JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

J. Agric. Food Chem. **2006,** *54,* 713–719 **713**

Direct Aqueous Injection Liquid Chromatography/Electrospray Ionization-Mass Spectrometry/Mass Spectrometry Analysis of Water for Atrazine, Simazine, and Their Chlorotriazine Metabolites

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A method is reported for the determination of atrazine, simazine, and their respective dealkylated chlorotriazine metabolites in ground, surface, and finished drinking water. Water samples are diluted 1:4 in an injection vial prior to analysis using liquid chromatography/electrospray ionization-mass spectrometry/mass spectrometry (LC/ESI-MS/MS). The lower limit of method validation is 0.10 μg/L (ppb) for 2-chloro-4-(ethylamino)-6-isopropylamino)-s-triazine (atrazine, G-30027), 2-chloro-4, 6-(diethylamino)-s-triazine (simazine, G-27692), 2-amino-4-chloro-6-(isopropylamino)-s-triazine (deethylatrazine, DEA, or G-30033), 2-amino-4-chloro-6-(ethylamino)-s-triazine (deisopropylatrazine, DIA, or G-28279), and 2,4-diamino-6-chloro-s-triazine (didealkylatrazine, DDA, or G-28273). The overall mean procedural recoveries (and % relative standard deviations) for atrazine, simazine, DEA, DIA, and DDA are 98 (4.4), 102 (3.6), 99 (4.8), 103 (4.0), and 109% (4.8%), respectively, in finished drinking water; 108 (2.7), 104 (5.4), 113 (4.5), 111 (5.2), and 105% (5.3%), respectively, in groundwater; and 96 (6.9), 103 (4.2), 102 (4.4), 102 (5.2), and 102% (8.2%), respectively, in surface water. The method validation was conducted under U.S. EPA FIFRA Good Laboratory Practice Guidelines 40 CFR 160.

KEYWORDS: Direct aqueous injection; atrazine; simazine; dealkylated chlorotriazine metabolites; good laboratory practices (GLP); mass spectrometry/mass spectrometry

INTRODUCTION

Atrazine [2-chloro-4-(ethylamino)-6-(isopropylamino)-s-triazine] and simazine [2-chloro-4,6-(ethylamino)-s-triazine] are herbicides manufactured, formulated, and sold under various trademarks by several agrochemical companies. Atrazine is most often used in corn, sorghum, and sugar cane production for the control of broadleaf and grass weeds, whereas simazine is primarily used for weed control in corn, citrus, grape, and other fruit and vegetable crops. These compounds metabolize in plants and animals (*1*) and undergo environmental degradation via chemical and microbiological transformation processes to form dealkylated chlorotriazines (*2*), conversion to hydroxytriazines (*3*, *4*), and eventual mineralization to carbon dioxide and ammonia (*5*). The dealkylated chlorotriazine metabolites consist of deethylatrazine (DEA), deisopropylatrazine (DIA), and didealkylatrazine (DDA). All three of these compounds can result from the degradation/metabolism of atrazine, but only DIA and DDA can result from the degradation/metabolism of simazine. Metabolite levels in surface water are typically a fraction of parent and show a clear seasonal pattern with metabolite-to-parent ratios lowest in the second quarter of the year and increasing during the rest of the growing season. The names and experimental codes of these compounds are listed in **Table 1**, and their structures are shown in **Figure 1**.

The U.S. EPA established a maximum contaminant level (MCL) in drinking water of 3.0 μg/L for atrazine and 4.0 μg/L for simazine (*6*). In 2004, five companies signed a memorandum of agreement to conduct a water monitoring program for atrazine in community water systems on surface water that have exceeded an annual average of approximately one-half of the MCL for atrazine at least once since 1997 (*7*). Parent atrazine is measured in this program using a validated immunoassay method (*8*), and estimates of total chlorotriazine levels based on the summation of atrazine, DEA, DIA, and DDA in surface water samples are calculated using four quarterly regression equations (*9*, *10*). The equations have been demonstrated to provide conservative estimates (i.e., the tendency is to predict higher levels than measured) when compared to the sum of measured chlorotriazine parent and metabolite levels. The

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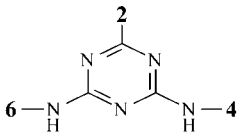
10.1021/jf052968q CCC: $33.50
Published on Web 01/14/2006

Table 1. Chemical Names and Code Numbers for Atrazine, Simazine, DEA, DIA, and DDA

Syngenta code	common name	chemical name	CAS number
G-30027	atrazine	2-chloro-4-(ethylamino)-6-isopropylamino-s-triazine	1912-24-9
G-27692	simazine	2-chloro-4, 6-diethylamino-s-triazine	122-34-9
G-30033	DEA	2-amino-4-chloro-6-isopropylamino-s-triazine	6190-65-4
G-28279	DIA	2-amino-4-chloro-6-(ethylamino)-s-triazine	1007-28-9
G-28273	DDA	2,4-diamino-6-chloro-s-triazine	3397-62-4



	Compound	Substitution at ring position 2	4	6
1.	Atrazine	-Cl	$-C_2H_5$	$-CH(CH_3)_2$
2.	Simazine	-Cl	$-C_2H_5$	$-C_2H_5$
3.	Deethylatrazine	-Cl	-H	$-CH(CH_3)_2$
4.	Deisopropylatrazine	-Cl	$-C_2H_5$	-H
5.	Didealkylatrazine	-Cl	-H	-H

Figure 1. Structures of atrazine, simazine, DEA, DIA, and DDA.

purpose of the work described here was to develop a method that could be used to accurately determine the concentration levels of five chlorotriazine components (atrazine, simazine, DEA, DIA, and DDA) without increasing sample workup and processing or relying on regression equation estimates.

The occurrence and fate of atrazine and simazine and their respective dealkylated chlorotriazine degradates in water have been the subjects of numerous publications over the past two decades, and as a consequence, more than 1000 methods have been reported using a wide variety of sample preparation procedures and detection schemes (*11*). The analysis of triazine compounds was recently reviewed (*12*). Generally, techniques such as gas chromatography/mass selective detection (GC/MSD) (*13*, *14*) have been preferred to support large-scale water monitoring studies due to its sensitivity and confirmatory ability. However, the application of liquid chromatography/mass spectrometry (LC/MS) continues to increase for the analysis of aqueous samples.

Direct injection liquid chromatography/electrospray ionization-mass spectrometry/mass spectrometry (LC/ESI-MS/MS) has been successfully applied to the analysis of a wide range of compounds in various sample matrices including opioids and cocaine (*15*) and alkyl phosphates (*16*) in urine, propamocarb (*17*) and N-methyl carbamate pesticides (*18*) in wine, and organophosphorus pesticides in vegetable extracts (*19*). Several applications to the analysis of pesticides in water have been reported and include the determination of dimethyl tetrachloroterephthalate (*20*), 4-chloro-2-methylphenoxyacetic acid (*21*), various organophosphorus pesticides (*22*), carbamates, thiocarbamates, and phenylureas (*23*), and acetanilide degradates (*24*). In this work, direct aqueous injection LC/ESI-MS/MS is used to quantify five triazine compounds in water with minimal sample manipulation prior to injection.

EXPERIMENTAL PROCEDURES

Standards. Analytical grade standards of atrazine (97.9 or 97.2%), simazine (99.7%), DEA (94%), DIA (96%), and DDA (97%) were obtained from the Technology and Projects Department of Syngenta Crop Protection, Inc. (SCP) (Greensboro, NC). Individual stock standards were prepared by weighing 10.0 mg of either atrazine or simazine or 5.0 mg of either DEA, DIA, and DDA (corrected for % purities) into each of five 100 mL volumetric flasks (one compound in each flask) followed by dilution to the mark with methanol. The smaller quantities of metabolites weighed and the use of methanol as solvent were due to solubility limitations. A 2 μg/mL mixed standard was prepared by transferring 10 mL of the atrazine and simazine stock solutions and 20 mL of the DEA, DIA, and DDA stock solutions to a 500 mL volumetric flask followed by dilution to the mark with 5/95 methanol/high-performance liquid chromatography (HPLC) grade water. Serial dilutions of the mixed standard were prepared in water to create working standards at the 0.00001−0.0001 ng/μL concentration range (equivalent to a range of 0.0005−0.005 ng injected for a 50 μL injection volume). These standards were used for calibration and fortification purposes. All standard solutions were stored in amber-colored glass bottles at refrigerator temperature (4 °C).

Solvents and Reagents. HPLC grade methanol (Fisher cat. no. A452SK-1) and water (Fisher cat. no. W5SK-4) were used for preparation of the standards and mobile phase. Deionized water was obtained from the Picopure water purification system in the laboratories of SCP.

Preparation of Solutions. HPLC grade methanol was mixed with HPLC grade water (5/95, v/v) to prepare the sample dilution solvent system. Methanol and water were also used as mobile phases A and B.

Sample Storage. Water samples to be analyzed for residues of atrazine, simazine, and their dealkylated chlorotriazine metabolites should be stored in amber glass bottles in the dark at refrigerator temperature (4 °C) until analyzed. Previous work in this laboratory demonstrated stability for at least 2 years for all five analytes when samples were stored under these conditions (*25*). Note that all of the results reported in this study are for laboratory-fortified ground, surface, and DI water that were analyzed almost immediately after fortification.

Water Sample Sources. The groundwater used in this study was obtained from Macon County, GA, and surface water was obtained from High Point Lake in Guilford County, NC. Finished water was city drinking water from a tap in Greensboro, NC. These water samples were analyzed by Agvise Laboratories (Northwood, ND), and the resultant characterization data are shown in **Table 2**.

Sample Preparation. Field water sample volumes of 200 μL were mixed with 800 μL of 5/95 (v/v) methanol/water in an HPLC injection vial (methanol was added in order to mimic the initial mobile phase composition, which improves peak shape, especially for the early eluting analytes). Alternatively, 1 mL of water sample can be mixed with 4 mL of 5/95 (v/v) methanol/water to obtain a final methanol/water ratio of 4% prior to transfer of a portion to an HPLC injection vial. However, water samples shown to be free of signal suppression causing components can be analyzed without dilution. In this case, 40 μL of methanol can be added to 1.0 mL of water sample (3.8% ratio) to increase the sensitivity of the measurement. Samples visibly containing strong color or particulates may be subjected to centrifugation prior to analysis. Sample injection was typically performed overnight.

Procedural recovery samples can be obtained by judicious choice of mixed standard concentration, its volume, and the volume of sample to be fortified. For example, the addition of 1.0 mL of a 0.010 μg/mL mixed standard to a 100 mL aliquot portion of water produced a 0.10 ppb fortification. A minimum of two recovery samples should be included in every analytical set: one at the lower limit of method validation (LLMV) and one at a value believed to be higher than the highest expected residue concentration in the field samples.

Table 2. Characterization Data for the Three Types of Water Used in This Method Validation Study

	finished water	surface water	ground-water
location	Greensboro tap water	High Point Lake	Macon County, GA
pH	7.5	7.3	7.0
calcium (ppm)		7.2	15
magnesium (ppm)		2.8	1.0
potassium			2.0
sodium (ppm)	9.3	7.2	2.0
sulfate sulfur (ppm)	19.8		9.0
nitrate nitrogen (ppm)			<0.10
carbonate (mequiv/L)			0
bicarbonate (mequiv/L)			0.69
chloride (ppm)			2
alkalinity (mg $CaCO_3$/L)			36
hardness (mg $CaCO_3$/L)		30	43
conductivity (mmhos/cm)		0.12	0.16
sodium adsorption ratio (SAR)		0.58	0.1
total dissolved solids (ppm)	79	114	110
turbidity (NTU)	0.05	3.11	106

Instrumentation. Analyses were performed using a Perkin-Elmer Series 200 liquid chromatograph (LC) interfaced to an Applied Biosystems, MDS Sciex API-4000 tandem mass spectrometer utilizing TurboSpray at 700 °C and operated in the positive ion mode. The software was Analyst 1.4. A Zorbax SB-CN, 4.6 mm × 75 mm, 3.5 μm particle size (Agilent P/N 866953-905) LC column was used at a flow rate of 0.40 mL/min and maintained at a temperature of 45 °C. Mobile phase A was water, and mobile phase B was methanol. The gradient was as follows: time 0, 95% A and 5% B; time 2.0 min, 35% A and 65% B; time 8.0 min, 35% A and 65% B; and time 8.0 min, 95% A and 5% B. The injection volume was 50 or 100 μL. The total run time was 18 min. The ions selected for multiple reaction monitoring (MRM) and acquisition parameters are listed in **Table 3**.

Table 3. MRM Transitions Selected for Each Analyte and Acquisition Parameters[a]

analyte	MRM transition	period/dwell	retention time (min)
DDA (G-28273)	146.0/104.0	period 1 (dwell 3000 ms)	6.3
DIA (G-28279)	174.2/96.2	period 2 (dwell 100 ms)	7.7
DEA (G-30033)	188.3/146.1	period 2 (dwell 100 ms)	8.2
simazine (G-24628)	202.1/132.1	period 2 (dwell 100 ms)	9.1
atrazine (G-30027)	216.1/174.2	period 2 (dwell 100 ms)	9.7

[a] Acquisition parameters: CUR, 10; GS1, 50; GS2, 50; IS, 5500; TEM, 700; CAD, 2; EP, 10; scan type, MRM; polarity, positive; resolution Q1, unit; resolution Q2, unit; and ion source, turbo spray.

Sample Analysis. Each analytical set consisted of eight analytical standards of various concentrations, reagent blank, control, and 15 controls fortified with the analytes at the 0.10−3.0 μg/L (ppb) concentration level for procedural recovery purposes. Additional standards were dispersed throughout the sequence as a means of checking system stability and column performance. When analyzing true field-collected samples, we also highly recommend analyzing at least one in duplicate or triplicate in order to evaluate repeatability (within-run variance).

RESULTS AND DISCUSSION

LC-MS/MS Analyses. Representative MRM chromatograms of a 0.001 ng injected mixed standard (lowest concentration of standard injected and used to construct the calibration plots), controls, and 0.10 ppb procedural recovery samples for atrazine, simazine, DEA, DIA, and DDA in surface water are shown in **Figures 2**−**6**, respectively (note the different time scales on the *x*-axes). Figures for surface water are shown because this is generally the most challenging matrix type with regard to

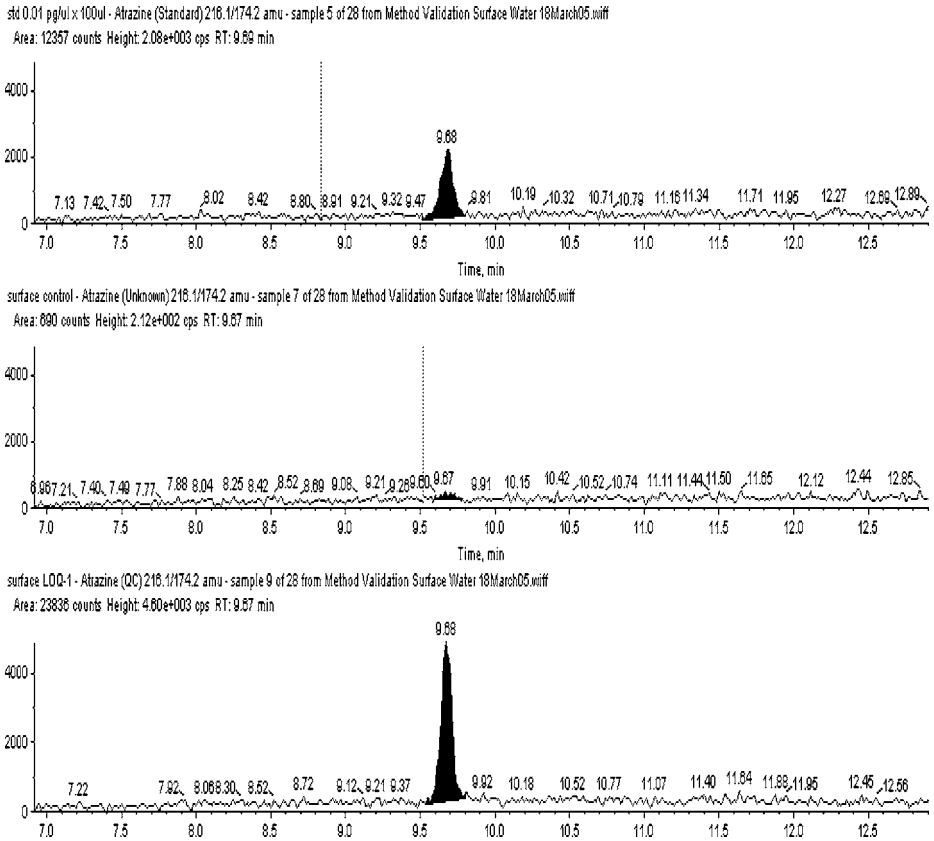


Figure 2. Representative MRM chromatograms from the analysis of surface water for atrazine: top, 0.001 ng of injected standard; middle, control; and bottom, 0.10 PPB procedural recovery sample.

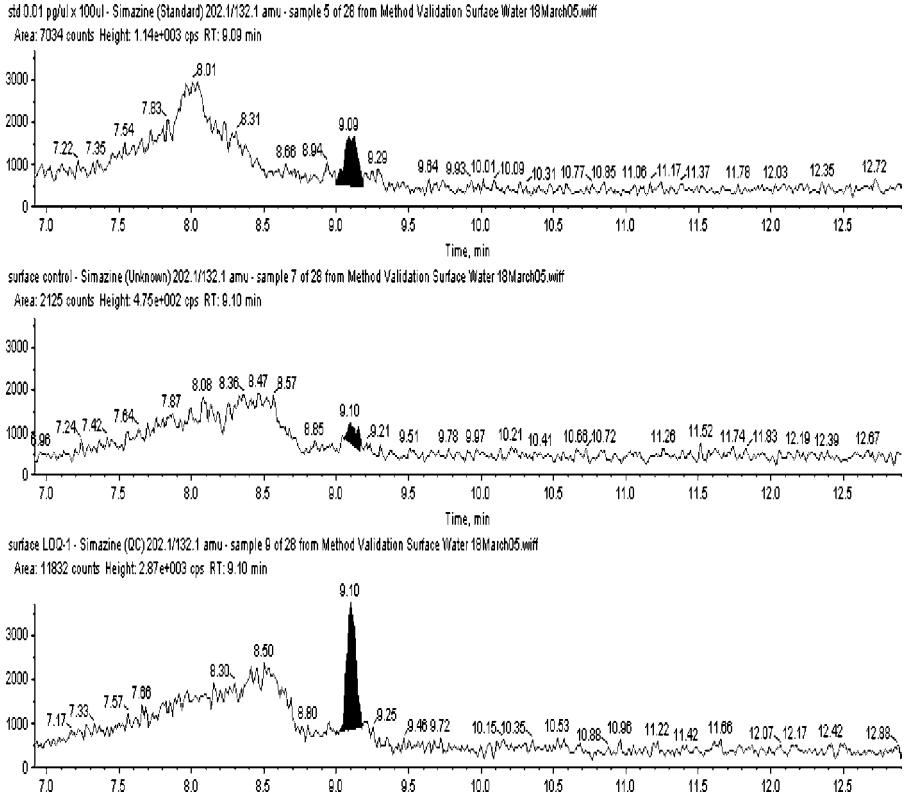


Figure 3. Representative MRM chromatograms from the analysis of surface water for simazine: top, 0.001 ng of injected standard; middle, control; and bottom, 0.10 PPB procedural recovery sample.

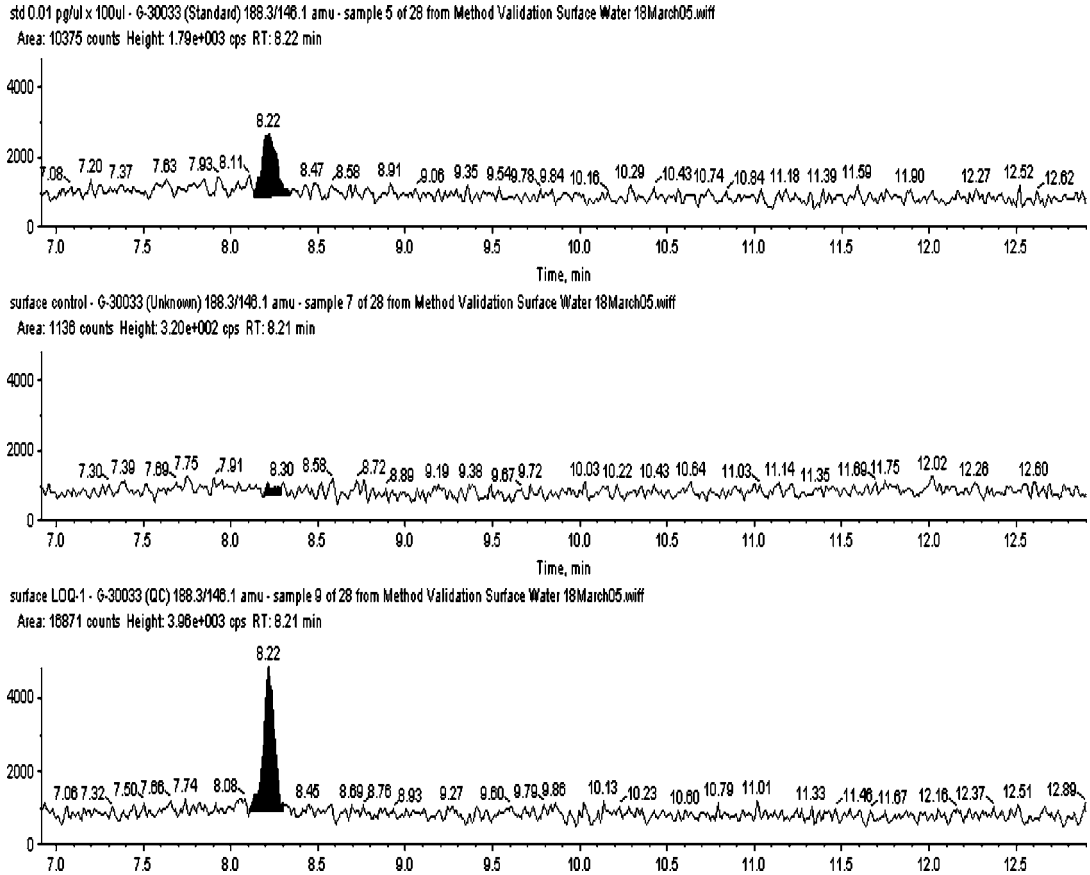


Figure 4. Representative MRM chromatograms from the analysis of surface water for DEA: top, 0.001 ng of injected standard; middle, control; and bottom, 0.10 PPB procedural recovery sample.

suppression or interference issues. The signal-to-noise ratio (S/N) is ≥5 in all cases for standard injections at the 0.001 ng injected level, and the S/N ratio is ≥10 for the procedural recovery samples fortified at the LLMV. The nanograms injected

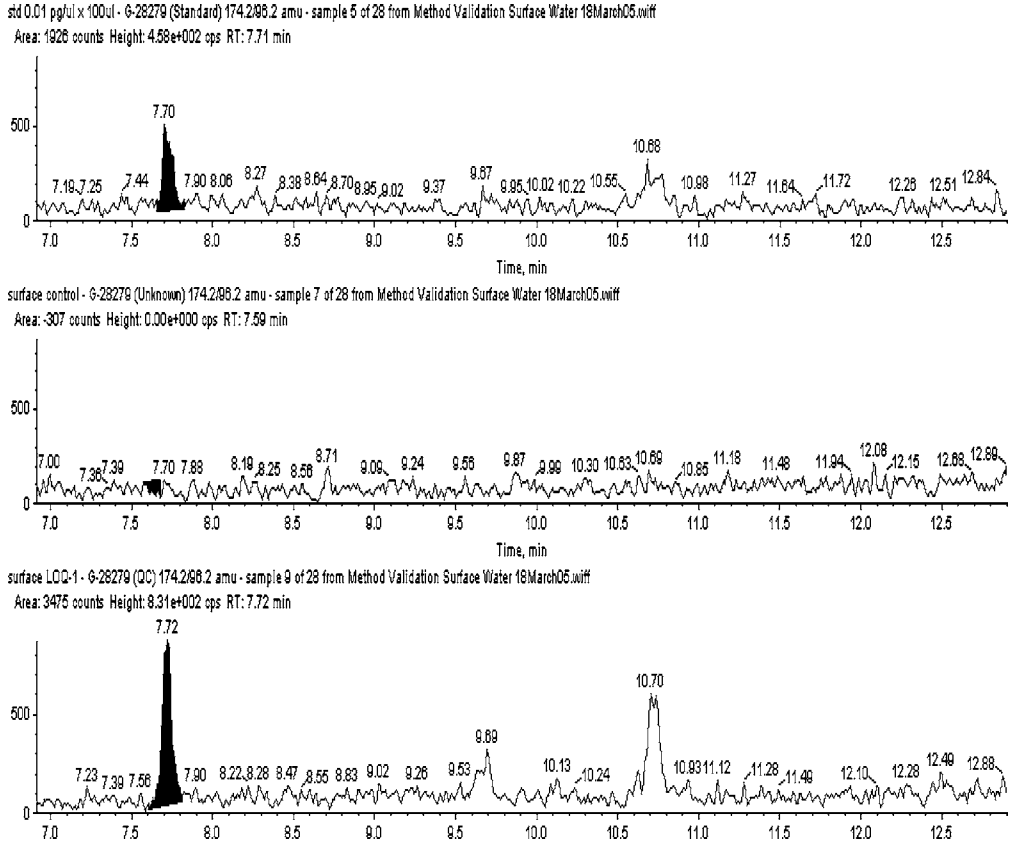


Figure 5. Representative MRM chromatograms from the analysis of surface water for DIA: top, 0.001 ng of injected standard; middle, control; and bottom, 0.10 PPB procedural recovery sample.

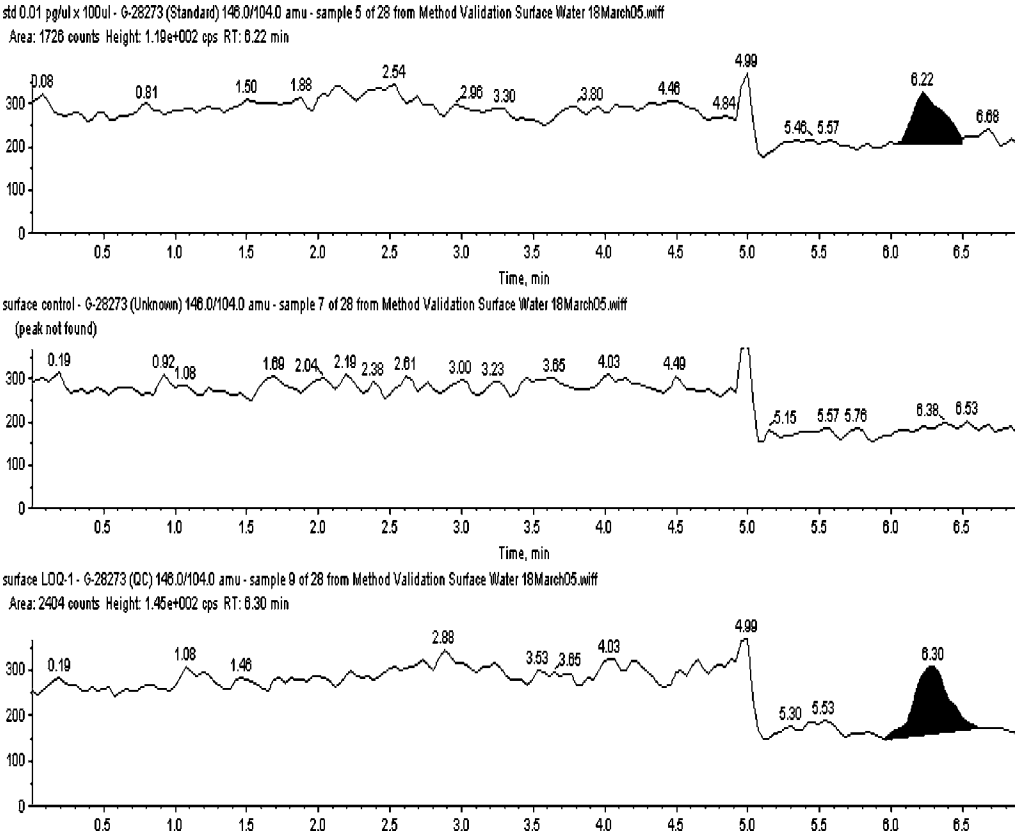


Figure 6. Representative MRM chromatograms from the analysis of surface water for DDA: top, 0.001 ng of injected standard; middle, control; and bottom, 0.10 PPB procedural recovery sample.

and their respective responses for each analyte were used for construction of the calibration plots, and all were linear with correlation coefficients >0.99 throughout the study. The responses for peaks detected in the control samples were

Table 4. Summary of Procedural Recovery Data and % Relative Standard Deviation for All Analytes at Each Fortification Level

	atrazine	simazine	DEA	DIA	DDA
finished water					
0.10 ($n = 5$)	101 (2.9)	105 (3.4)	99.9 (6.6)	104.1 (5.2)	106 (5.3)
0.20 ($n = 5$)	96.3 (2.0)	101 (3.9)	99.2 (4.2)	94.6 (6.2)	106 (6.1)
3.0 ($n = 5$)	94.6 (2.5)	99.9 (1.3)	97.7 (2.1)	101 (1.0)	112 (2.0)
overall ($n = 15$)	97.9 (4.4)	102.4 (3.6)	98.8 (4.8)	102.5 (4.0)	108.7 (4.8)
groundwater					
0.10 ($n = 5$)	108 (1.7)	102 (9.1)	110 (1.3)	108 (6.5)	99.4 (5.3)
0.20 ($n = 5$)	111 (1.9)	105 (3.3)	119 (2.1)	116 (1.4)	109 (2.1)
3.0 ($n = 5$)	106 (2.5)	106 (1.4)	109 (3.7)	108 (3.1)	107 (3.0)
overall ($n = 15$)	108 (2.7)	104 (5.4)	113 (4.5)	111 (5.2)	105 (5.3)
surface water					
0.10 ($n = 5$)	93.4 (10.4)	103 (2.0)	100 (2.3)	89.9 (2.5)	94.1 (2.1)
0.20 ($n = 5$)	99.4 (5.8)	107 (4.5)	104 (1.7)	105 (5.6)	100.0 (4.3)
3.0 ($n = 5$)	95.8 (2.5)	99.3 (1.1)	101 (7.1)	103 (5.9)	111.1 (5.2)
overall ($n = 15$)	96.2 (6.9)	103.1 (4.2)	101.7 (4.4)	102.0 (5.2)	101.7 (8.2)

subtracted from the responses for the peaks detected in the procedural recovery samples prior to calculation of % recovery.

A cyano column was used in this work in order to provide sufficient retention for DDA (and to a lesser extent DIA and DEA) to obtain reproducible peak shape and ensure adequate separation of this polar compound from the void volume. DDA elutes too quickly on C-2, C-8, and C-18 columns. Although using an intermediate polarity column, the mobile phase composition is such that the separation is still in reverse phase mode as demonstrated by increasing retention with decreasing analyte polarity.

It is relatively common practice to add low concentration levels of acetic or formic acid (0.1% or so) to the mobile phase when using ESI in order to increase the abundance of M + 1 ions. In this work, the addition of acid slightly suppressed the observed ESI signal, especially for the parent compounds, atrazine and simazine, when using a methanol/water mobile phase system. Signal enhancement by adding acid to the mobile phase is attained for all five analytes when using acetonitrile instead of methanol, but methanol provides better overall separation and peak shape for the more polar analytes.

Method Performance. A summary of the procedural recovery data is shown in **Table 4**. Mean percent procedural recoveries (and percent relative standard deviations) for atrazine, simazine, DEA, DIA, and DDA were 98 (4.4), 102 (3.6), 99 (4.8), 103 (4.0), and 109% (4.8%), respectively, in finished drinking water ($n = 15$ for each analyte); 108 (2.7), 104 (5.4), 113 (4.5), 111 (5.2), and 105% (5.3%), respectively, in groundwater ($n = 15$ for each analyte); and 96 (6.9), 103 (4.2), 102 (4.4), 102 (5.2), and 102% (8.2%), respectively, in surface water ($n = 15$ for each analyte). Thus, there is overall good accuracy and precision. The % relative standard deviations are slightly higher in surface water than in finished or groundwater.

A dilution factor of 1:4 was required to circumvent suppression issues when analyzing surface water samples and appeared to be the largest dilution factor possible while still maintaining sufficient sensitivity to accurately quantify residues at the 0.10 ppb concentration level, at least using the instrumentation and operating parameters described herein. An injection volume of 10 μL was also studied in order to determine if the dilution step could be eliminated. However, the surface water used in this study and our experiences with various field surface water samples collected at different sites revealed that suppression still occurred in some instances. Thus, without a reliable, advanced indicator of which samples would require dilution, all water matrix types were diluted 1:4 prior to analysis during this method validation. Ion suppression or enhancement (created by coelution of known and unknown sample components) need to be evaluated any time new water sample matrix types are to be studied. In this work, a series of standard additions experiments were performed prior to the validation to evaluate the magnitude of the suppression and determine the dilution factor required. The surface water used in this study contained considerably more hardness than the ground and finished water (see **Table 2**), and these components may have contributed to the observed suppression. No attempt was made to characterize other organic components of the samples.

Although this validation study was conducted using the operating parameters described in this report, we recommend using a column temperature of 25 °C instead of 45 °C because this improves the peak shape and retention for DDA. In addition, 50 μL is preferred over 100 μL for the injection volume simply to inject fewer unknown sample containing components that might adversely affect column performance and/or ESI signal intensity. Alternate injection volumes (e.g., 10 μL) can be used and the dilution of samples eliminated when the absence of suppression is demonstrated, and the injection accuracy and precision are verified as acceptable.

The LLMV for all five analytes is 0.10 μg/L (ppb) because this was the lowest procedural recovery concentration tested. The limit of detection (LOD) is 0.001 ng injected and is defined as the lowest concentration of standard injected and used for construction of the calibration plot. These definitions are only slightly more conservative than the 3 and 10 Ω (standard deviations) used by the U.S. EPA for LOD and limit of quantitation (LOQ) (*26*−*28*), respectively, since our S/N ratios for the lowest concentration of standard injected and lowest procedural recovery tested are about 5 and 10, respectively. Thus, these instrumental figures of merit are likely valid measures of the best attainable LOD and LOQ for the entire procedure since sample manipulation other than dilution is not performed.

Conclusions. The results presented herein demonstrate the accuracy and precision of this FIFRA GLP guideline 40 CFR 160 validated analytical method and its applicability to the analysis of atrazine and simazine and their respective dealkylated chlorotriazine metabolites (DEA, DIA, and DDA) in water at a LLMV of 0.10 μg/L (ppb). The method is less costly than previously reported methods since minimal preinjection sample manipulation (dilution when needed to avoid suppression issues) is required, and therefore, it meets the objective to be a cost efficient alternative to immunoassay methods. Typically, 60−70 samples can be injected overnight. The utility of isotope dilution analysis with C-13-labeled triazine standards will be examined in future studies to evaluate its potential as an approach to circumvent issues related to the presence of suppression-causing sample components.

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Received for review November 28, 2005. Revised manuscript received December 13, 2005. Accepted December 14, 2005.

JF052968Q