquid Chromatographic Gradient Profiles and MS Parameters

UPLC BHE C_{18}, 1.7 μm			
total time	flow rate (μL/min)	A (%)	B (%)
0.0	400	92	8
9.0	400	5	95
9.1	400	0	100
11.0	400	0	100
11.1	400	92	8
14.0	400	92	8
Q-Exactive Parameters			
sheath gas flow rate		60	
auxiliary gas flow rate		30	
sweep gas flow rate		2	
spray voltage (kV)		3.50	
capillary temperature (°C)		350	
S-lens level		55.0	
heater temperature (°C)		350	

operated in either full MS-SIM or full MS/dd-MS^2 (TopN) positive mode. In full MS-SIM, the Q-Oritrap performs full MS scan without high-energy collision dissociation (HCD) fragmentation. The full MS scan ranges were set as dual from m/z 65.0 to 950.0 (0−12.0 min) and from m/z 460.0 to 950.0 (9.1−11.0 min). The mass resolution was tuned into 70000 FWHM at m/z 200. Automatic gain control (AGC) target (the number of ions to fill C-Trap) was set at 1.0E6 with a maximum injection time (IT) of 250 ms. All quantitative data in this study were acquired using full MS-SIM mode. In full MS/dd-MS^2 (TopN), which is used for confirmatory purpose, the Q-Orbitrap performs data-dependent scans. This experiment comprises a full MS scan followed by a data-dependent scan with a fragmentation energy applied. Ions of the second scan event enter the HCD collision cell, and ions of the first do not. That is, it first scans the list of masses that are included in the inclusion list as shown in Table 1, column 4. At this stage, mass resolution was set at 70000 FWHM, AGC target at 1.0E6, maximum IT at 250 ms, and scan range from m/z 65.0− 950.0. As long as the targeted compounds were detected within a 10 ppm mass error window and their intensities reached the threshold (for example, 8.3E4), precursor ions that were selected by the quadrupole were sent to the HCD collision cell of the Q-Exactive mass spectrometer. Here, they were fragmented with normalized collision energy (NCE) to obtain product-ion spectra. At this stage, the mass resolution was set at 17500 FWHM, AGC target at 2E5, maximum IT 120 ms, isolation window 4.0 m/z, NCE 35%, underfill ratio 5.0%, intensity threshold 8.3E4, apex trigger 3−6 s, and dynamic exclusion 10.0 s. Other mass spectrometric parameters are shown in Table 3.

Sample Preparation and Extraction Procedure. Sample extraction and cleanup procedures followed the buffered QuEChERS[13] or AOAC Official Method 2007.01[14] with a slight modification. For the fortification experiment, fruit and vegetable samples (15.0 g/ sample) were weighed into individual 50 mL polypropylene centrifuge tubes (VWR International, Canada). Five hundred microliters per four-level sample spike pesticide standard working solution was added into four centrifuge tubes to provide 10.0, 90.0, 240.0, and 400.0 μg/kg of pesticides equivalent in sample, followed by the addition of 15 μL of 100.0 μg/mL internal calibration standard working solution (100.0 μg/kg equivalent in sample). Tubes were capped, mixed, and left to stand for 15 min at room temperature. Then, 15 mL of acetonitrile/ acetic acid (99 + 1, v/v) mixture was added to individual samples and mixed for 45 s, followed by adding 1.5 g of anhydrous sodium acetate and 6.0 g of anhydrous magnesium sulfate from ENVIRO CLEAN extraction columns. The centrifuge tubes were capped, shaken at 1500 rpm using a Geno/Grinder 2010 (SPEX SamplePrep, USA) for 1 min, and then centrifuged at 3000 rpm (∼2100g) for 3 min using an Allegra 6 centrifuge (Beckman Coulter Inc., USA). Supernatants were transferred (7 mL/sample) into individual 15 mL polypropylene centrifuge tubes or ENVIRO CLEAN extraction columns that contain

900 mg of MgSO$_4$, 150 mg of C$_{18}$, and 300 mg of PSA for regular samples or 900 mg of MgSO$_4$, 150 mg of ChloroFiltr, and 300 mg of PSA for cucumber and lettuce samples (rich in chlorophyll). The centrifuge tubes were capped, shaken by hand for 45 s, and centrifuged at 3000 rpm (∼2100g) for 3 min. One milliliter of supernatants (1 g sample/mL) was transferred into individual 5 mL Pyrex brand centrifuge tubes, precalibrated with 1 mL volume accuracy (VWR International, Canada). Each of the sample extracts was evaporated to 0.1−0.2 mL, which took approximately 0.5 h, using an N-EVAP nitrogen evaporator (Organomation Associates Inc., USA) at 30 °C under a stream of nitrogen. The extracts were made up to 0.5 mL with methanol, vortexed for 30 s, and then made up to 1.0 mL with 0.1 M ammonium acetate and vortexed again for 30 s. One hundred microliters of each extract was transferred into a Mini-UniPrep vial (Whatman Inc., USA), and 500 μL of solvent buffer was added. The vials were capped, vortexed for 30 s, and pressed to filter the solution. Sample extracts were ready for UHPLC/ESI Q-Orbitrap injection.

Preparation of Matrix-Matched Calibration Standards and Calculation. Matrix-matched calibration standards were prepared by adding standards and internal standards to blank sample extracts after sample extraction and cleanup. A blank fruit or vegetable sample (15.0 g/sample) was weighed into a 50 mL centrifuge tube, and the sample was processed through the extraction procedure as described above. Two hundred and fifty microliters of each six-level pesticide standard mix working solution was transferred into each of six blank sample extracts (1.0 mL/tube), providing 5.0, 25.0, 100.0, 200.0, 300.0, and 500.0 μg/kg of per standard equivalent in samples. Then, 50 μL of 2.0 μg/mL internal calibration working solution was added to each sample (100.0 μg/kg equivalent in sample). The extracts were made up to 0.5 mL with methanol, vortexed for 30 s, made up to a volume of 1.0 mL with 0.1 M ammonium acetate, and vortexed again for 30 s. The extracts were diluted six times prior to UHPLC/ESI Q-Orbitrap injection.

Matrix-matched standard calibration curves for each individual pesticide were constructed using LCquan software. Concentration (μg/kg; ppb) versus the ratio (analyte area/IS area) of each individual pesticide was plotted. Deuterium-labeled standards carbendazim-d_4, carbofuran-d_3, and thiabendazole-d_4 were used as internal standards for their respective native compounds for quantification. Other pesticides used carbofuran-d_3 as an internal standard for quantification. In general, quadratic function was applied to the calibration curves based on the line of best fit. Occasionally, linear regression may be used for quantification. The $1/x$ weighting was used to improve the accuracy for quantification of pesticides at low concentrations. Responses for the unknown concentration or fortified samples were compared to the curves to calculate the amount of pesticide residues (μg/kg; ppb) in samples. Matrix-matched calibration standards were prepared fresh for each batch of samples.

Experimental Design and Method Validation. The method was validated according to the nested experimental design, which was described elsewhere.[15] The main factors of variances associated with the method performance or measurement uncertainties of an in-house validated method were concentrations or spike levels of analytes, matrix effects, day-to-day variation, and within-day variation of the method. The last two factors are designated as the intermediate precision. In this study, there were a total of five fruits (i.e., apple, banana, grape, orange, and strawberry), two green vegetables (i.e., cucumber and lettuce), and three nongreen vegetables (i.e., carrot, potato, and tomato). For each matrix, samples were spiked at four levels, that is, 10.0, 90.0, 240.0, and 400.0 μg/kg, in triplicate. Spike experiments were repeated on two different days or by two analysts. Overall recovery, intermediate precision, and measurement uncertainty were calculated using a combined computer program that consisted of SAS codes (SAS Software Release 9.1, SAS Institute Inc., USA) along with a Microsoft Excel (Microsoft Office 2002) workbook.

■ RESULTS AND DISCUSSION

QuEChERs. Pesticides were extracted from fruits and vegetables (15 g/sample) following the buffered QuEChERS
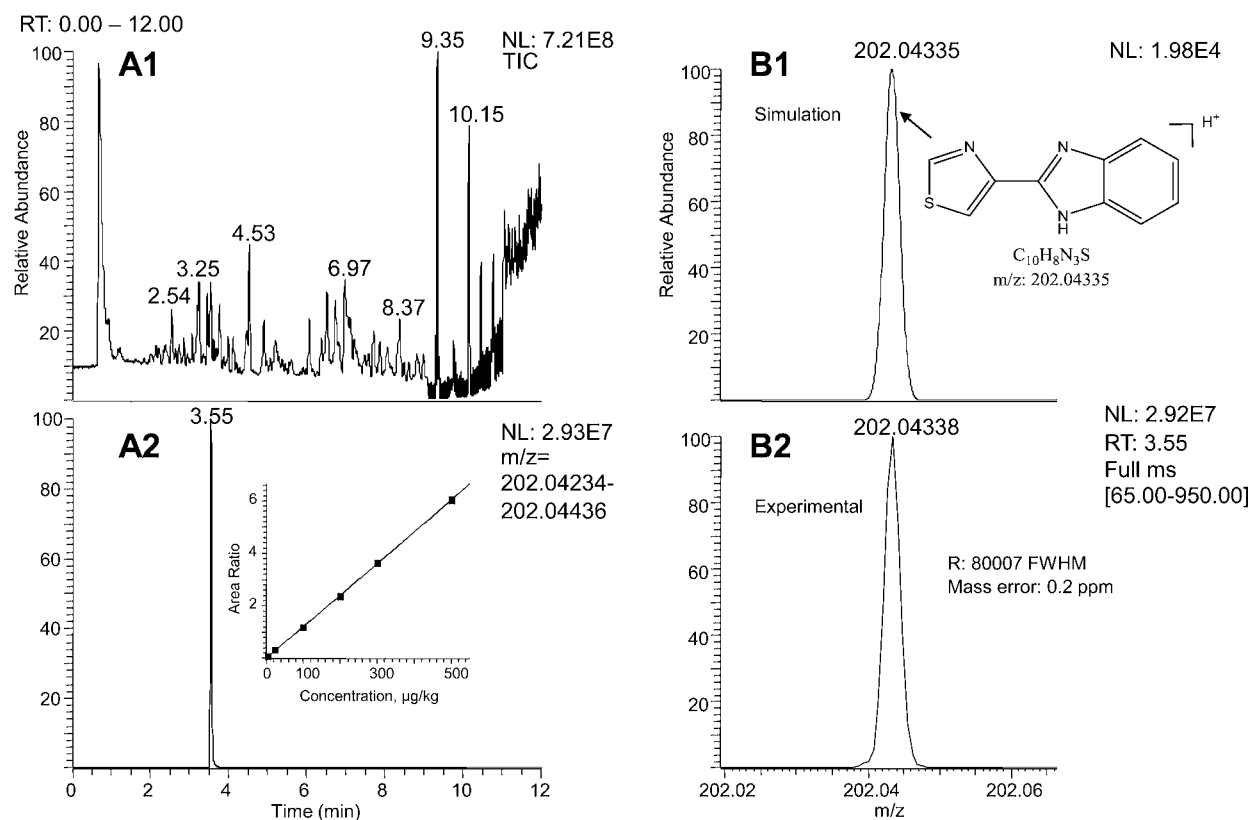
Figure 1. UHPLC/ESI Q-Orbitrap MS chromatograms and spectra: (A1) total ion chromatogram; (A2) extracted ion chromatogram of thiabendazole with a mass tolerance of 5 ppm and its matrix-matched standard calibration curve; (B1) simulated mass spectrum of thiabendazole $[M + H]^+$ m/z 202.04335 with a resolution of 80000 FWHM; (B2) experimental mass spectrum of thiabendzole $[M + H]^+$ m/z 202.04335. Pesticide spike concentration level (a total of 166 pesticides): 90 μg/kg in a blank apple sample.

method[13] or AOAC Official Method 2007.01.[14] The whole procedure consisted of three steps including (1) extraction with acetonitrile containing 1% acetic acid, $MgSO_4$, and sodium acetate; (2) cleanup by dispersive solid-phase extraction (d-SPE) using $MgSO_4$, PSA, and C_{18} for fruits and nongreen vegetables or using $MgSO_4$, PSA, and ChloroFiltr for green vegetables such as lettuce (chlorophyll-rich samples) (ChloroFiltr is a white, cross-linked polymeric powder, a strong yet selective sorbent to remove chlorophyll from green plants while leaving polar pesticides behind in the acetonitrile extract); (3) concentration, reconstitution, and filtration. Concentration and reconstitution served as an additional cleanup step to remove particles or pigments, which were precipitated during the process. Extracts were diluted six times prior to UHPLC/Q-Orbitrap injections. The QuEChERS method proved to be a practical extraction procedure for UHPLC/ESI Q-Orbitrap analysis of pesticide residues in fruits and vegetables.

Ultrahigh-Performance Liquid Chromatography. One hundred and sixty-six pesticides and three isotopically labeled standards (Table 1, column 1) were chromatographically separated within 12 min under a gradient profile (Table 3) using an UPLC BEH C_{18} column. Figure 1 presents an example of a total ion current (TIC) chromatogram (Figure 1A1) and the extracted ion chromatogram (Figure 2A2) of thiabendazole based on exact mass measurement at m/z 202.04335. Under most circumstances, an extracted ion presented as the sole LC peak or showed a peak with baseline separation from others, as a result of the superior resolving power of both UHPLC and Q-Orbitrap mass spectrometry. All pesticides were eluted between 1.0 and 11.0 min, and their peak shape was of Gaussian

distribution with a baseline peak width of 5−10 s. The retention times were reproducible with variations under ±0.2 min within and between batches for most of the pesticides, except for emamectin B_{1a}, fenpropidin, spiroxamine, and spinosyns A and D. Overall, the tolerance of retention time matching of any pesticide did not exceed ±2.5% relative to the retention time of its standard in the same batch. Because Q-Orbitrap MS has a scan rate of 3 Hz when its resolution is set at 70000 FWHM at m/z 200, it scans fast enough to generate sufficient data points for quantification. For example, there were more than 20 data points across the chromatographic peak with a 7 s baseline peak width.

Q-Orbitrap Mass Spectrometry. The Orbitrap mass spectrometer utilizes an electrostatic axially harmonic Orbital trapping technique.[16] It is a Fourier transform-based mass analyzer, which operates with an image current detection system and application of Fourier transform mathematical operations for generating mass spectra from time domain transients produced by the image current into the frequency domain, and the frequency can be calibrated as accurate mass. The Orbitrap mass spectrometer measures radio frequency (RF) rather than ion deflection (electric/magnetic sectors), ion stability (quadrupole mass analyzer), or time of transit (TOF).[17] The Ion Cyclotron Resonance (ICR) and Orbitrap analyzers outperform any other commonly used mass spectrometers with respect to the maximum mass resolution and accuracy routinely achievable even for small numbers of ions.[18]

In an Orbitrap, stable ion trajectories combine rotation around an axial central electrode with harmonic oscillations

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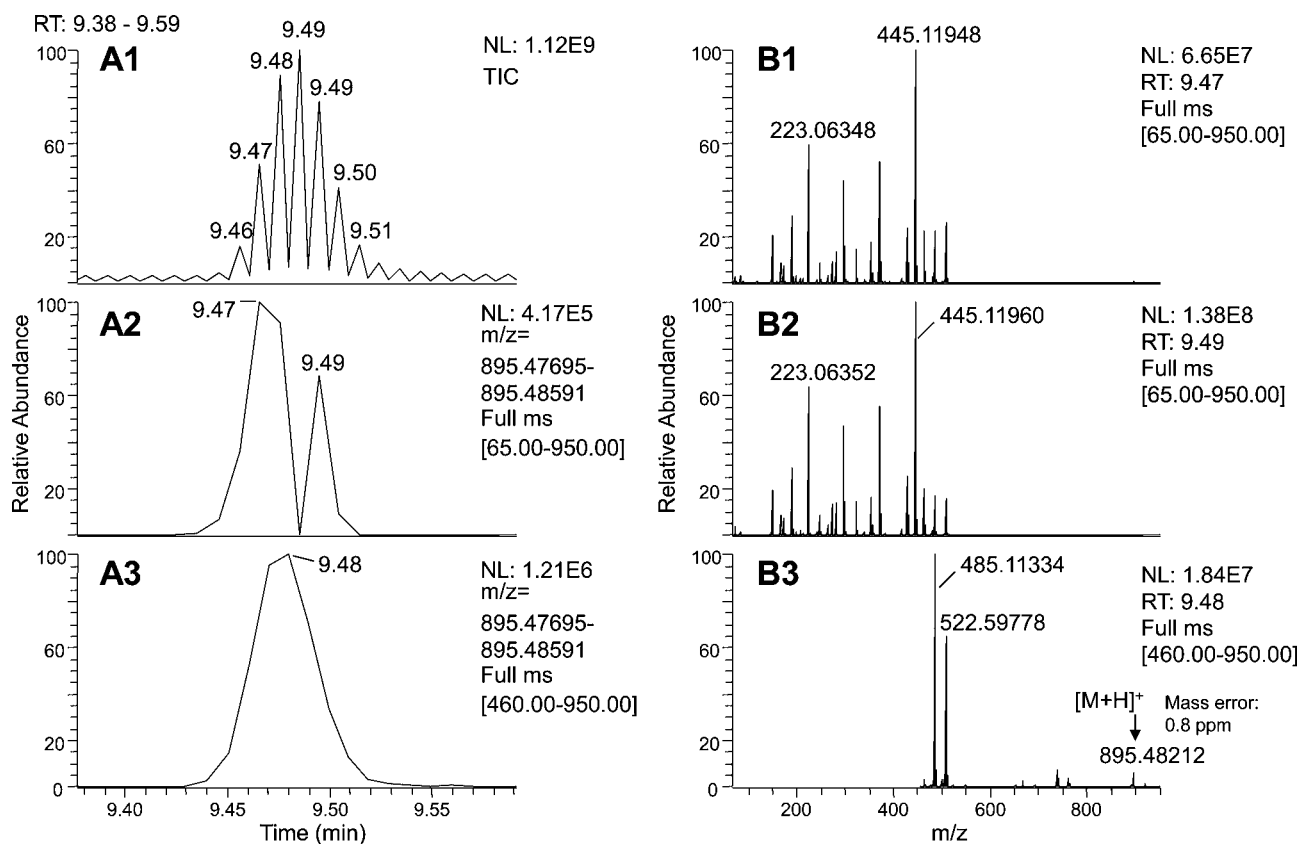dx.doi.org/10.1021/jf303939s | J. Agric. Food Chem. 2012, 60, 12088−12104

Figure 2. UHPLC/ESI Q-Orbitrap MS chromatograms and spectra: (A1) expanded chromatogram with two full MS scan ranges; (A2) extracted ion chromatogram of abamectin B_{1a} $[M + Na]^+$ m/z 895.48143 from the full MS scan with the mass range from m/z 65.0−950.0; (A3) extracted ion chromatogram of abamectin B_{1a} $[M + Na]^+$ m/z 895.48143 from the full MS scan with the mass range from m/z 460.0−950.0; (B1) mass spectrum from chromatogram A1 at 9.47 min; (B2) mass spectrum from chromatogram A2 at 9.49 min; (B3) mass spectrum from chromatogram A3 at 9.48 min. Pesticide spike concentration level (a total of 166 pesticides): 90 μg/kg in a blank cucumber sample.

along it. The frequency (ω) of these harmonic oscillations along the z-axis depends only on the ion mass-to-charge ratio (m/z or m/q) and the field curvature (k), that is, $\omega_z = (k/(m/q))^{1/2}$.[16] Two split halves of the outer electrode of an Orbitrap detect the image current produced by the oscillating ions. By fast Fourier transformation (FFT) of the image current, the instrument obtains the frequencies of these axial oscillations and therefore the mass-to-charge ratios of the ions. The role of high resolution is essential to the mass measurement and plays together with the accurate mass. If resolving power is not sufficient, then no accurate mass can be measured in the case of extremely close matrix interference masses, which is very common in food sample matrices.

An Orbitrap instrument is formatted as a stand-alone Orbitrap (i.e., Exactive), linear ion trap Orbitrap (i.e., LTQ Orbitrap Xl or LTQ Orbitrap Velos), or quadrupole Orbitrap (i.e., Q-Exactive). In the current study, a Q-Exactive, namely, Q-Orbitrap, mass spectrometer, was used. The Q-Orbitrap can be operated as a single-stage Orbitrap mass analyzer (i.e., full MS-SIM or full MS scan, referred to as Q-Orbiotrap MS in the text) or a tandem quadrupole Orbitrap mass spectrometer (i.e., full MS/dd-MS² or product-ion scan, referred to as Q-Orbitrap dd-MS² in the text).

Full MS-SIM. In routine practice, the Q-Orbitrap was operated in its full MS-SIM mode, that is, Q-Orbitrap MS, which acquired full MS scan data (Figure 1A1) that allowed for screening and quantifying the pesticides listed in Table 1 (this is called "targeted analysis") or retrospectively looking into

unknowns (this is called "nontargeted analysis"), for example, fragment identification (Table 1, columns 7 and 8). The Q-Orbitrap MS is ideal and practical for quantification, and its matrix-matched standard calibration curves showed good linear or quadratic regression (Figure 1A2). Due to its high resolution (operated at 70000 FWHM at m/z 200), the Q-Orbitrap MS also provided accurate mass measurements (mass accurate < 5 ppm) (Figure 1B1,B2) and enabled confidence in differentiating coeluting, isobaric analytes in complex matrices.

It is important to note that the number of ions that are injected into an Orbitrap analyzer is controlled by the AGC target value of C-Trap (curved linear trap), which eventually minimizes the space charge effect. Therefore, when the intensity of any ion in a single scan (or in-scan) is too high, the ion of interest may not be able to get into the C-Trap. For example, when the Q-Orbitrap MS scanned the mass range from m/z 65.0 to 950.0, abamectin B_{1a}, which eluted at 9.48 min, was discriminated by coeluent m/z 445.12003 ($[C_2H_6SiO]_6$, polysiloxane) (Figure 2B1,B2). The in-scan intensity of the polysiloxane ion was strong (up to 1.38E8, Figure 2B2), which dominated the capacity of the C-Trap and deferred abamectin B_{1a} from entering the C-Trap. As a result, the UHPLC peak of abamectin B_{1a} appeared to be rugged with missing data points in the middle of the peak, and its peak height was only 4.17E5 (Figure 2A2); therefore, the quantitative result was not repeatable. To eliminate the coeluting interference in an in-scan spectrum, a second mass scan range, that is, m/z 460.0−950.0, in the same retention
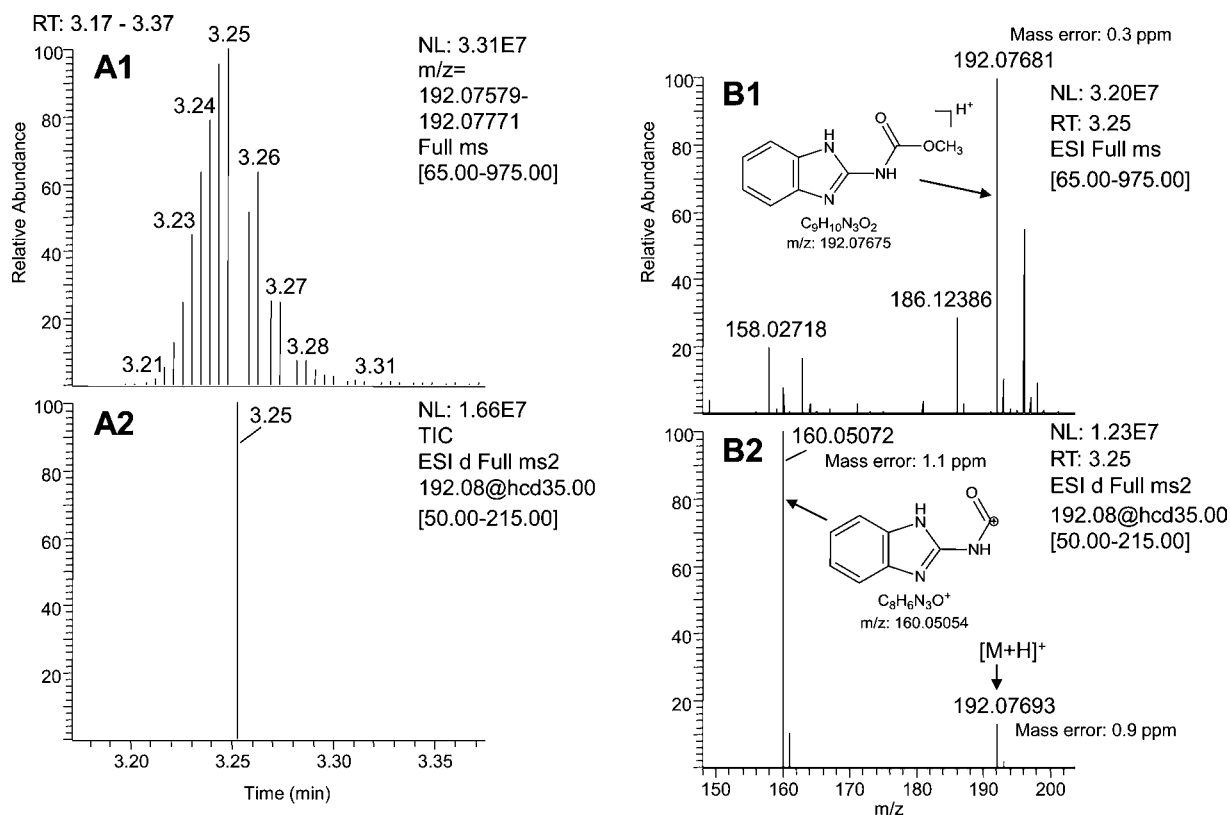
Figure 3. UHPLC/ESI Q-Orbitrap MS chromatograms and spectra from a full MS/dd-MS^2 experiment: (A1) extracted ion chromatogram (displayed as a stick per scan) of carbendazim $[M + H]^+$ m/z 192.07675 with a mass tolerance of 5 ppm; (A2) dd-MS^2 total ion chromatogram of carbendazim $[M + H]^+$ m/z 192.07675; (B1) mass spectrum (full MS scan) from chromatogram A1 at 3.25 min; (B2) dd-MS^2 or a product-ion spectrum of carbendazim $[M + H]^+$ m/z 192.07675 from chromatogram A2 at 3.25 min. Pesticide spike concentration level (a total of 166 pesticides): 90 μg/kg in a blank potato sample.

time window was set and the m/z 445.12003 (i.e., polysiloxane) was filtered out from the range by the quadrupole (Figure 2B3). As a result, the UHPLC peak of abamectin B_{1a} turned out to be smooth and its peak height reached 1.21E6 (Figure 2A3). The sensitivity (peak height) increased almost 3 times compared to the one without exclusion (Figure 2A2), and the repeatability improved significantly as well. Figure 2A1 showed the TIC of two mass range scans that alternated as low point (for m/z 450.0−950.0) and high point (for m/z 65.0−950.0) in the chromatogram.

Full MS/dd-MS^2. When operated in full MS/dd-MS^2 mode, a product-ion spectrum with accurate mass measurement is obtained automatically according to a list of targeted accurate masses (for example, Table 1, column 4) within a 10 ppm mass error window, and this is defined as a data-dependent scan (dd-MS^2). Its data are qualitative, more for confirmation than for quantification (Figure 3). This experiment comprises a full MS scan followed by a triggered data-dependent scan (dd-MS^2). Therefore, in a full MS/dd-MS^2 experiment, Q-Orbitrap acquires two sets of data, that is, full MS scan and dd-MS^2 data sequentially. The full MS scan data are retrospective, and dd-MS^2 data are targeted because it aims at accurate masses that are included in the inclusion list. As shown in Figure 3A1, before 3.25 min, the Q-Orbitrap performed full MS scan in the mass range of m/z 65.0−950.0 with a mass resolution of 70000 FWHM. When it detected an ion at m/z 192.07675 with its intensity ≥8.30E4 (the threshold), the dd-MS^2 scan with a mass resolution of 17500 FWHM was triggered. The precursor ion was first selected by the quadrupole and then was sent to the

HCD collision cell for high-energy collision fragmentation. After one dd-MS^2 scan, the Q-Orbitrap was back to perform a full MS scan again. dd-MS^2 is a valuable approach to obtain a product-ion spectrum for confirmation where a MS library may be required for mass spectral matching, and the product-ion spectrum with accurate mass measurement is also essential for chemical structural elucidation.

In the current study, the collision energy for fragmentation, that is, normalized collision energy (NCE), was set at 35%. Apparently, it worked well for carbendazim that a spectrum containing both precursor and product ions was obtained (Figure 3B2). The NCE and the degree of fragmentation were correlated and compound-dependent. Therefore, a generic setting of NCE may not be appropriate for all analytes to generate fragment-rich spectra. "Stepped NCE" or "stepped collision energy" provides an alternate solution. In this case, NCE is used as the center energy. Stepped NCE is a percentage of this center energy. The Q-Orbitrap is able to perform a three-step (i.e., the center energy plus one above and one below the center energy) fragmentation on the precursor ion. All fragments created in the three-step are collected sequentially in the HCD and sent to the Orbitrap analyzer for one scan detection. Once again, stepped NCE may work for some but not others unless optimized NCE is obtained for each individual analyte. In the present study, only NCE (set at 35%) was used to acquire dd-MS^2 data. Further study is required to explore whether more than two diagnostic ions can be generated for each individual pesticide using dd-MS^2 by generic NCE or stepped NCE. Otherwise, the optimal collision

energy may be required to obtain more than two diagnostic ions for confirmation.

Figure 3A1 is the extracted ion chromatogram of the carbendazim at m/z 192.07675 from the full MS/dd-MS^2 experiment, and Figure 3A2 indicates the chromatogram of the dd-MS^2 scan of carbendazin at m/z 192.07675. As a result, the dd-MS^2 product-ion (Figure 3B2) spectrum was obtained in addition to the full MS spectrum (Figure 3B1). The exact mass measurements of both precursor and fragment ions, for example, from the product-ion spectrum (Figure 3B2), were essential to confirm the identity of a pesticide, that is, carbendazim, in this example.

Matrix Effects. The matrix could either enhance or suppress ionization of pesticides; its effects might vary from sample to sample and ultimately affect the UHPLC/ESI Q-Orbitrap MS quantitative results. To evaluate matrix effects, the responses of pesticides in sample extracts were compared to those of pesticide standards prepared in solvent buffer at the same concentration level, for example, 100 μg/kg equivalent in sample. As seen in fruit matrices (Figure 4A), up to 4.7% of

	Ion suppression ≥30%	Ion suppression <30% or ion enhancement ≤10%	Ion enhancement >10%
Apple	0.0	97.1	2.9
Banana	0.0	97.1	2.9
Grape	0.0	98.2	1.8
Orange	4.7	84.7	10.6
Strawberry	1.2	88.2	10.6

Matrix effects

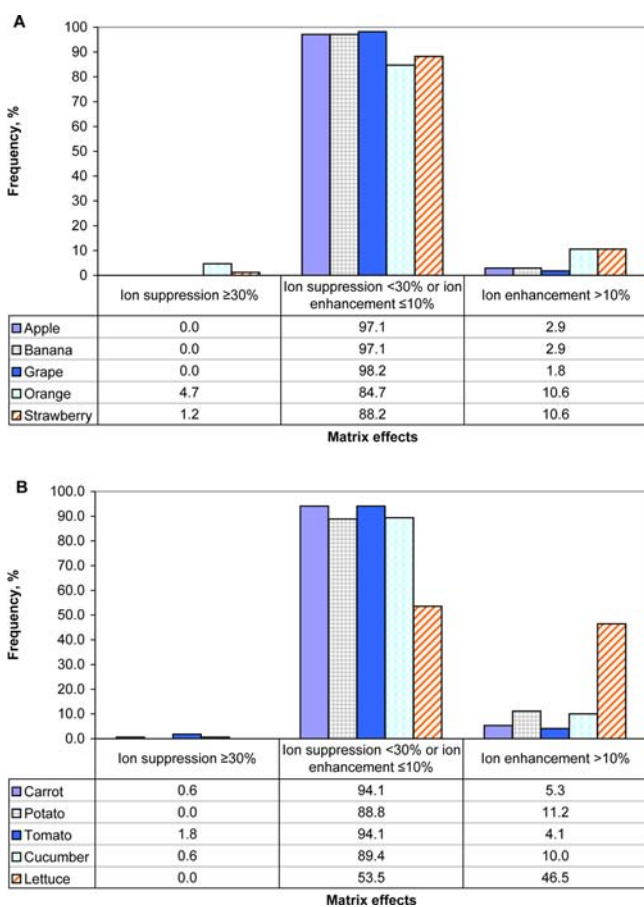|	Ion suppression ≥30%	Ion suppression <30% or ion enhancement ≤10%	Ion enhancement >10%
Carrot	0.6	94.1	5.3
Potato	0.0	88.8	11.2
Tomato	1.8	94.1	4.1
Cucumber	0.6	89.4	10.0
Lettuce	0.0	53.5	46.5

Matrix effects

Figure 4. UHPLC/ESI Q-Orbitrap MS matrix effects. The 166 pesticides were prepared in matrix extracts (a total of 10 matrices) and solvent buffer at a concentration of 100 μg/kg equivalent in sample.

pesticides experienced ion suppression ≥30% and up to 10.6% of pesticides had ion enhancement >10%. Similar results were observed in vegetables except for lettuce (a chlorophyll-rich matrix) (Figure 4B), of which 46.5% pesticides were enhanced. On the basis of our experiences, the degree of ion suppression and enhancement from UHPLC/ESI Q-Orbitrap MS was not

severe and comparable to that of LC/ESI-MS/MS, which was published elsewhere for the same types of matrices.[13]

Matrix-matched standard calibration curves and/or isotopically labeled standards were required to compensate for matrix effects so as to improve the UPLC/ESI Q-Orbitrap MS quantitative accuracy, especially for chlorophyll-rich matrices. Due to their availability, three deuterium-labeled standards, that is, carbendazim-d_4, carbofuran-d_3, and thiabendazole-d_4, were used as internal standards for quantifying their respective native compounds, and carbofuran-d_3 was utilized for other pesticides. The calibration curves were observed to be linear or quadratic with coefficients of determination (R^2) $\geq$ 0.97. Because of matrix effects, ion source contamination, or other unidentified factors, the responses of some pesticides either decreased or increased slightly over time. To average out the response changes during the course, the matrix-matched standard calibration curves were constructed on the basis of the two injections, that is, before and after spike samples, to improve the method performance.

Quantification and Method Performance. The UHPLC/ESI Q-Orbitrap MS method was validated according to a nested design reported elsewhere[15] to evaluate the method performance characteristics including accuracy expressed as overall recovery, intermediate precision, and measurement uncertainty (MU). Four factors, that is, concentrations or spike levels of pesticides, matrix effects, day-to-day variation, and within-day variation, were included for the evaluation, and the experimental details were described under Materials and Methods. Because of differences in matrices or sample cleanup procedures, data were grouped into three sets so that statistics were valid. One set of data was from fruits, one from green vegetables (cleanup by ChloroFiltr), and one from nongreen vegetables. The method performance results are summarized in Table 2 and illustrated in Figure 5. Depending on the type of matrices, about 90.3−91.5% of the pesticides had recoveries between 81 and 110%, 92.1−97.6% had intermediate precision ≤20%, and 89.7−95.2% had measurement uncertainty ≤40%.

Clodinafop-propargyl, naptalam, pyridate, quizalofop, spinosyn A, and spiromesifen had measurement uncertainty ≥50% in at least one of the matrices and were considered to be problematic pesticides for quantification, which was the same as reported in other studies.[19,20] Apparently, low recovery and/or poor intermediate precision contributed to the large measurement uncertainty (Table 2). In general, 97.0−98.8% of the pesticides have MU ≤ 50%, which was a recommended default value in European Union (EU) Document No. SANCO/12495/2011 for pesticide analysis and enforcement decisions (MRL exceedances).[21] Therefore, the UHPLC/ESI Q-Orbitrap MS can serve as an ideal and practical tool for quantification over all.

Pesticide Confirmation. The confirmation of any pesticides using the UHPLC/ESI Q-Orbitrap mass spectrometer was based on mass accuracy (i.e., <5 ppm) and chromatographic retention time tolerance (i.e., ±2.5%).[21,22] The UHPLC/ESI Q-Orbitrap provided a measured mass accuracy <5 ppm and retention time tolerance within ±2.5%. The requirements for confirmation in EU Document No. SANCO/12495/2011 include two diagnostic ions (preferably the precursor ion and its fragment ion) having mass accuracy of <5 ppm. In general, dd-MS^2 is able to achieve the goal or obtain a product-ion spectrum that includes both precursor and product ions with accurate masses. Figure 3 showed an example of UHPLC/ESI Q-Orbitrap confirmation of carbendazim
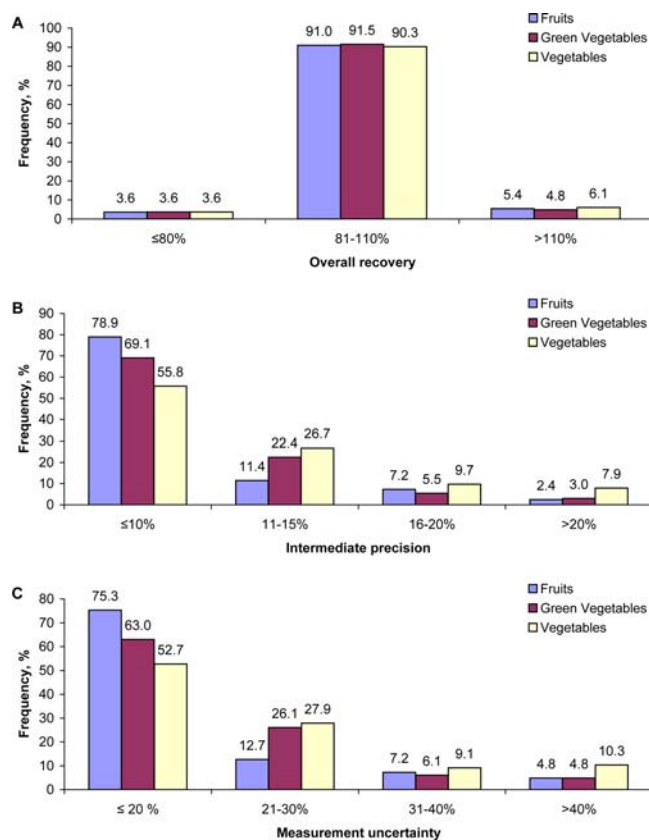
Figure 5. UHPLC/ESI Q-Orbitrap MS method performance for analysis of 166 pesticides in fruits and vegetables: (A) overall recovery; (B) intermediate precision; (C) measurement uncertainty.

spiked at 90 μg/kg in a potato sample. Figure 3B1 is the mass spectrum of a full MS scan, whereas Figure 3B2 is that of a dd-MS^2 product-ion scan. The mass accuracy for the precursor ion and product ion was 0.9 or 1.1 ppm, respectively, and therefore confirms the identity of carbendazim.

Method Sensitivity. The lowest concentration levels of individual pesticides (Table 2, columns 5, 9, and 13), which referred to the method sensitivity, were determined according to the recommended default LC peak height value, that is, 1.0 × 10^4, reported elsewhere for Orbitrap.[23,24] The signal-to-noise (S/N) ratio approach was not used because it became impractical for a high-resolution mass spectrometer as a result of the background noise often not present in the chromatogram. As shown in Table 2, under most circumstances (except for prodiamine in green vegetables), the UHPLC peak height was >1.0 × 10^4, and this means that 87.3−92.7% of pesticides could be detected and quantified ≤5 μg/kg. Therefore, the method proved to be sensitive and was able to quantify most of the pesticides at 10 μg/kg, a default concentration for a pesticide with no MRL.

In conclusion, UHPLC/ESI Q-Orbitrap proved to be an important and powerful tool for determination of 166 pesticide residues in fruits and vegetables. UHPLC/ESI Q-Orbitrap MS, that is, full MS scan, provided superior method accuracy, repeatability, and sensitivity for quantification. The method development was simple because the instrumental parameter settings were generic and, therefore, no optimization for individual pesticides was required. Generally, about 90.3−91.5% of the pesticides had recoveries between 81 and 110%, 92.1−97.6% had intermediate precision of ≤20%, and 89.7−

95.2% had measurement uncertainty of ≤40%. UHPLC/ESI Q-Orbitrap dd-MS^2 provided product-ion spectra with accurate mass measurement that allowed unambiguous confirmation of pesticides. Overall, the method can be potentially used in routine monitoring programs for food safety.

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■ ACKNOWLEDGMENTS

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