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Analysis of Pesticides in Dried Hops by Liquid Chromatography−Tandem Mass Spectrometry

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An analytical method was developed for the determination of eleven agrochemicals [abamectin (as B1a), bifenazate, bifenthrin, carfentrazone-ethyl, cymoxanil, hexythiazox, imidacloprid, mefenoxam, pymetrozine, quinoxyfen, and trifloxystrobin] in dried hops. The method utilized polymeric and NH_2 solid phase extraction (SPE) column cleanups and liquid chromatography with mass spectrometry (LC-MS/MS). Method validation and concurrent recoveries from untreated dried hops ranged from 71 to 126% for all compounds over three levels of fortification (0.10, 1.0, and 10.0 ppm). Commercially grown hop samples collected from several field sites had detectable residues of bifenazate, bifenthrin, hexythiazox, and quinoxyfen. The control sample used was free of contamination below the 0.050 ppm level for all agrochemicals of interest. The limit of quantitation and limit of detection for all compounds were 0.10 and 0.050 ppm, respectively.

KEYWORDS: Pesticides; residue method; hops; liquid chromatography−mass spectrometry; LC-MS/MS

INTRODUCTION

As United States hop growers endeavor to compete in a global market, they are faced with many challenges. At home, growers must combat various pest and pathogen pressures to produce a commodity that is both high in yield and quality. Pests and pathogens of interest include, but are not limited to, the two-spotted spider mite, hop aphid, bertha and western yellow striped army worm, hop looper, powdery mildew, downey mildew and garden symphylans (*1*). Abroad, growers must be acutely aware of other country's import tolerances established for pesticide residues on a given commodity (*2*). For example, during the growing process agrochemical applications must be timed to provide adequate crop protection, as well as, mitigate the resulting pesticide residues, if any, on the raw agricultural commodity such that the import tolerance of the importing country is not exceeded. For U.S. domestic production and hops imported into the United States, the growers must conform to U.S. Environmental Protection Agency (U.S. EPA) tolerances (*3*). The primary use of hop cones is in the beer brewing process to impart bitterness, flavors, and aroma. Lesser uses include the addition of hops to various tea blends and oil extracts have been used as flavoring in production of beverages, candy and desserts (*4*).

In 2007, U.S. hop growers grew 30,911 acres of hops, which produced 60,253,100 pounds of hop cones with a production value of $169,310,000 (*5*). Of this production, roughly 60−65% was slated for export (*1*). Because of the market value associated with this commodity, the U.S. Hop Industry Plant Protection Committee approached the University of California at Davis, Department of Environmental Toxicology's IR-4/Trace Analytical Laboratory with the desire to develop a multiresidue method to screen for several of the most commonly applied pesticides on dried hop cones (**Table 1**). The target limit of quantitation (LOQ) was set at 0.1 ppm for all compounds. The rationale for the LOQ was to have a method that could quantitate the majority of compounds below the tolerances set by the U.S. EPA.

Analysis of the target compounds in raw agricultural commodities can be accomplished by various means including gas chromatography (GC), high performance liquid chromatography (HPLC), gas chromatography coupled to a mass spectrometer (GC-MS) and liquid chromatography coupled to a tandem mass spectrometer (LC-MS/MS) (*6–16*). In fact, many of the target compounds have been successfully extracted and determined together from high moisture crops in previously developed multi residue methods (*17, 18*). Many of the methods in the literature are quite sensitive and selective for the compounds of interest, but were not intended for use with such a complicated matrix

Table 1. Compound-Specific U.S. EPA Tolerances on Dried Hops

compound	tolerance (ppm)	citation
abamectin[a]	0.20	40CFR180.449
bifenazate	15.0	40CFR180.572
bifenthrin	10.0	40CFR180.442
carfentrazone-ethyl	0.05	40CFR180.515
cymoxanil	1.0	40CFR180.503
hexythiazox	2.0	40CFR180.448
imidacloprid	6.0	40CFR180.472
mefenoxam[b]	20.0	40CFR180.408
pymetrozine	6.0	40CFR180.556
quinoxyfen	3.0	40CFR180.588
trifloxystrobin	11.0	40CFR180.555

[a] Listed as avermectin in CFR. [b] Tolerance established as metalaxyl.

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Table 2. Compound-Specific Information for Chromatography and Mass Spectrometry Conditions

compound	Q1[a] mass (amu)	Q3[a] mass (amu)	DP[b] (V)	FP[c] (V)	EP[d] (V)	CEP[e] (V)	CE[f] (V)	CXP[g] (V)	RT[h] (min)
abamectin (B_1a)	890.5[i]	305.1	1	370	9	38	38	8	9.92
bifenazate	301.0	198.2	16	360	10	32	15	4	5.25
bifenthrin	440.1[i]	181.1	1	370	6.5	18	21	4	10.51
carfentrazone-ethyl	412.0	346.1	66	350	12	18	27	6	5.64
cymoxanil	198.9	128.0	6	290	8.5	12	13	4	4.01
hexythiazox	353.1	228.1	11	340	11.5	32	19	4	7.38
imidacloprid	256.0	208.9	21	370	10.5	18	21	4	3.59
mefenoxam	280.1	219.9	11	330	10.5	12	19	4	4.84
pymetrozine	217.9	105.2	21	370	12	14	31	4	3.17
quinoxyfen	307.9	197.0	36	370	10.5	14	47	4	7.45
trifloxystrobin	409.1	186.1	11	370	12	30	21	4	6.11

[a] Q1 and Q3 represent compound-specific transitions monitored. [b] Declustering potential. [c] Focusing potential. [d] Entrance potential into first quadrupole. [e] Collision cell entrance potential. [f] Collision energy. [g] Collision cell exit potential. [h] Retention time [i] $[NH_4]^+$ adduct.

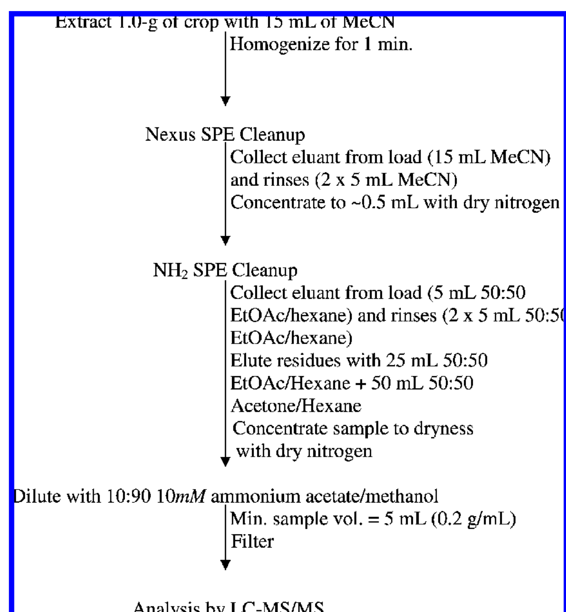

Figure 1. Basic sample flowchart for analysis.

Table 3. Average Recoveries from Dried Hops

compound	fortification level (ppm)		
	0.10[a] ($n = 9$)	1.0[a] ($n = 6$)	10[a] ($n = 6$)
abamectin (B_1a)	102 ± 9	95 ± 3	89 ± 5
bifenazate	113 ± 11[b]	95 ± 6	87 ± 2
bifenthrin	87 ± 7	83 ± 5	74 ± 2
carfentrazone-ethyl	97 ± 10	94 ± 5	102 ± 2
cymoxanil	85 ± 5	88 ± 4	83 ± 2
hexythiazox	86 ± 9	91 ± 9	86 ± 2
imidacloprid	104 ± 12	97 ± 7	97 ± 2
mefenoxam	101 ± 8	103 ± 3	93 ± 3
pymetrozine	98 ± 19	88 ± 7	89 ± 2
quinoxyfen	97 ± 8	91 ± 3	95 ± 1
trifloxystrobin	100 ± 10	96 ± 2	95 ± 3

[a] Values are mean percent recovered ± standard deviation; n is the number of replicates. [b] For bifenazate at the 0.1 ppm level $n = 6$.

as dried hop cones (*19*). Improved cleanup steps are required to reduce the resins and oils associated with the hop extract, which can complicate analyses by causing chromatographic interferences or enhancement/suppression of the ionization process in the ionization source (*20*).

In the present study, a rapid and selective method was developed to determine the residue levels of 11 pesticides in dried hop cones. The new method utilizes acetonitrile extraction, solid phase extraction (SPE), and LC-MS/MS.

MATERIALS AND METHODS

Materials. Abamectin (CAS Registry No. 71751-41-2, 82% B_1a), Bifenazate (CAS Registry No. 149877-41-8, 99%), Cymoxanil (CAS Registry No. 57966-95-7, 99%), Pymetrozine (CAS Registry No. 123312-89-0, 99%), and Trifloxystrobin (CAS Registry No. 141517-21-7, 99%) were obtained from Chem Service Inc., West Chester, PA. Bifenthrin (CAS Registry No. 82657-04-3, 98%) and Carfentrazone-ethyl (CAS Registry No. 128639-02-1, 98%) were obtained from FMC Corp., Princeton, NJ. Imidacloprid (CAS Registry No. 138261-41-3, 98%) was obtained from Bayer Corp., Agriculture Division, Stilwell, KS. Hexythiazox (CAS Registry No. 78587-05-0, 99%) was obtained from Nippon Soda Co., Japan. Quinoxyfen (CAS Registry No. 124495-18-7, 99%) was obtained from Dow AgroSciences LLC, Indianapolis, IN. Mefexonam (CAS Registry No. 70630-17-0, 98%) was obtained from Novartis Crop Protection Inc., Greensboro, NC. All solvents and reagents were pesticide grade or better. Water was prepared using a Milli-Q reagent water system. Specifications for SPE and filtration are cited below.

Preparation of Standard Solutions. Stock solutions (1.00 mg/mL) of each compound of interest were prepared by adding 25 mg (corrected for purity) of the analytical grade compound to separate 25 mL volumetric flasks and bringing up to volume with acetone (except for pymetrozine, which was diluted with methanol). The stock solutions were stored generally at −20 °C and were stable for 1 month. A high-level fortification solution was prepared by taking 0.5 mL aliquots of each stock solution and diluting up to volume in a 50 mL volumetric flask with acetonitrile (MeCN), resulting in a 10 μg/mL mixed solution. A low-level fortification solution was prepared by taking a 5 mL aliquot of the 10 μg/mL mixed solution and diluting up to volume in a 50-mL volumetric flask with MeCN, resulting in a 1.0 μg/mL mixed solution. Calibration solutions for LC-MS/MS analysis were prepared by taking various volumes of the 10 and 1 μg/mL mixed solutions and diluting up to volume in 10 mM ammonium acetate/methanol (10:90, v/v), resulting in calibration standards over a range of 10−500 pg/μL. Fortification and calibration solutions were stored at ~5 °C and were stable for 1 month.

Collection of Field Samples and Sample Processing. For each growing season (2006 and 2007), composite samples of dried commercial varieties from Idaho, Oregon, and Washington were shipped to our facility frozen from the Washington State Department of Agriculture Plant Protection facility. Hop samples (~800 g each) were chopped with equal portions of dry ice using a Hobart food chopper (Hobart Corp., Troy, OH). Each chopped sample was stored in a labeled ~1 L jar, and a lined lid was loosely closed on top to allow the dry ice to dissipate during storage at −20 °C.

Extraction. A 1.0-g aliquot of crop was weighed into a 50 mL disposable tube (recovery samples were fortified at this point) and 15 mL of MeCN was added. The sample was blended using an Ultra-Turrax T-25 (Janke & Kunkel, IKA-Labortechnik, Germany) for 1 min at 13500 rpm.

Solid Phase Extraction (SPE). ABS Elut-Nexus SPE columns (0.5 g/12 mL, Varian Inc., Harbor City, CA) were preconditioned with 5 mL of MeCN. When the solvent reached the top of the packing, the

Table 4. Residue Results from Commercial Hops (Parts per Million)

compound	cascade[a]	CTZ[a]	Galena[a]	Nugget[a]	Willamette[a]
abamectin	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10
bifenazate	2.08, 0.25	1.03, 0.79	2.40, 0.36	2.15, 0.327	5.49, 1.47
bifenthrin	<0.10, <0.10	<0.10, 0.14	<0.10, <0.10	<0.10, <0.10	<0.10, 0.10
carfentrazone-ethyl	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10
cymoxanil	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10
hexythiazox	<0.10, 0.60	0.12, 0.31	0.16, 0.16	0.76, 0.32	0.23, 0.32
imidacloprid	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10
mefenoxam	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10
pymetrozine	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10
quinoxyfen	<0.10, 0.45	0.15, 0.35	0.13, <0.10	<0.10, <0.10	<0.10, 0.12
trifloxystrobin	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10	<0.10, <0.10

[a] Values represent an average of duplicate analyses from each sampling year. The first value is the 2006 sample, and the second value is the 2007 sample.

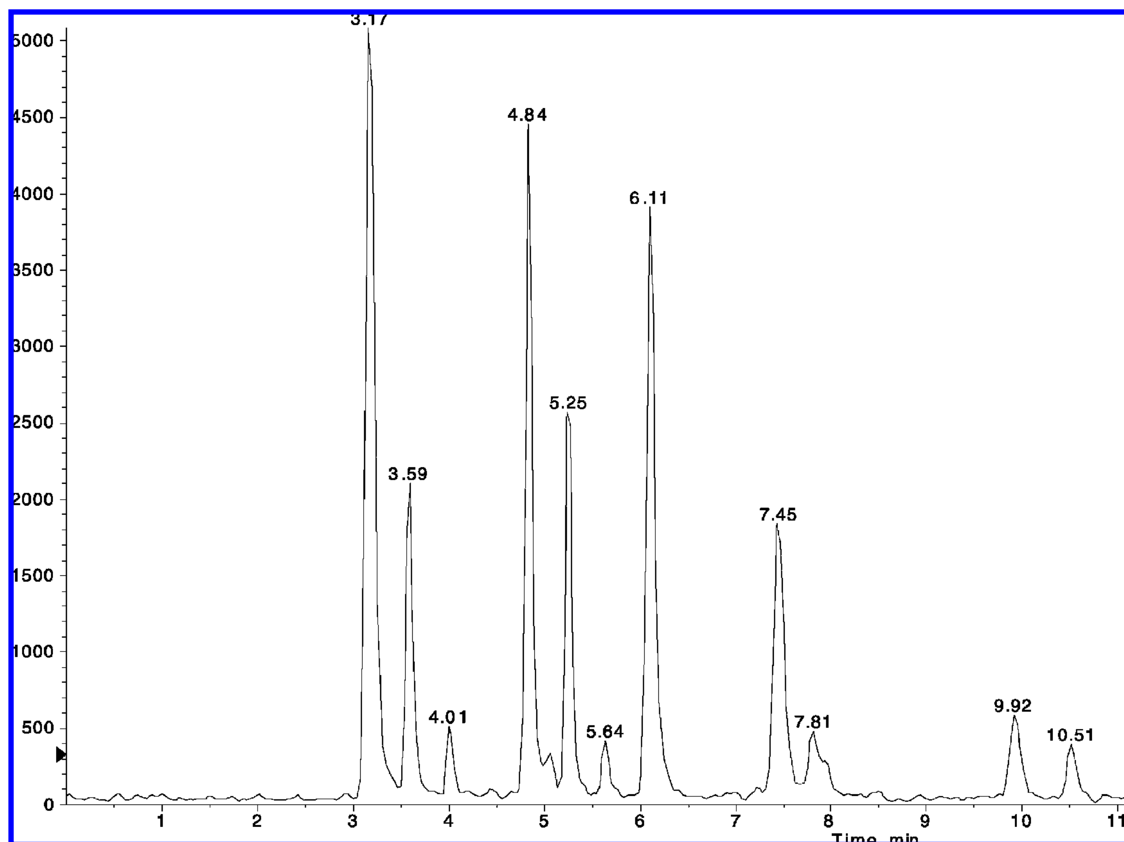

Figure 2. Total ion chromatogram of 20 pg/μL (equivalent to 0.1 ppm) calibration standard: pymetrozine (3.17 min), imidacloprid (3.59 min), cymoxanil (4.01 min), mefenoxam (4.84 min), bifenazate (5.25 min), carfentrazone-ethyl (5.64 min), trifloxystrobin (6.11 min), hexythiazox (7.38 min), quinoxyfen (7.45 min), abamectin (9.92 min), and bifenthrin (10.51 min).

unfiltered sample extract was loaded to the SPE. Mild vacuum was applied and the eluant was collected in a 45 mL conical tube at a flow rate of ~ 1−2 drops per second. Once the extract was loaded to the SPE, the 50 mL disposable tube was rinsed with 5 mL of MeCN and was added to the SPE. Following the rinse, the filter cake above the SPE packing was rinsed with an additional 5 mL of MeCN. The eluted sample was transferred to a TurboVap tube and the 45 mL conical tube was rinsed with 5 mL of acetone and pooled with the MeCN fraction. The extract was then concentrated to ~ 0.5 mL with dry nitrogen and water bath at 35 °C using a TurboVap II workstation (Caliper Life Science, Hopkinton, MA). The concentrated sample was dissolved into 5 mL of ethyl acetate/hexane (50:50, v/v) and subjected to a second cleanup by SPE. Mega Bond Elut-NH_2 SPE columns (5 g/20 mL, Varian Inc., Harbor City, CA) were conditioned with 15 mL of ethyl acetate/hexane (50:50, v/v). When the solvent reached the top of the packing, the sample was loaded to the SPE. Mild vacuum was applied and eluant was collected in a 45 mL conical tube at a flow rate of ~1−2 drops per second. The TurboVap tube from the previous concentration step was rinsed twice with 5 mL of ethyl acetate/hexane (50:50, v/v) and the rinse solvent was added to the SPE. An SPE reservoir was attached to the SPE and sample elution was continued with an additional 25 mL of ethyl acetate/hexane (50:50, v/v). Once the ethyl acetate/hexane aliquot was completely loaded to the SPE, the TurboVap tube from the previous concentration step was rinsed with 5 mL of acetone/hexane (50:50, v/v). The resulting sample was transferred to a clean TurboVap tube and the 45 mL conical tube was placed back into the vacuum manifold. The final elution step was completed with 45 mL of acetone/hexane (50:50, v/v) and the resulting sample was pooled with the previous fraction in the TurboVap tube. Sample extracts were then concentrated to near dryness using the TurboVap II workstation mentioned above. The final sample was dissolved into an appropriate volume with 10 mM ammonium acetate/methanol (10:90, v/v) and filtered through a 0.2 μm Acrodisc syringe filter (Pall Corporation, Ann Arbor, MI) prior to analysis by LC-MS/MS. For determinations at 0.1 ppm, final sample volume was 5 mL (0.2 g/mL).

Sample Analysis. Sample analysis was conducted with a Perkin-Elmer Series 200 autosampler and binary micropumps (Perkin-Elmer,

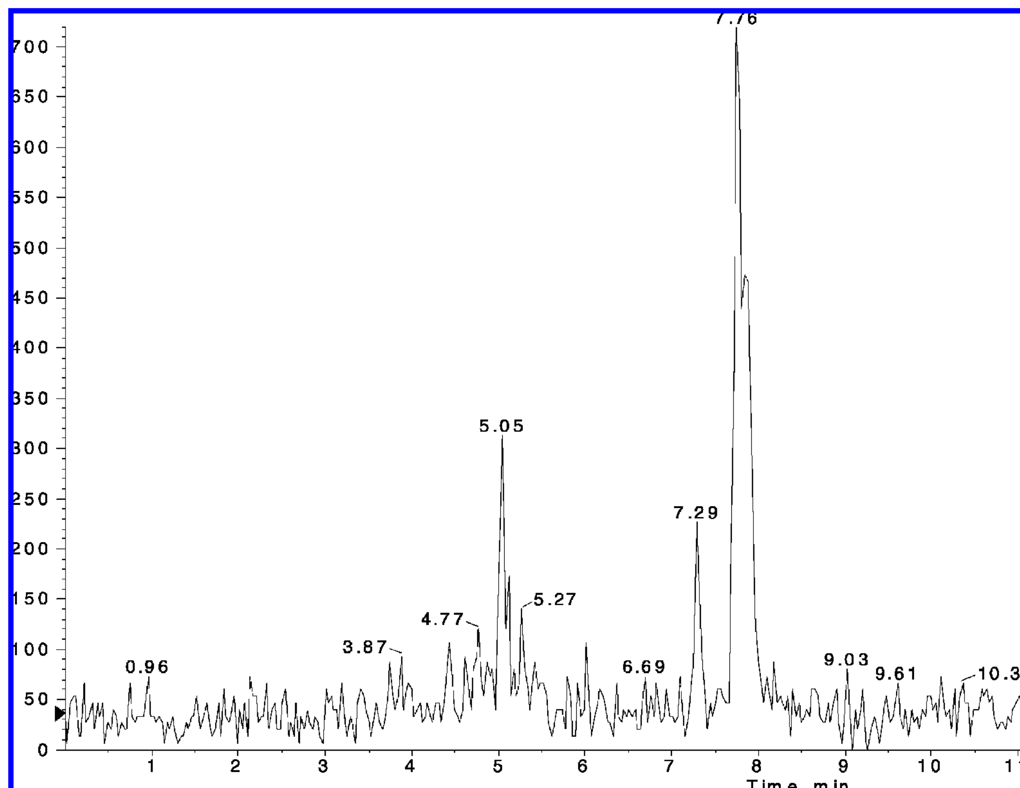

Figure 3. Total ion chromatogram of Idaho control. No residues were detected above 0.05 ppm for expected retention times of target compounds. Refer to **Table 2** for expected retention times.

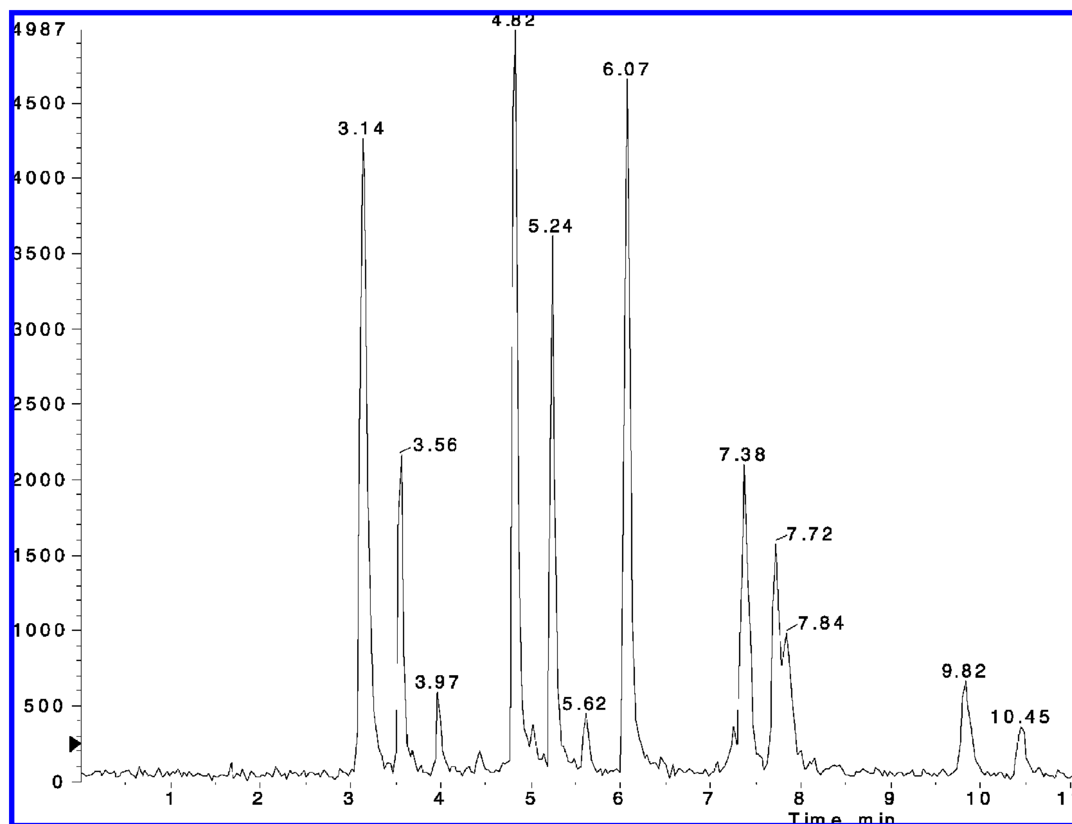

Figure 4. Total ion chromatogram of 0.1 ppm recovery from Idaho control sample: pymetrozine (3.14 min), imidacloprid (3.56 min), cymoxanil (3.97 min), mefenoxam (4.82 min), bifenazate (5.24 min), carfentrazone-ethyl (5.62 min), trifloxystrobin (6.07 min), hexythiazox (7.38 min), quinoxyfen (7.45 min), abamectin (9.82 min), and bifenthrin (10.45 min).

Shelton, CT) coupled to an Applied Biosystem API-2000 tandem mass spectrometer via a atmospheric pressure chemical ionization source (APCI) (Applied Biosystem, Palo Alto, CA). The APCI source was operated in positive ionization mode with drying nitrogen gas at 425 °C. Curtain gas, ion source gas 1, ion source gas 2, and collision cell gas were operated at 50, 85, 15, and 5 psi, respectively. The mass

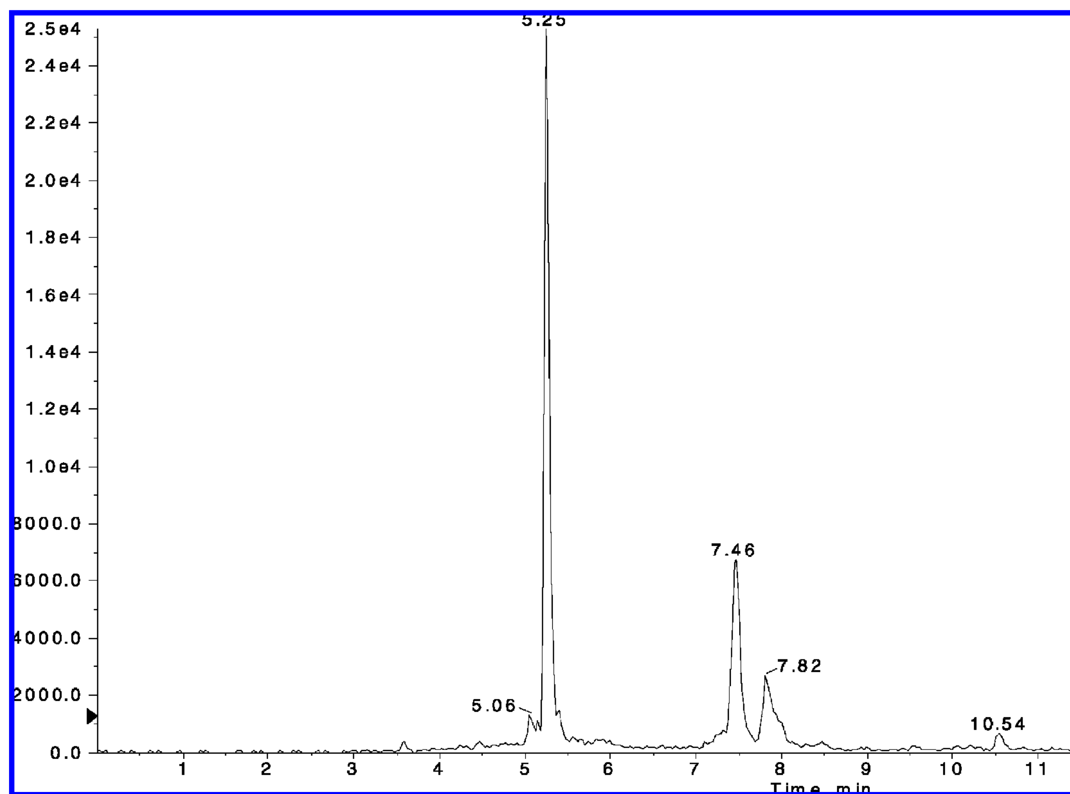

Figure 5. Total ion chromatogram of 2007 CTZ sample: 0.79, 0.31, 0.35, and 0.14 ppm of bifenazate (5.25 min), hexythiazox (7.38 min), quinoxyfen (7.46 min), and bifenthrin (10.54 min), respectively.

spectrometer was operated in multiple reactant monitoring mode (MRM). See **Table 2** for compound conditions. Chromatographic separation was accomplished with a Agilent Zorbax Eclipse Plus C_{18} column (100 × 3.0 mm i.d., 3.5 μm particle size, Agilent Technologies, Palo Alto, CA). Initial mobile phase composition was 80:20 (v/v) 10 mM ammonium acetate/methanol with a flow rate of 600 μL/min. The mobile phase program consisted of 0−0.5 min 80:20, 0.5−3 min ramp gradient to 10:90, 3.0−8.0 min hold 10:90, 8.0−8.1 min ramp gradient to 5:95, 8.1−14.0 min hold 5:95, 14.0−14.1 min ramp gradient back to 80:20, 14.1−17.0 min hold 80:20. Injection volume was 10 μL. Sample residues were quantified using a linear standard curve method (*R* (*2*) = 0.98 or better for all compounds). See **Figure 1** for the basic sample flowchart used for analysis.

RESULTS AND DISCUSSION

The method developed showed acceptable recoveries over three levels of fortification for each of the eleven compounds of interest (**Table 3**). The method limits of quantitation (LOQ) and detection (LOD) were determined to be 0.10 and 0.050 ppm, respectively. LOD was defined as roughly ten times the signal-to-noise for the least sensitive compound (carfentrazone-ethyl), and LOQ was defined as two times the LOD. The defined LOQ was successfully tested for each compound such that recoveries fell between 70−120% with standard deviations ≤20%. It should be noted that abamectin is applied to the crop as a mixture of ≥80% B_1a and ≤20% B_1b (*21*). Since the B_1a is the most prevalent form, it was decided to screen for that form only, with the thought that if a measurable amount was determined, then a second analysis could be conducted to determine both. Also, the B_1b form showed poor sensitivity in early mass spectrometer optimizations, thus not lending itself to a general screen. Mefenoxam, also know as metalaxyl-M, is an enantiomer of metalaxyl. Both compounds share a registration on hops, as well as, the same ion transition for MS/MS determination (*13*). While there would be a small retention shift between the enantiomers, this method could also approximate metalaxyl residues. The 0.1 ppm LOQ determined for carfentrazone-ethyl is actually twice the established tolerance. Here again, if residues were measured above the LOD (0.05 ppm), then a separate analysis could be conducted to determine carfentrazone-ethyl more accurately.

The untreated control sample used for the fortification studies was obtained from a 40CFR Part 160 Magnitude of Residue project on cyazofamid on hops (*22*). The field history from this sample showed that none of the target compounds have been applied during the growing season and the concentrated extract showed no significant residues above the method LOD for each of the target compounds. Commercially grown hop samples received at our facility represent specific varieties grown in Washington, Idaho, and Oregon. Each sample consists of a subsample from a composite sample produced from several thousand bales by the Washington State Department of Agriculture Plant Protection facility in Yakima, WA. Of the compounds screened during the 2006 and 2007 growing seasons, only bifenazate, bifenthrin, hexythiazox, and quinoxyfen had residues above the LOQ (**Table 4**). Sample analysis was duplicated for each commercially grown sample and measured residues correlated within 20% of each other. Typical chromatograms of standards and hop extracts can be seen in **Figures 2–5**.

Due to the popularity of Anastassiades' method (*17*) of extracting several pesticides of wide ranging physical-chemical properties from plant material, the procedure was used as a starting point in method development for hops. However, the aforementioned method is generally for crops with relatively higher moisture content. Moreover, the single primary secondary amine sorbent (PSA) cleanup step did not provide adequate sample cleanup of hop extracts. Wong et al. had success with a lower moisture crop, ginseng root, by adding a C_{18} sorbent

cleanup step prior to the graphitized carbon black/PSA cleanup (*23*). The results from Wong et al., as well as, results gained from work published by our facility on flonicamid determination on hops (*24*) lead to the adoption of a two-step SPE cleanup system.

In earlier residue evaluations on dried hop cones developed by our group, acetone was used as the extraction solvent (*19*). Because of acetone's extraction strength many undesirable matrix components (waxes, resins and oils) were coextracted and subsequently required size exclusion gel permeation chromatography (GPC) to provide adequate sample cleanup. Unfortunately, with GPC excessive amounts (>500 mL) of dichloromethane and cyclohexane were required per sample. The development of this two SPE cleanup procedure provided adequate cleanup without relying on the use of chlorinated solvents and also reduced overall organic solvent usage. Furthermore, by using the milder MeCN extraction procedure, a significant amount of undesirable matrix components were retained by the Nexus polymeric material allowing for adequate cleanup by the simpler Nexus-NH_2 SPE system. Also, the elimination of the GPC step reduced the overall analysis time by 50%. With the method presented herein, 12 samples can be completed in ∼4 h and analyzed by LC-MS/MS in approximately 15 h (overnight).

Initial MS/MS compound optimizations were conducted with the electrospray and APCI sources in both positive and negative ionization modes. Although electrospray in positive ionization mode provided reasonable response for all compounds, APCI was chosen as the ionization source for this study. Typically, APCI does not suffer from the same enhancement/suppression issues that can occur using the electrospray with difficult matrixes. By minimizing enhancement/suppression, the need for internal standards is eliminated, which reduces cost by not having to buy expensive and often unavailable isotope-labeled compounds.

As a result of the combination of Nexus and NH_2 SPE cleanups with LC-MS/MS determination by APCI, a rugged and selective method was developed for the screening of 11 compounds in dried hop cones. LC-MS/MS instrumentation continues to undergo rapid and significant improvements in versatility and analyte sensitivity. As a result, the screening method presented should accommodate a greater number of compounds at even lower quantitation levels.

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