Applications Note



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Developing New Methods for Pesticides in Dietary Supplements Advantages of the QuEChERS Approach

New requirements for dietary supplements to be manufactured under cGMP regulations have created a need for methods to detect pesticides in these complex, largely botanical products. QuEChERS offers a simple, cost-effective approach that can reduce matrix interferences as well as variation among technicians. Here we demonstrate a procedure that incorporates a QuEChERS extraction, cSPE cleanup and GC-TOFMS, resulting in good recoveries for a wide range of pesticide chemistries in dandelion root powder.

Introduction

Recently the FDA announced that makers of dietary supplements (e.g. vitamins, herbal and botanical pills, etc.) will have to adhere to current Good Manufacturing Practices (cGMPs), marking a major shift in regulatory oversight and testing for the industry. Previously, compliance was voluntary, but in 2003, due to public and industry concern, the FDA proposed requiring dietary supplement manufacturers to adhere to cGMP standards. The final rule was issued in June 2007 and is in full effect June 2010 [1]. Basic GMPs require implementing comprehensive procedures to ensure product quality and safety. Since many dietary supplements are largely derived from botanical sources, they must be tested for pesticide contaminants in order to meet cGMP regulations. As a result of this requirement, labs are working to develop and validate methods, an endeavor which is complicated by the wide range of pesticides and matrices to be tested.

Labs can begin method development with the FDA Pesticide Analytical Manual (PAM), which includes procedures for plant materials. While PAM Method 303 is an appropriate starting point, it has several disadvantages, including high solvent consumption, manual procedures that contribute to analytical variation, and the inability to extract polar pesticides. As an alternative, we developed a QuEChERS-based method for analyzing pesticides in dietary supplements that has several advantages over PAM 303 (Table I). QuEChERS is an approach that was developed by the USDA Eastern Regional Research Center as a simple, rapid, effective, yet inexpensive way to extract pesticide residues from fruits and vegetables, followed by a novel dispersive solid phase extraction (dSPE) cleanup of the extract. Because of these benefits, the approach has become popular and has been expanded to include numerous other matrices. We chose QuEChERS as an alternative to PAM 303 because of its speed, simplicity, and low solvent use, as well as its ability to produce good extraction efficiencies for relatively polar pesticides [2].

Based on preliminary studies, we knew that while the extraction part of QuEChERS would be successful, the dSPE cleanup step probably did not have the capacity to handle the matrix complexity of most dietary supplements. Thus, we compared dSPE to a cartridge solid phase extraction (cSPE) cleanup and established a procedure that uses a QuEChERS extraction, cSPE cleanup, and GC-TOFMS for accurate determinations of 46 pesticides in dandelion root powder. This approach saves time and can reduce analyst variation by minimizing manual preparation with prepackaged extraction salts and snap-and-shoot standards. As shown in Figure 1, it also uses much less solvent, salt, and sorbent, making it a greener, more cost-effective method than PAM 303.

	PAM 303 Method	QuEChERS + cSPE	Benefits of QuEChERS + cSPE
Solvent used (mL)	1,850	92	20x less solvent; cleaner, greener, & cost-effective
# of Solvents	4	3	
Salt and sorbent used (g)	35	6.6	5x less salt/sorbent
Glassware/lab equipment	 Separatory funnel (1L capacity) Filter apparatus Florisil column 	CentrifugeSPE manifold	Fast, easy batch processing
Manual preparation	Salt solutionStandardsFlorisil column	None—prepackaged salts and cSPE cartridge are ready to use	Highly reproducible; less manual prep means less human error

Table I Decrease costs and increase reproducibility with a GMP-friendly QuEChERS

 approach to analyzing pesticides in dietary supplements.

Procedure

Sample Wetting and Fortification

Fully processed dandelion root powder obtained from a dietary supplement manufacturer was used for this work. The powder was wetted and then fortified with 46 pesticides representing different chemical classes that have been previously reported in dietary supplements [3]. Typically, QuEChERS methods use 10-15 grams of material with high water content (>80%). Therefore, to prepare for a QuEChERS extraction with a dry commodity, it is critical to use a reduced amount of material and wet it with water prior to extraction. In this work, 1 g of dietary supplement powder was combined with 9 mL of water. After shaking to mix well, the wetted supplement was fortified with 200 μ L of a 2 ng/ μ L pesticides spiking solution resulting in a 400 ng/g spike level, relative to the original commodity. Also, 100 μ L of QuEChERS Internal Standard Mix for GC/MS Analysis (cat.# 33267) was added. The sample was then allowed to soak for 2 hours prior to extraction.

Figure 1 QuEChERS extraction and cSPE cleanup simplifies sample prep for pesticides in dietary supplements. **OuEChERS Extraction** PAM Extraction 1. **Wet** 1 g of matrix powder with 9 mL of water. 1. Weigh 20-25 g and fortify as necessary. Fortify as necessary, then soak 2 hours. 2. Add 350 mL 65:35 acetonitrile:water. 2. Add 10 mL acetonitrile. 3. Blend 5 min. and filter. 3. Shake 1 min. 4. **Transfer** to a 1 L separatory funnel and add 100 4. Add Q-sep[™] Q110 extraction salts. mL petroleum ether (hexanes). 5. **Shake** 1 min. 5. **Shake** 1-2 min. 6. Centrifuge 5 min. at 3,000 U/min. 6. Add 10 mL saturated sodium chloride and 600 mI water 7. **Shake** 45 seconds and allow layers to separate. 8. **Wash** organic layer with 100 mL water and transfer to a graduated cylinder. **cSPE** Cleanup 9. **Wash** organic layer again with another 100 mL 1. Prepare 6mL Resprep[®] Combo SPE Cartridges as water and transfer to cylinder. follows. Add magnesium sulfate to a level approxi-10. Add 15 g sodium sulfate to organic fraction. mately half the height of either the GCB or PSA 11. Shake vigorously, then evaporate to ~100 mL. bed. Rinse cartridge with 20 mL of 3:1 acetonitrile:toluene. 2. Load 1 mL of extract on cartridge and elute with ¥ 50 mL 3:1 acetonitrile:toluene. 3. Evaporate to approximately 0.5-1 mL using dry nitrogen gas and a 35-40°C water bath. PAM Cleanup 4. Add 3 mL toluene and evaporate to just under 0.5 mL. 1. **Prepare** a Florisil[®] cleanup column as follows. 5. Rinse evaporation vessel with toluene and adjust Add Florisil® to a 22 mm x 300 mm column to a final volume to 0.5 mL. height of 4 inches, then top with 1/2 inch sodium sulfate.

Solvent Usage: 92 mL, 3 solvents

- 2. **Transfer** extract to column for cleanup.
- Elute in 3 separate fractions as follows:
 a. 200 mL 6% diethyl ether in petroleum ether.
 b. 200 mL 15% diethyl ether in petroleum ether.
 c. 200 mL 50% diethyl ether in petroleum ether.
- 4. For each fraction: **evaporate** solvent, **adjust** final volume, and **add** internal standards as necessary for GC injection.

Solvent Usage: 1,850 mL, 4 solvents

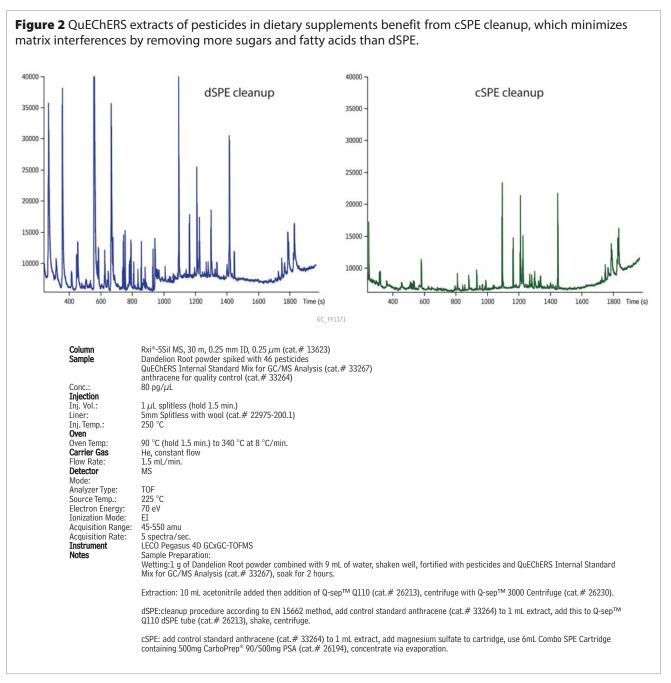
QuEChERS Extraction

The EN 15662 QuEChERS method was used for sample extraction [4]. 10 mL of acetonitrile was added to the wetted sample. After a 1 minute shake, Q-sepTM Q110 buffering extraction salts (cat.# 26213, 4 g MgSO₄, 1 g NaCl, 1 g trisodium citrate dihydrate, 0.5 g disodium hydrogen citrate sesquihydrate) were added. Following another 1 minute shake, the sample was centrifuged for 5 minutes at 3,000 U/min. with a Q-sepTM 3000 centrifuge (cat.# 26230). Lastly, 5 μ L of quality control standard anthracene (cat.# 33264) was added to a 1 mL aliquot of extract to indicate fatal losses of planar compounds to Carboprep[®] 90 during cleanup.

Extract Cleanup

Two approaches were explored for extract cleanup: dSPE and cSPE. For dSPE, 1 mL of extract was added to a Q210 dSPE tube containing 150 mg MgSO₄ and 25 mg PSA (cat.# 26215), shaken for 2 minutes, and then centrifuged for 5 minutes. The resulting final extract was then analyzed by GC-TOFMS.

For cSPE cleanup [5], 1 mL of extract was processed with a 6 mL Resprep[®] Combo SPE Cartridge (cat.# 26194), which is designed for pesticide residue cleanup and contains 500 mg CarboPrep[®] 90 and 500 mg primary secondary amine (PSA). To prepare the SPE cartridge, magnesium sulfate was first added to a level approximately one-quarter height of the total bed; then the cartridge was rinsed with 20 mL of 3:1 acetonitrile: toluene, which was discarded. For cleanup, 1 mL of extract was loaded onto the prepared cartridge and then eluted with 50 mL 3:1 acetonitrile: toluene. The eluent was then evaporated and solvent exchanged using dry



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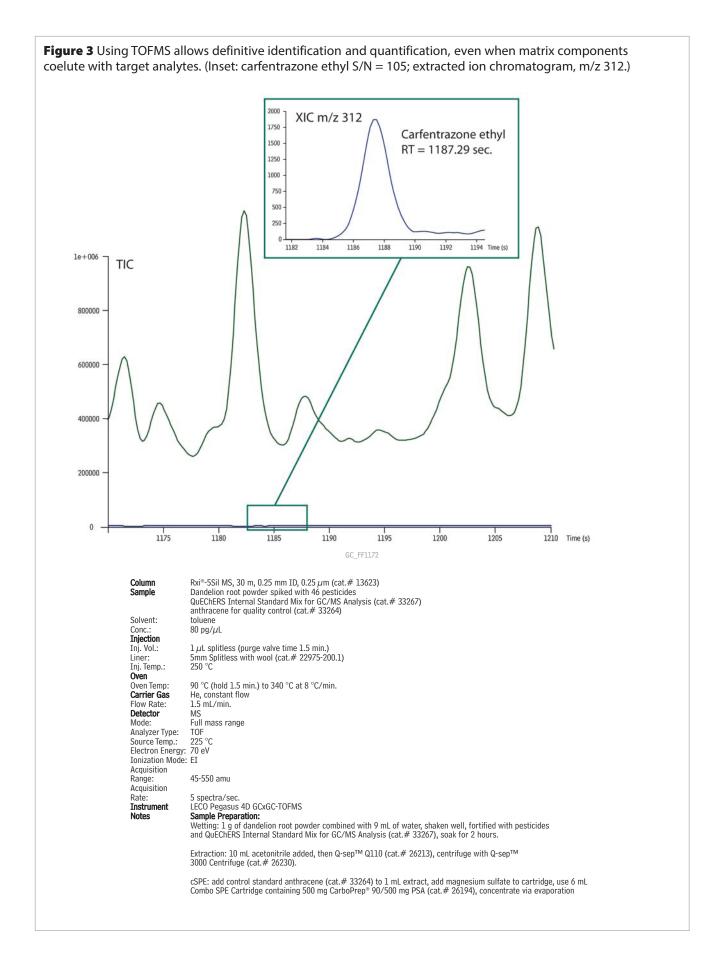


Table II This QuEChERS-based method provides good recoveries for a variety of pesticides found in dietary supplements.

Compound	RT (sec.)	Recovery (%)	Class	Туре
1,2,3,5-Tetrachlorobenzene	418.0	46	Organochlorine	Chemical intermediate
Pentachlorobenzene	587.0	51	Organochlorine	Metabolite
Tetrachloronitrobenzene	648.8	72	Organochlorine	Fungicide
2,3,5,6-Tetrachloroaniline	678.0	64	Organochlorine	Fungicide
alpha-BHC	739.4	69	Organochlorine	Insecticide
Hexachlorobenzene	744.4	56	Organochlorine	Impurity
Pentachloroanisole	754.6	62	Organochlorine	Metabolite
peta-BHC	780.5	88	Organochlorine	Insecticide
Pentachloronitrobenzene	784.2	62	Organochlorine	Fungicide
Pentachlorobenzonitrile	790.0	70	Organochlorine	Impurity
gamma-BHC	791.2	85	Organochlorine	Insecticide
Diazinon	816.6	71	Organophosphorus	Insecticide
Chlorothalonil	819.2	100	Organochlorine	Fungicide
delta-BHC	836.4	85	Organochlorine	Insecticide
Pentachloroaniline	857.6	75	Organochlorine	Metabolite
Pentachlorothioanisole	931.2	66	Organochlorine	Metabolite
PCB 52	932.0	-	Organochlorine	Internal standard
Chlorpyrifos	952.6	92	Organophosphorus	Insecticide
Dacthal	958.8	83	Organochlorine	Herbicide
Parathion	963.2	91	Organophosphorus	Insecticide
Heptachlor epoxide	1008.4	93	Organochlorine	Metabolite
Procymidone	1027.4	100	Organonitrogen	Fungicide
Endosulfan I	1059.8	70	Organochlorine	Insecticide
1,4'-DDE	1094.6	90	Organochlorine	Metabolite
Dieldrin	1097.8	91	Organochlorine	Insecticide
Nyclobutanil	1100.6	100	Organonitrogen	Fungicide
Endosulfan II	1141.6	110	Organochlorine	Insecticide
Oxadixyl	1149.4	100	Organonitrogen	Fungicide
4,4'-DDD	1152.2	98	Organochlorine	Insecticide, Breakdown product
2,4'-DDT	1155.0	94	Organochlorine	Insecticide
Carfentrazone ethyl	1188.0	110	Organonitrogen	Herbicide
Endosulfan sulfate	1194.8	105	Organochlorine	Metabolite
Fenhexamid	1202.4	94	Organonitrogen	Fungicide
1,4'-DDT	1203.8	96	Organochlorine	Insecticide
Piperonyl butoxide	1237.6	93	Other	Insecticide synergist
[prodione	1261.0	110	Organochlorine	Fungicide
Cypermethrin 1	1466.8	130	Pyrethroid	Insecticide
Cypermethrin 2	1474.8	86	Pyrethroid	Insecticide
Cypermethrin 3	1478.6	75	Pyrethroid	Insecticide
Cypermethrin 4	1481.8	100	Pyrethroid	Insecticide
Pyraclostrobin	1538.0	92	Organonitrogen	Fungicide
Fluvalinate 1	1541.4	100	Pyrethroid	Insecticide
Fluvalinate 2	1546.8	94	Pyrethroid	Insecticide
Difenoconazole 1	1562.0	99	Triazole	Fungicide
Difenoconazole 2	1566.6	81	Triazole	Fungicide
Azoxystrobin	1596.0	93	Organonitrogen	Fungicide

nitrogen gas and a 35-40 °C water bath. Evaporation was allowed to proceed until approximately 0.5-1 mL eluent was left, at which point about 3 mL of toluene was added. The mixture was evaporated to just under 0.5 mL, and then the evaporation vessel was rinsed with toluene to bring the sample to a final volume of 0.5 mL. The resulting final extract was then analyzed by GC-TOFMS.

Standards

Matrix-matched standards were prepared at 80 pg/µL, as 80 pg/µL is the expected final concentration in extract of the 400 ng/g matrix spikes (assuming 100% recoveries). Matrix-matched standards were prepared by adding standard solution to the final extract (post-cleanup) from a control sample. Actual recoveries were calculated by comparing peak areas for fortified samples that were extracted and cleaned, to areas of a matrix-matched standard, using the internal standard quantification method.

GC-TOFMS

A LECO Pegasus III GC-TOFMS instrument was used and all data were processed with LECO ChromaTOF[™] software. Gas chromatography was performed using an Rxi[®]-5Sil MS column (30m x 0.25mm x 0.25µm, cat.# 13623). Instrument conditions are shown in Figure 1. Temperature and flow settings yielded an analysis time of 32.75 minutes.

Results

One aspect of this investigation was to compare the applicability of two sample cleanup methods, dSPE and cSPE for QuEChERS extracts of pesticides in dietary supplements. While dSPE has the advantage of improved speed and less solvent usage, it does not have the sorbent capacity to adequately clean up these samples (Figure 2). Since cSPE uses more sorbent, it is a better choice for dietary supplements (and other complex samples, e.g. spices, essential oils) as it can remove more matrix components, such as fatty acids, sugars, and pigments. QuEChERS methods developed for dietary supplements of botanical origin can benefit from the extra sorbent capacity of cSPE, which reduces GC inlet/column contamination and chromatographic interference from complex botanical matrices.

Even with effective extraction and cleanup techniques, dietary supplements can be challenging to analyze due to their complexity. Coelutions are common and pesticide residues can be overwhelmed by abundant matrix compounds not only qualitatively, but also by interfering with quantification masses. Figure 3 plots the total ion chromatogram (TIC) and extracted ion m/z 312 corresponding to the quantitation mass for carfentrazone ethyl. It is clear that target pesticide signals can be obscured in the TIC. LECO ChromaTOF[™] software was able to identify target pesticides by comparison with reference spectra using automatic peak find and spectral deconvolution algorithms, along with calibration and quantification. TOFMS makes this powerful data processing possible with very fast acquisition rates and unbiased mass spectra, and by having pg level sensitivity in full mass range mode, which allows the potential for finding non-target pesticides. An alternate GC/MS approach for targeted pesticides in dietary supplements would be to use selected ion monitoring with a typical quadrupole mass spectrometer.

Overall, the combination of QuEChERS extraction, cSPE cleanup, and GC-TOFMS used in this method produced good recoveries for most compounds tested (Table II). Although early eluting compounds trended toward lower recoveries, most analytes, including more polar compounds, showed excellent recoveries. The potential for good recoveries of polar pesticides is a major advantage to QuEChERS methods; this difference is due to the use polar acetonitrile as the extraction solvent, rather than petroleum ether (hexanes) which is used in PAM 303. The lower recoveries here of early eluting compounds may be due to evaporative loss during concentration steps, due to their higher volatility. Additionally, in the case of planar compounds, reduced recoveries may be due to interaction with the CarboPrep® 90 sorbent used to remove pigments and other matrix compounds, although the planar quality control standard, anthracene, did not show drastic losses during cSPE Overall, the chromatography and recovery results seen for a broad range of pesticides in dandelion root demonstrate the utility of the QuEChERS approach for dietary supplement testing.

Conclusion

Demonstrated here is a QuEChERS approach that helps accomplish the pesticide testing now required for dietary supplements. The basic methodology presented here for dandelion root can be modified for other analytes and matrices and illustrates the advantages of the QuEChERS approach for labs developing cGMP methods. Analytical benefits include reduced interferences and good recoveries, even of polar compounds. Other benefits include an overall savings of both materials and prep time compared to the PAM 303 method, and better expected reproducibility due to the straight-forward procedure with fewer manual preparations.

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- Convenient, multiple adsorbent beds in a single cartridge.
- For use in multiple-residue pesticide analysis, to remove matrix interferences.

SPE Cartridge	qty.	cat#
6mL Combo SPE Cartridge		
Packed with 500mg CarboPrep 90/500mg Aminopropyl, Polyethylene Frits	30-pk.	26193
6mL Combo SPE Cartridge		
Packed with 500mg CarboPrep 90/500mg PSA, Polyethylene Frits	30-pk.	26194
6mL SPE Cartridge		
Packed with 500mg PSA, Polyethylene Frits	30-pk.	26195
6mL Combo SPE Cartridge		
Packed with 200mg CarboPrep 200 and 400mg PSA, PTFE Frits	30-pk.	26127
6mL Combo SPE Cartridge		
Packed with 250mg CarboPrep 200 and 500mg PSA, PTFE Frits	30-pk.	26128
6mL Combo SPE Cartridge		
Packed with 500mg CarboPrep 200 and 500mg PSA, PTFE Frits	30-pk.	26129



Sc	orbe	nt G	iuid	e
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Sorbent	Removes
MgSO ₄	excess water
PSA*	sugars,
	fatty acids,
	organic acids,
	anthocyanine
	pigments
C18	lipids,
	nonpolar
	interferences
GCB**	pigments,
	sterols,
	nonpolar
	interferences
*PSA—prin	mary and
secondary a	amine exchange
material	
**GCB—gi	raphitized
carbon blac	:k

- Q-sep[™] QuEChERS Tubes for Extraction and Clean-Up of Pesticide Residue Samples from Food Products
- Fast, simple sample extraction and cleanup using dSPE.
- Fourfold increases in sample throughput.
- Fourfold decreases in material cost.
- · Convenient, ready to use centrifuge tubes with ultra pure, preweighed adsorbent mixes.

Description	Material	Methods	qty.	cat#
50mL Centrifug	ge Tubes for Sample Extraction			
	4g MgSO4, 1g NaCl, 1g trisodium citrate			
	dihydrate, 0.5g disodium hydrogen citrate			
Q110	sesquihydrate	European EN 15662	50-pk.	26213
Q150	6g MgSO₄, 1.5g NaOAc	AOAC 2007.1	50-pk.	26214
Empty 50mL		European EN 15662,		
Centrifuge Tub	e —	AOAC 2007.1	25-pk.	26227
2mL Micro-Cer	ntrifuge Tubes for dSPE			
(clean-up of 1r	nL extract)			
Q210	150mg MgSO ₄ , 25mg PSA	European EN 15662	100-pk.	26215
Q211	150mg MgSO ₄ , 25mg PSA, 25mg C18	—	100-pk.	26216
Q212	150mg MgSO₄, 25mg PSA, 2.5mg GCB	European EN 15662	100-pk.	26217
Q213	150mg MgSO4, 25mg PSA, 7.5mg GCB	European EN 15662	100-pk.	26218
Q250	150mg MgSO4, 50mg PSA	AOAC 2007.1	100-pk.	26124
Q251	150mg MgSO4, 50mg PSA, 50mg C18	AOAC 2007.1	100-pk.	26125
Q253	150mg MgSO4, 50mg PSA, 50mg GCB	_	100-pk.	26123
	150mg MgSO₄, 50mg PSA, 50mg C18,			
Q252	50mg GCB	AOAC 2007.1	100-pk.	26219
15mL Centrifug	ge Tubes for dSPE			
(clean-up of 6r	nL extract)			
Q350	1200mg MgSO ₄ , 400mg PSA	AOAC 2007.1	50-pk.	26220
Q351	1200mg MgSO4, 400mg PSA, 400mg C18	AOAC 2007.1	50-pk.	26221
	1200mg MgSO4, 400mg PSA, 400mg C18,			
Q352	400mg GCB	AOAC 2007.1	50-pk.	26222
Q370	900mg MgSO4, 150mg PSA	European EN 15662	50-pk.	26223
Q371	900mg MgSO₄, 150mg PSA, 15mg GCB	European EN 15662	50-pk.	26224
Q372	900mg MgSO₄, 150mg PSA, 45mg GCB	European EN 15662	50-pk.	26225
Q373	900mg MgSO4, 150mg PSA, 150mg C18	_	50-pk.	26226
Q374	900mg MgSO4, 300mg PSA, 150mg GCB		50-pk.	26126





Q-sep[™] 3000 Centrifuge

for QuEChERS

- Meets requirements of AOAC and European QuEChERS methodology.
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Centrifuge includes 50 mL tube carriers (6), 50 mL conical tube inserts (6), 4-place 15 mL tube carriers (6), and 2 mL tube adaptors (24).

Description	qty.	cat.#
Q-sep 3000 Centrifuge, 110V	ea.	26230
Q-sep 3000 Centrifuge, 220V	ea.	26231
Replacement Accessories		
50mL Tube Carrier for Q-sep 3000 Centrifuge	2-pk.	26232
50mL Conical Tube Insert for Q-sep 3000 Centrifuge	6-pk.	26249
4-Place Tube Carrier for Q-sep 3000 Centrifuge	2-pk.	26233
2mL Tube Adaptors for Q-sep 3000 Centrifuge	4-pk.	26234



Rxi[®]-5Sil MS Columns (fused silica)

(low polarity Crossbond® silarylene phase; selectivity close to 5% diphenyl/95% dimethyl polysiloxane)

ID	df (µm)	temp. limits	length	cat. #	
0.25mm	0.25	-60 to 330/350°C	30-Meter	13623	

QuEChERS Quality Control Standards for GC/MS Analysis

Cat.# 33268:	Cat.# 33264:				
PCB 138	anthracene				
PCB 153					
50μ g/mL each in acetonitrile, 5mL/ampul					
C	at. # 33268 (ea.)				
100µg/mL in acetonitrile, 5mL/ampul					
Ci	at. # 33264 (ea.)				

QuEChERS Internal Standard Mix for GC/MS

Analysis (6 components) PCB 18 50µg/mL PCB 28 50 PCB 52 50 triphenyl phosphate 20 tris-(1,3-dichloroisopropyl)phosphate 50 triphenylmethane 10 In acetonitrile, 5mL/ampul cat. # 33267 (ea.)



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- Hyperlinked bibliography organized by matrix
- QuEChERS flyer FFFL1183, with method-based product selection guide





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9001 - 17025 - Guide 34