Analytical method validation for terbutryn using gas chromatography/ion trap, gas chromatography/mass selective detector, and liquid chromatography/triple quadrupole mass spectrometers

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Abstract Analytical methods including solvent extraction followed by gas chromatography/ion-trap (GC/IT) with scan and MS/MS mode, a GC/mass selective detector (GC/MSD), and liquid chromatography/triple quadrupole mass spectrometers (LC/MS/MS) were optimized to identify and quantify terbutryn. The spike recovery was 96.5% using GC/IT with scan mode and 103.5% with MS/MS mode, 90.3% by GC/MSD, and 92.5% by LC/MS/MS. The limit of detection (LOD) was 0.0015 mg/kg by GC/IT with scan, 0.026 mg/kg with MS/MS mode, 0.015 mg/kg with GC/MSD, and 0.026 mg/kg by LC/MS/MS. Of the four methods, GC/IT with scan mode was determined to be the most sensitive (with LOD: 0.0015 mg/kg and limit of quantitation (LOQ): 0.0047 mg/kg), rapid (retention time: 9.6 min) and the most precise method (relative standard deviation: 17%) for the quantification of terbutryn. GC/IT with scan mode proved to be the more sensitive analytical method for terbutryn than other methods in this study, showing better accuracy and rapid analysis.

Keywords Terbutryn · Gas chromatography/mass selective detector · Gas chromatography/ion trap · Liquid chromatography/triple quadrupole mass spectrometers

Introduction

Analytical methods used for the identification of triazine residues in the environment have been developed for environmental and public health applications. Exposure to triazine herbicide is thought to occur primarily via food sources when it is applied to soil or sprayed over crop fields [1]. Terbutryn (C₁₀H₁₉N₅S, 2-t-butylamino-4-ethylamino-6-methylthio-s-triazin), a triazine compound, is a colorless to white crystalline powder without a distinct odor. Large volumes of terbutryn have been used as an aquatic herbicide since the mid-1980s, as it controls submerged and free-floating weeds and algae in water courses and reservoirs [2, 3]. Terbutryn is a selective systemic herbicide useful for most grasses and broadleaved weeds of various crops, such as cereals, beans, and fruit trees in agricultural settings [4, 5].

The United State (US) Environmental Protection Agency has classified terbutryn as a possible human carcinogen [6]. Also, it has been reported that terbutryn exhibits genotoxicity in freshly isolated human leukocytes [7]. In long term animal studies, terbutryn intake at 150 mg/kg bw (body weight)/day causes follicular hyperplasia, liver adenomas, and body weight loss in rats [8], and lethal dose 50 (LD 50) of oral administration was estimated to 2045 and 3884 mg/kg in rats and mice, respectively [9]. Terbutryn is easily adsorbed in soils with high organic or clay content and is not volatile in water and therefore will adsorb to suspended particulate matter and sediment [10]. Regarding on human concerns, terbutryn should not exceed

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0.4 mg/L in drinking water by the Australian drinking water guidelines [8], and the maximum concentration of up to 5.6 and 0.13 µg/L was detected in ground water in Germany and UK, respectively [11, 12]. The acceptable daily intake for terbutryn is estimated to be 0.01 mg/kg bw based on *in vivo* toxicity experiments. It has been reported that oral exposure to terbutryn in human is mainly from the residues in foods [8].

Several approaches exist for the identification of terbutryn in water, soil, and agricultural products. For instrumental analysis, nitrogen–phosphorus detector, gas chromatography with flame ionization detector, electron-capture detector, mass spectrometer detector (MSD), high-performance liquid chromatography (HPLC) with diode-array detector and fluorescence detectors are commonly used [13–17]. Terbutryn can be identified simultaneously with other triazine herbicides such as atrazine, simazine, prometryne and their metabolites [18–20], but most methods are not selective for terbutryn. Moreover, very little information on the analytical methods for terbutryn quantification using various instrumental conditions is available. In this study, we sought to optimize and compare several sensitive analytical methods to quantify low concentrations of terbutryn.

Materials and methods

Reagents

Ethyl acetate and acetonitrile were the sample pesticide and HPLC grade, respectively (Fisher Scientific, Pittsburgh, PA). Terbutryn was purchased from Fluka (Buchs, Switzerland). Sodium sulfate (anhydrous) was purchased from Fisher Scientific Co., Ltd (Fair Lawn, NJ). Mili-Q water and methanol (Fisher Scientific, PA, USA) were filtered with a 0.45 µm filter.

Fortifications and calibration standards

Terbutryn working solution (50 µg/mL) and ametryn were used as an internal standard (50 µg/mL) and dissolved in methanol. Triplicate fortified samples (1 mg/kg) were created by adding the terbutryn working solution (100 µL) to pureed cabbage (5 g). Terbutryn working solutions were in ethyl acetate for GC/IT and GC/MSD and in acetonitrile for LC/MS/MS within the range of 0.01–5.0 µg/mL (Table 1). For GC/IT and GC/MSD, 10 µL of the internal standard solution was added to standard solutions (0.5 mL) and sample extracts. Prior to LC/MS/MS analysis, the internal standard (20 µL) was added to the standard solutions (1 mL) and sample extracts.

Sample preparations for analysis of terbutryn

In a 250-mL homogenization vessel, sample (5 g), sodium sulfate (30 mL) and ethyl acetate (100 mL) were added and the samples homogenized for 30 s with a homogenizer (IKA-WEREKE, Germany), before being filtered. Ten milliliters of the sample aliquots was then evaporated until dry using a multi-sample Turbovap LV Evaporator (Zymark, Hoptkinton, MA, USA) with nitrogen gas (5–15 psi) for 5 min at 60 °C. The dry extract was redissolved in acetonitrile (2 mL) and filtered through a 0.45 µm nylon filter (Fisher Scientific, Pittsburgh, PA, USA) for LC/MS/MS, and with ethyl acetate (2 mL) for GC/IT as well as GC/MSD. All extracts were stored at 4 °C until use.

Analysis of terbutryn in cabbage extracts

The method validation involved triplicate fortified samples of the cabbage (1 mg/kg). The LOD and LOQ values were obtained by the standard deviation (SD) of results from seven injection of a low concentration of terbutryn standard, Terbutryn at 0.01 µg/mL was analyzed by GC/IT and GC/MSD, and at 0.025 µg/mL by LC/MS/MS, which had at 3:1 of signal-to-noise ratio. The LOD and LOQ were calculated from the following equations: $LOD = 3.14 \times SD$ and $LOQ = 10 \times SD$. Matrix effects using LC/MS/MS were evaluated by comparison of the response of terbutryn (1 µg/mL) in pure solvent methanol in blank extracts.

GC-ion trap (IT) analysis

A Varian CP-3800 GC integrated with a Saturn 2200 ion trap mass spectrometer (Varian, Sugar Land, TX, USA) equipped with a 30 m × 0.25 mm i.d. ($d_f = 0.25 \mu\text{m}$) DB5-MS bonded-phase fused-silica capillary column (J&W Scientific, Folsom, CA, USA) was used for terbutryn analysis. Varian workstation software (Ver. 6.5, Walnut Creek, CA, USA) was also used. The sample injection volume was 1.0 µL in the split and splitless injection mode. Split time was 1.25 min and the split ratio was 20:1. The helium carrier gas flow rate was held steady at 1 mL/min. The injector temperature and interface temperature were 240 and 280 °C, respectively. The oven temperature was programmed to increase from 60 °C (stable for 0.5 min) and then to 150 °C at a rate of 40 °C/min, to 220 °C (20 °C/min), and to 260 °C (10 °C/min), to 300 °C (30 °C/min) and held for 0.42 min at 300 °C. The total analysis time was 12 min and the retention times of terbutryn and ametryn were 9.6 and 9.4 min, respectively (Table 1). Two analytical methods to quantify terbutryn were compared, using both full scan and MS/MS. The mass spectral identification of terbutryn was operated with electron impact ionization (EI) at 70 eV and an emission current of 10 µA

Table 1 Calibration method by GC/IT, GC/MSD, and LC/MS/MS analyses

	GC/IT		GC/MSD	LC/MS/MS
	Full scan	MS/MS		
Internal calibration ^a	$y = -1.0286x^2 + 3.4815x + 0.0157$	$y = -1.9624x^2 + 7.1179x + 0.038$	$y = -0.1487x^2 + 1.5107x + 0.0064$	$y = -0.821x^2 + 10.6x - 0.00000544$
Standard range (µg/mL)	1.0, 0.25, 0.1, 0.025 and 0.01	1.0, 0.25, 0.1, 0.025 and 0.01	1.0, 0.1, 0.025, and 0.01	5.0, 1.0, 0.25, 0.1 and 0.025
R^2	0.9998	0.9992	0.9998	0.9986
RT for terbutryn (min)	9.6 ± 0.002	9.6 ± 0.005	9.3 ± 0.008	4.9 ± 0.005
RT for ametryn, IS (min)	9.4 ± 0.002	9.4 ± 0.005	9.1 ± 0.008	4.8 ± 0.005

RT retention time

^aNon-weighting and quadratic calibration for GC/IT and GC/MSD, whereas weighting ($1/x^2$), and quadratic calibration for LC/MS/MS

in full scan and MS/MS mode. MS acquisition was from an m/z value of 100 with a 1 s scan time to an m/z value of 300 with a 0.4 s scan time. In MS/MS mode, the conditions were as follows: ionization storage level of m/z 48, ejection amplitude of 20 V, isolation window of m/z 3, isolation time of 5 ms, non-resonant excitation mode, excitation storage level of m/z 106, excitation amplitude of 66 V, and excitation time of 20 ms. In full scan mode, the full spectrum was assessed for confirmation, and the sum of ions m/z 170, m/z 226 and m/z 241 were together used for quantification (Table 2). In MS/MS mode, the transition m/z 241 → 226 was used as the input for quantification. Extracted ametryn ion (m/z 227) and ions (m/z 170, m/z 185 and m/z 212) were quantified in full scan and MS/MS mode, respectively (Table 2). Quantification was achieved using the internal standard calibration curve (four points) with the peak area and non-weighted and quadratic regression (Table 1).

GC-mass selective detector (MSD) analysis

A gas chromatograph (HP 6890 series; Hewlett Packard, MN, USA) integrated with a quadrupole mass spectrometer

was used for mass spectral identification of terbutryn at an MS ionization voltage of 70 eV. A DB5-MS bonded-phase fused-silica capillary column (15 m × 0.25 mm i.d., d_f = 0.25 µm; J&W Scientific, Folsom, CA, USA) was used. The instrument was used with Hewlett Packard Chemstation software B.01.00 (Ramsey, MN, USA). For the analytical conditions, the sample injection volume was 1.0 µL in splitless mode and the carrier gas was helium at 1.0 mL/min. The injector and interface temperature were 250 and 280 °C, respectively. The oven temperature was programmed from 60 to 250 °C at 15 °C/min. SIM (selected ion monitoring) mode was used to quantify terbutryn. Full-scan MS analyses were performed within the range from m/z 50 to 500, and the scan rate was 1.53 scan/s. The total analysis time was 12.67 min. Retention time for terbutryn was 9.3 min and 9.1 min for ametryn. Terbutryn ions, m/z 241 (quantitation) and m/z 226 (confirmation) were chosen. Also analyzed were ametryn ions at m/z 212 (quantitation) and m/z 227 (confirmation) (Table 2). The internal standard calibration curve (five points) using the peak area with a non-weighted and quadratic regression (Table 1) were used for quantification. Terbutryn in the unknown cabbage samples were identified by comparison

Table 2 Detection limits, transition ion, and quantitation ion of terbutryn and ametryn (internal standard) by for GC/IT, GC/MSD, and LC/MS/MS analyses

Instruments	Terbutryn (mg/kg)		Transition ion (m/z)		Quantitation ion (m/z)	
	LOD	LOQ	Terbutryn	Ametryn	Terbutryn	Ametryn
GC/IT (scan mode)	0.015	0.047			170, 226, 241	227
GC/IT (MS/MS)	0.026	0.085	241 → 226	227 → 172, 185, 212	226	172, 185, 212
GC/MSD	0.015	0.048			241	212
LC/MS/MS	0.026	0.083	242 → 186, 91	228 → 186	91	186

LOD limit of detection, LOQ limit of quantification

with the mass spectral fragmentation pattern of the standard compound and MS library in the NIST AMDIS version 2.1 software.

LC–MS/MS

A liquid chromatograph (Perkin Elmer series 200 LC; NY, USA) comprised of a Perkin Elmer series 200 quaternary pumping system, together with a Perkin Elmer Series 200 auto sampler, and an in-line mobile phase degasser (Columbia, MD, USA) were used. For the chromatographic analysis, a reverse phase column (Waters Xterra® RP18, 150 mm × 4.6 mm × 3.5 μm; MA, USA) was used with a C18 guard column (4 × 3.0 mm i.d., Phenomenex, Torrance, CA, USA). The HPLC was connected to a triple-quadrupole MS (Perkin-Elmer SCIEX API 2000 LC/MS/MS; CT, USA). The Analyst version 1.4.2 software (SCIEX; CA, USA) was used. An injection volume of 15 μL and a flow rate was 0.5 mL/min was also used. The mobile phase consisted of isocratic elution using methanol/water (95/5, v/v) at 0.1% formic acid for 7 min. The retention time for terbutryn was 4.9 and 4.8 min for ametryn. MS data was acquired with the positive ion electrospray ionization/multiple reaction monitoring (ESI/MRM) mode under the following conditions: temperature 350 °C, dwell time of 0.4 s. The curtain, auxiliary 1, and auxiliary 2 gases, and collision induced dissociation (CID) were set to 50, 40, 20, and 6 psi, respectively (Table 3). The terbutryn peak area from the transition of m/z 242 to m/z 186 was used for confirmation and that of m/z 242 to m/z 91 was used for quantitation. Ametryn peak area from the transition of m/z 228 to m/z 186 was used as the IS (Table 2). Quantification was achieved with the internal standard calibration curve (five points) using the peak area with weighted ($1/x^2$) quadratic regression (Table 1).

Statistical analysis

Experimental data were presented as mean ± standard deviation (SD). Significant differences between varieties were assessed using one-way ANOVA Duncan's test ($p < 0.05$) based on the SPSS system.

Results and discussion

Development of method

The technique for liquid extraction used in the present study was found to be straightforward, efficient and cost-effective. Spike recoveries are presented in Table 4. Although ethyl acetate was used as the extraction solvent, the method could be further optimized for extraction volume, extraction time and the total number of extractions. Sensitivity could also be improved by evaporating to a lower final volume and the introduction of clean-up steps. The identification of these analytes was confirmed by matching retention times and spectrums of standards. High spike recovery by GC/IT with MS/MS mode might be a result of matrix enhancement in the injector or column. In addition, the difference in the matrix effect on terbutryn and ametryn (internal standard) might cause the high spike recovery. The mass spectra for terbutryn and ametryn were consistent with previous reports [21–23]. The check was positive for terbutryn by LC/MS/MS and GC/IT, but the concentration detected was lower than 0.006 mg/kg. Terbutryn was identified in the blinded samples by GC/MSD, GC/IT, and LC/MS/MS. The LC/MS/MS analysis took the shortest time (7 min) in comparison to GC/MSD (12.67 min) and GC/IT (12 min). Terbutryn and ametryn presented the complete chromatographic resolution in GC/MSD, GC/IT, and LC/MS/MS, but there was an exception in full scan chromatogram for standard solution of 0.01 μg/mL in GC/MSD. Therefore, for identification, analytes were confirmed by comparing ion ratios of the unknowns to those of the standards.

The EI generated more structural information than ESI, and the fragment ions provided useful qualitative and quantitative data. The predominant ion of terbutryn and ametryn by GC/IT and GC/MSD was $[M]^+$. For GC/IT with scan mode, major ions in the EI mass spectra of terbutryn were m/z 241, m/z 226, m/z 185, and m/z 170, which is consistent with a previous report [24]. In this study, the sum of extracted ions m/z 241, 226, and 170 was used for quantification in GC/IT with scan mode and its quantification produced not only a good correlation coefficient

Table 3 Mass parameters of multiple reaction monitoring (MRM) for detecting terbutryn and ametryn (internal standard) by using LC/MS/MS

	Q1 ^a , mass (amu)	Q3 ^b , mass (amu)	Parameter (volt)				
			DP ^c	EP ^d	FP ^e	CE ^f	CXP ^g
Terbutryn	242	186	25	11	400	26	8.6
	242	91	25	11	400	37	5.5
Ametryn	228	186	25	11	400	23.4	21

^aFirst mass-filtering device; ^bSecond mass-filtering device; ^cDeclustering potential; ^dEntrance potential; ^eFocusing potential; ^fCollision energy; ^gCollision cell exit potential

Table 4 Quantification results of terbutryn in cabbages by using GC/IT, GC/MSD, and LC/MS/MS

Instruments	Blank (mg/kg)	Check (mg/kg)	Unknown-1 (mg/kg)	Unknown-2 (mg/kg)	Spike-1 (mg/kg)	Spike-2 (mg/kg)	Recovery (mg/kg)	RSD (%)
GC/IT (scan mode)	0.001	0.006	0.646 ± 0.070 ^b	0.162 ± 0.002 ^a	0.985 ± 0.149 ^a	0.787 ± 0.100 ^a	96.5 ± 16	17
GC/IT (MS/MS)	0.003	0.003	1.042 ± 0.103 ^a	0.220 ± 0.055 ^a	1.331 ± 0.207 ^a	1.034 ± 0.193 ^a	103.5 ± 20	19
GC/MSD	n.d.	n.d.	0.794 ± 0.059 ^b	0.170 ± 0.011 ^a	0.961 ± 0.123 ^a	0.714 ± 0.089 ^a	90.3 ± 15	21
LC/MS/MS	n.d.	0.0005	0.647 ± 0.012 ^b	0.170 ± 0.008 ^a	0.998 ± 0.054 ^a	0.780 ± 0.050 ^a	92.5 ± 15	16

n.d. not detected; Values are the mean ± SD (n = 3). Letters indicate significant levels computed by Duncan's multiple-range test at a = 0.05 after the ANOVA

($r^2 = 0.9992$) but also better accuracy ($\leq 6\%$ error) than by using m/z 226 ($\leq 13\%$) in GC/IT with MS/MS mode. Although the extracted ions (m/z 241) with GC/MS produced the best correlation coefficients ($r^2 = 0.9998$), overall quantification was less accurate ($\leq 16\%$ error). The extracted ions m/z 241, 226, and 170 by GC/IT with scan mode was the most sensitive for terbutryn quantification. During ESI and APCI optimization for LC/MS/MS, ESI positive mode was found to be superior to positive APCI mode. Therefore, ESI was used since it had less noise and higher abundance for terbutryn. The predominant ion for terbutryn and ametryn analysis by LC/MS/MS was $[M + H]^+$, while those produced by CID with m/z 242 were m/z 186 and 91. The major ions for IS were m/z 186 following CID and m/z 228 in the full scan spectrum.

Analytical methods comparison

The internal calibrations generated linear curves ($> r^2 = 0.9986$), and were effective for the quantification of terbutryn by GC/MSD, GC/IT, and LC/MS/MS. GC/IT with scan mode was the most sensitive (with LOD: 0.0015 mg/kg and LOQ: 0.0047 mg/kg) and showed better precision (CV: 17%), although positive LC/ESI/MS/MS was the most rapid (4.9 min) method for terbutryn quantification (Tables 2, 4).

The CV value above 20% by GC/MSD could be explained by the loss of material during evaporation and extraction steps (Table 4). Recoveries ranged from 70.2 to 105.5% and the precision value (% RSD) was below 20%, which were acceptable according to EU guidelines [2]. The

recovery, LOD, and LOQ in this study were similar or better than previous work using LC/ESI/MS/MS, GC/IT, and LC/UV detectors, but the precision was higher, ranging from 16 to 21%, especially by GC/IT with MS/MS mode and GC/MSD [21, 25]. Terbutryn is known to be sensitive to thermal degradation, which can occur in both the injector and the capillary column in GC [26]. The concentration of the spikes and unknown samples was similarly detected in GC/IT, GC/MSD, and LC/MS/MS, and they were injected in triplicate (Table 4). No matrix effects were observed by LC/MS/MS (Table 5).

GC/IT in scan mode was superior for quantifying terbutryn when compared to GC/IT with MS/MS mode, GC/MSD/SIM, and LC/ESI/MS/MS, because it was a sensitive and reproducible method. The total run time of terbutryn was more rapid than previous reports using GC/IT with scan mode [21, 27], providing the shortest run time in LC/MS/MS.

In conclusion, several analytical methods were validated for the identification and quantification of terbutryn, including chromatography/ion-trap (GC/IT) with scan and MS/MS mode, GC/mass selective detector (GC/MSD), and liquid chromatography/triple quadrupole mass spectrometers (LC/MS/MS). All methods showed different instrumental sensitivity and recovery and GC/IT with scan mode demonstrated the best performance for spike recovery (96.5%), LOD (0.0015 mg/kg), LOQ (0.0047 mg/kg) and RSD (17%), with good accuracy and precision. These findings suggest that the use of GC/IT with scan mode is a viable method to analyze low quantities of terbutryn residue in foodstuff or agricultural materials.

Table 5 Matrix effect for response of terbutryn (1 µg/mL) by using LC/MS/MS

	Terbutryn Peak area (m/z 242 → 91)	Ametryn (IS) Peak area (m/z 228 → 186)	Terbutryn RT (min)	Calculated amount (µg/g)
Std with check	42,000	43,600	4.9	0.9830
Std with methanol	41,900	43,500	4.9	0.9829

RT retention time, Std standard, IS internal standard

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Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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