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Mass spectrometric confirmation criterion for product-ion spectra generated in flow-injection analysis Environmental application

R.B. Geerdink[a,*], W.M.A. Niessen[b], U.A.Th. Brinkman[c]

[a]*Institute for Inland Water Management and Waste Water Treatment, RIZA, P.O. Box 17, 8200 AA Lelystad, Netherlands*

[b]*Hyphen MassSpec Consultancy, Leiden, Netherlands*

[c]*Department of Analytical Chemistry and Applied Spectroscopy, Free University, De Boelelaan 1083, 1081 HV Amsterdam, Netherlands*

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Abstract

The suitability of a confirmation criterion recently recommended in the Netherlands for gas chromatography with mass spectrometric detection (GC–MS), was evaluated for flow-injection analysis (FIA) with atmospheric pressure chemical ionisation MS–MS detection. The main feature of the criterion is that the relative ion abundances of the four diagnostic ions are taken into account. That is, for lower-intensity peaks, relative standard deviations may be higher; this is an advantage with chemical ionisation MS procedures. A series of triazines and their degradation products were used as test compounds. Tap and surface water samples spiked at 0.33 μg/l were analysed by means of a selected reaction monitoring MS–MS procedure. For all analytes but hydroxysimazine (3 transitions), 4–9 transitions could be selected which invariably met the demands of the criterion. Some of the transitions used originate from the ^{37}Cl isotopic mass of the parent compounds which provides additional structural information. Data for twenty surface water samples analysed by means of FIA–MS–MS as well as GC–MS and liquid chromatography with diode array UV and MS–MS detection gave essentially the same results over the 0.1–1.0 μg/l range. In two samples desethylatrazine was reported by FIA–MS–MS whereas this compound was not detected by GC–MS. For a first test, this is a promising result.

Keywords: Water analysis; Pesticides; Triazines

1. Introduction

Today, mass spectrometric detection is increasingly used in LC- and GC-based methods. The reduced cost of benchtop detectors, and the urgent demand for improved selectivity and structural information are valid explanations. However, when using MS-based detection procedures, the need for a proper identification criterion is self-evident. In, for example, GC with low-resolution MS detection, a deviation of ±20% of the relative ion abundance is used in the European Union as a criterion for residue regulations concerning substances having a hormonal or thyrostatic action [1].

Although many LC–MS papers dealing with confirmation or identification have been published over the years [2–10], the mass spectrometric identi-

*Corresponding author. Tel.: +31-320-298-788; fax: +31-320-049-218.

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fication criteria used are not always clear. Often, a criterion with three diagnostic ions and the retention time is considered sufficient [6,11,12]. However, the conditions that have to be fulfilled to meet the criterion are not unambiguous and are hardly discussed in the literature. Ioerger and Smith [13] who used a retention time criterion of within ±5 s, monitored five characteristic ions. According to them, at least three ion abundances calculated relative to the most abundant ion, should be within ±20% of the relative ion abundance of selected ion monitoring (SIM) ions monitored for a reference standard. Recently, Li et al. [6] suggested selected reaction monitoring (SRM) LC–MS acceptance criteria for the identification of compounds at ultra-trace levels. The results presented indicate that generally accepted qualitative criteria for SIM GC–MS techniques can be met by SRM LC–MS–MS techniques (retention time repeatability to within 2%, selection of at least two and preferably three non-contiguous precursor ion–product ion transitions, with repeatability of abundance of product ion to be within ±20% relative to standard).

In the Netherlands, a group of experts working in the field of pesticide analysis has recommended new GC–MS criteria for legislation of environmental analyses [14] which distinguishes identification (positive, present and negative, absent) and indication (probably present; to avoid false negative results) for electron-ionisation-based detectors. The criteria include the relative or absolute retention time of a compound which should be within ±0.2% (with a maximum of ±6 s) compared with the same compound in an external standard, and the ion abundances for at least three diagnostic ions which should be within $\pm(0.1 \cdot I_{std} + 10\%)$, where I_{std} is the relative intensity of the peak for the diagnostic ion in the last standard measured. With the latter criterion, ions with a low relative intensity may vary relatively more than ions with a high relative intensity. The practicality of this approach is, today, being studied by laboratories in the Netherlands.

In this paper, the GC–MS criterion briefly discussed above is applied for two triazines, atrazine and simazine, and three of their degradation products, desethylatrazine, hydroxyatrazine and hydroxysimazine, using flow-injection analysis (FIA)–MS–MS. The absence of retention time information is compensated by an additional diagnostic ion, i.e., for FIA–MS–MS four diagnostic ions should be present. In addition, one should keep in mind that most MS detectors used for FIA or LC use chemical ionisation with which the relative intensity of the detector signals is known to fluctuate much more than with electron ionisation. Environmental water samples of different origins were analysed with and without spiking, and a previously developed (solid-phase extraction, SPE) procedure [4] was applied to improve selectivity.

2. Experimental

2.1. Reagents

Methanol, water, ammonium acetate, ammonium hydroxide and acetic acid were of analytical or HPLC-grade quality and were obtained from J.T. Baker (Deventer, Netherlands). All analytes were from Riedel-de Haën (Hannover, Germany) or Promochem (Wesel, Germany).

Stock solutions of the analytes were prepared by dissolving 25 mg of each analyte in 50 ml methanol or methanol–water (50:50, v/v); the hydroxy degradation products only dissolve after the addition of three droplets of formic acid. Stock solutions were kept at −20°C. The stock solutions were used to prepare standard mixtures. These solutions were used to prepare external standard solutions [methanol–1 *M* ammonium acetate (90:10, v/v)] or spiked to tapwater and surface water samples. Samples and standard solutions were kept at +4°C.

2.2. Extraction procedure

To every 100 ml of sample, 7.8 g ammonium acetate (1 *M*) were added. Next, the pH was adjusted to 7.0±0.5 with ammonium hydroxide or glacial acetic acid. SPE was carried out on an ASPEC (Gilson, Villiers-le Bel, France) using 1000 mg PolarPlus cartridges (J.T. Baker) which were conditioned with 5 ml of methanol and, next, 5 ml of water. Samples (30 ml) were preconcentrated at a flow rate of 3 ml/min. Next, the cartridges were washed with 3 ml water and desorbed with 2×2.5 ml methanol–water (50:50; v/v) (fraction 1; degrada-

tion products) and, subsequently, 2×2.5 ml methanol (fraction 2; parent triazines).

For FIA–MS–MS analyses, each eluate was diluted to 9 ml with methanol and 1 ml of 1 *M* ammonium acetate was added. The flow-rate was set at 0.5 ml/min and the carrier stream was methanol–1 *M* ammonium acetate (90:10, v/v).

2.3. Apparatus

A triple-stage quadrupole mass spectrometer (TSQ-700, Finnigan MAT, San José, CA, USA) equipped with an atmospheric pressure chemical ionisation (APCI) interface and a DEC 5000 data system computer was used. Typical instrument parameters used as default were: sheath gas, 240 kPa; auxiliary gas, off; vaporiser temperature, 500°C; capillary temperature, 200°C; scan time, 0.7 s. The conversion dynode was set at −20 kV, the electron multiplier at 2.2 kV and the electrometer amplifier gain at 10^{-9} A/V. Argon (quality 5.0, Hoekloos, Schiedam, Netherlands) was used as the collision gas at 0.3–0.4 Pa. The MS–MS correction factor (MSMSC) was set to zero. Q1 and Q3 were tuned at unit mass resolution.

2.4. Analysis

Using the ASPEC, samples of 5 ml were injected into the carrier stream of the FIA–MS–MS system and analysed using a SRM procedure. With this procedure, detection is performed by means of tandem MS in which the signals of the product ions are acquired at the optimum collision offset voltage for each precursor *m/z* value selected. At least 8–10 scans are generated per analyte and used for confirmation. The complete procedure of the data acquisition is described in Ref. [3].

3. Results and discussion

3.1. Carrier stream composition

It has repeatedly been observed [5,15,16] in LC with atmospheric pressure ionisation (APCI or electrospray ionisation) MS that the eluent composition (pH, modifier, salt) can dramatically influence the intensity of the mass spectrum. In the present FIA study, unexpected results were observed when results for a standard mixture of triazines were compared with those of the same standard mixture after SPE. For desethylatrazine, 3–4-fold higher intensities were observed if SPE was performed, which could only be explained by the seemingly minor differences in solvent composition: the standard solution was prepared by diluting an acetonitrile-based stock solution (sample I) with methanol–water, while the SPE extracts only contained methanol as the organic modifier. In order to study this phenomenon in more detail, 9 ml of a fresh 2 μg/l desethylatrazine standard in methanol were diluted with 1.0 ml methanol (sample II), 0.1 ml acetonitrile and 0.9 ml methanol (sample III), 0.5 ml acetonitrile and 0.5 ml methanol (sample IV) or 1.0 ml acetonitrile (sample V). Fig. 1 shows relevant MS–MS traces of the four samples and the original acetonitrile-containing standard. Compared with the original standard (sample I), the signal intensity of desethylatrazine was 300% for sample II, 220% for sample III, 80% for sample IV and 40% for sample V.

Because of the obvious influence of even traces of acetonitrile, in all further experiments the sample composition was kept rigidly constant and the use of acetonitrile was avoided.

3.2. Mass selectivity

The retention time of an analyte is an important identification criterion in LC or GC procedures, but with FIA chromatographic selectivity is absent. However, when using MS–MS distinctly better selectivity can be obtained than with single-stage MS, e.g., when using a procedure such as SRM. The relevance of the retention time information may, then, well become unimportant. Moreover, SRM is more selective than the conventional SIM mode in GC–MS, since the selected parent ion must fragment to form the selected daughter ion in order to be detected. Actually, in FIA analysis the main uncertainty during the ionisation process is the contribution of the sample matrix.

In order to predict the selectivity of selecting a particular mass, the Wiley mass library was searched for molecular masses below 600. Fig. 2 shows a graph of the number of masses in successive 25-u

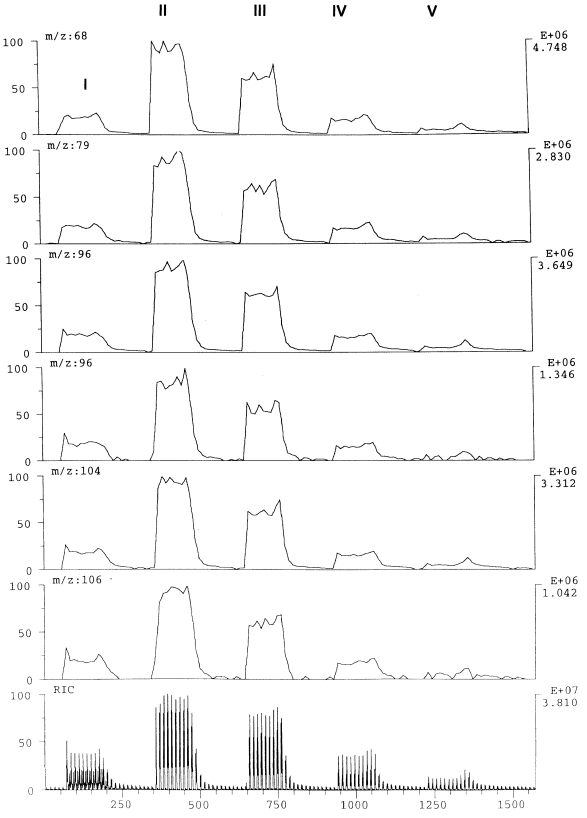

Fig. 1. FIA–MS–MS traces of desethylatrazine in (I) original standard containing traces of acetonitrile, (II–V) 9 ml standard (2 μg/l) in pure methanol diluted with (II) 1 ml methanol, (III) 1 ml acetonitrile–methanol (10:90), (IV) 1 ml acetonitrile–methanol (50:50) and (V) 1 ml acetonitrile. Note: mass traces originate from ^{35}Cl and ^{37}Cl precursor ions; see also Table 1.

intervals. From the graph, it is clear that 54% of the entries in the library have a molecular mass of 150–300. Consequently, the selectivity in this range will be rather poor. Unfortunately, all our target compounds are in this range. As an illustration, searching the Wiley library for the masses 201 (simazine) and 215 (atrazine) revealed 202 and 224 entries, respectively. However, searching for masses 201 and 215 and one chlorine atom caused a dramatic reduction to 14 and 17 entries, respectively. Upon further targeting to 7 (simazine) and 8 (atrazine) carbon atoms, and one chlorine atom, the number of target compounds decreased to seven in each case. Or, in other words, when introducing a sample directly into the MS, the selectivity towards

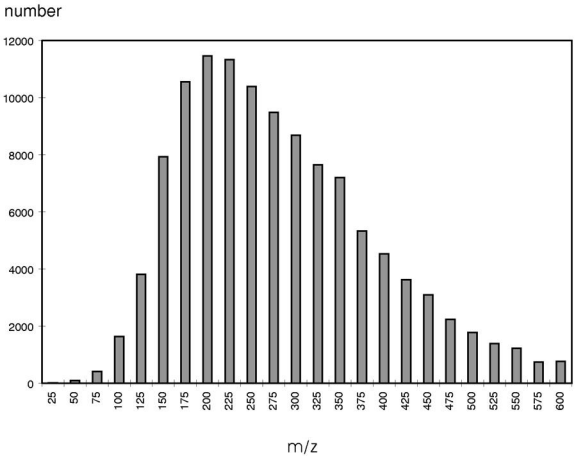

Fig. 2. Schematic presentation of number of m/z data in 25-u intervals present in Wiley library containing 115 000 entries.

compounds with the same molecular mass but different chemical characteristics, is rather promising.

3.3. Product-ion spectra

With an FIA procedure which combines large injection volumes (5 ml) and a moderate carrier flow-rate of 0.5 ml/min, 10 min of acquisition time is available to monitor all precursor–product ion transitions. The injection profile will be at plateau conditions for most of the time and all transitions will, therefore, be acquired at the same injected concentration and produce the same detection signal. This means that the height, or the area, of a product ion of a particular precursor–product ion transition can be used to generate a product-ion spectrum. Because of the long acquisition time, many precursor–product ion transitions can be selected and, even then, 8–10 scans can be acquired for a particular product ion. Moreover, isotopic precursor masses, i.e. ^{37}Cl masses of the triazines, can be selected. Under these conditions, the product-ion spectrum will resemble a full mass spectrum, which is the highest level of confirmation that can be provided by MS [12]. As an illustration, a composite product-ion spectrum constructed from nine SRM transitions of atrazine and a LC–MS mass spectrum of this compound {radio frequency (RF)-only daughter scan mode [17]} are shown in Fig. 3. In this study

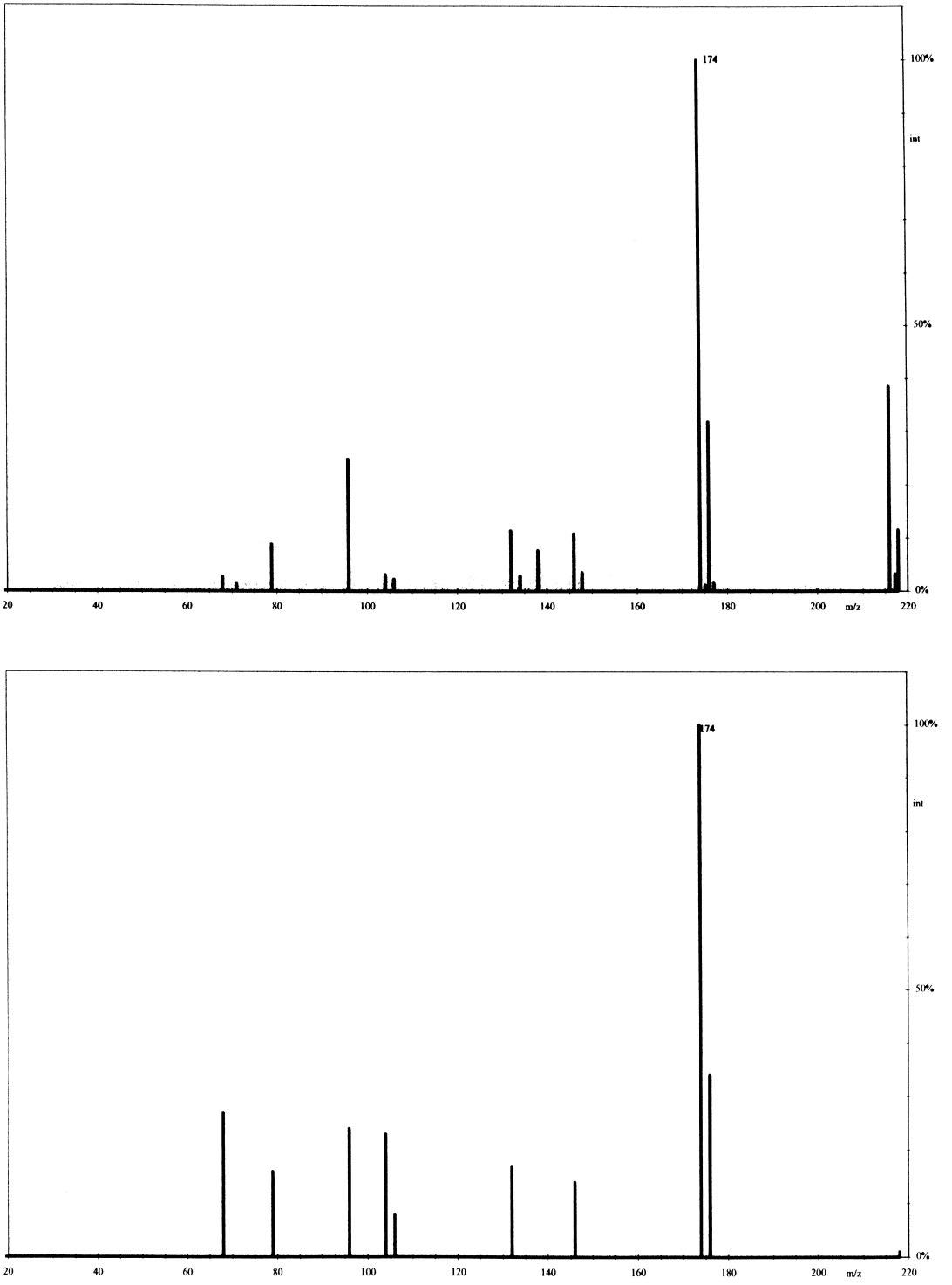

Fig. 3. A composite product-ion spectrum (bottom), constructed from nine SRM transitions of atrazine and an LC–MS mass spectrum (top) of this compound, obtained in the RF-only daughter scan mode [17].

all transitions were acquired in order to investigate the repeatability of their responses.

3.4. FIA–MS–MS criterion

In order to compensate for the loss of the retention time criterion typical for LC and GC, an extra transition should be added in the case of FIA–MS–MS. In other words, instead of three, at least four diagnostic ions should be used. Experimental work on the five analytes of interest revealed that from four to fourteen product ions could be acquired (Table 1). It should be noted that, for all but one analyte, part of the product ions were acquired by using ^{37}Cl or ^{13}C isotopes. In some cases, the relative ion abundances showed poor repeatability (RSDs$>$20%) and had, therefore, to be omitted from the acquisition list. As regards Table 1, the only serious problem was encountered with hydroxysimazine for which the precision in measuring the product ion peak intensity at m/z 86 was insufficient. That is, only three transitions could be recorded. Hydroxysimazine was nevertheless kept on the list of test compounds, one argument being that the identification potential of three transitions (in MS–MS) may well be equal to that of four diagnostic ions (in MS). The option to increase the total number of transitions by using a fragment ion as precursor ion, e.g., m/z 114, was not studied.

3.5. Examination of FIA–MS–MS criterion

Four sample series, each consisting of spiked tapwater (3 samples) and surface water (5 samples), spiked at 0.33 μg/l, and blank surface water (5 samples) were analysed in a 4-week period. During this period other analyses were also run on the instrument, another interface was used and cleaning and tuning of the instrument was periodically performed. The data were evaluated in a spreadsheet programme. They were recorded for a total of 12 SPE fractions I and II of the spiked tapwater samples, 20 fractions I and II of the blank surface water and spiked surface water samples and, in addition, 40 standard solutions. In order to somewhat limit the evaluation work load and to have a similar number of transitions for most analytes, eight transitions were selected from Table 1 for atrazine, simazine and desethylatrazine.

3.5.1. Standard solutions

The data for the mean relative ion abundances of the five analytes in the standard solutions are shown in Table 2. The repeatability (four series in 4 weeks; 40 standards), was found to be good with RSDs of

Table 1
Product ions of triazines and degradation products

Precursor ion	Product ion		Total
	^{35}Cl	^{37}Cl (^{13}C)	
Atrazine			14
216 (^{35}Cl)	43, 68, 79, 96, 104, 110, 132, 146, 174		
218 (^{37}Cl)		68, 106, 134, 148, 176	
Simazine			12
202 (^{35}Cl)	43, 68, 79, 96, 104, 110, 124, 132		
204 (^{37}Cl)		68, 106, 124, 134	
Desethylatrazine			12
188 (^{35}Cl)	43, 62, 68, 79, 96, 104, 110, 146		
190 (^{37}Cl)		68, 96, 106, 148	
Hydroxyatrazine			6
198 (^{35}Cl)	69, 86, 97, 114, 156		
199 (^{13}C)		157	
Hydroxysimazine			4
184 (^{35}Cl)	69, 86, 97, 114		

Table 2
Mean relative ion abundances of test analytes in standards ($n=40$), spiked tapwater ($n=12$) and spiked surface water ($n=20$)

Compound	Relative ion abundances[a]				
	Precursor ion	Product ion	Standard solution	Tap water	Surface water
Atrazine	**216**	**68**	27	26	27
	216	79	16	16	15
	216	96	24	24	24
	216	104	23	20	22
	216	132	17	17	17
	216	**146**	14	14	15
	216	**174**	100	100	100
	218	106	8	8	8
	218	**176**	34	33	35
Simazine	**202**	**68**	69	68	67
	202	96	60	61	62
	202	104	71	67	70
	202	**124**	100	100	100
	202	**132**	93	97	97
	204	68	22	19	22
	204	124	34	27	30
	204	**134**	33	37	38
Hydroxyatrazine	**198**	**69**	43	44	43
	198	86	50	56	56
	198	**97**	20	21	22
	198	**114**	37	35	36
	198	**156**	100	100	100
	199	157	10	26	35
Hydroxysimazine	**184**	**69**	51	55	58
	184	**97**	23	25	34
	184	**114**	100	100	100
Desethylatrazine	188	43	12	14	19
	188	62	8	8	7
	188	**68**	18	17	18
	188	79	21	23	23
	188	104	23	22	31
	188	**110**	15	15	23
	188	**146**	100	100	100
	190	**148**	34	40	53

[a] Precursor–product-ion transition in bold: transitions proposed for FIA–MS–MS criterion.

10–15% (data not shown; exceptions discussed below) for almost all precursor-to-product ion transitions.

If the criterion of $\pm(0.1\cdot I_{std}+10\%)$ referred to earlier in the text, is applied to the individual data and the mean relative ion abundances of Table 2 are used as I_{std}, then all transitions studied for atrazine, hydroxyatrazine, desethylatrazine and hydroxysimazine can be used. For simazine, however, the transitions 204→68, 204→124 and 204→134 showed very poor repeatability in the first two series due to the use of non-optimum MS conditions. Therefore, only 31 out of the 40 simazine-containing standards gave correct results for all eight transitions. In general, the repeatability of the relative ion abundances for standards was excellent for all compounds.

3.5.2. Samples

Comparison of the individual relative ion abun-

dances of atrazine and simazine in the spiked tap and surface water samples, with the relative ion abundances in the standards, showed all of them to be correct according to the criterion. This indicates that these two compounds can be analysed in both matrices at the present spiking level. The ^{35}Cl:^{37}Cl ratios were also correct in all instances.

For hydroxyatrazine, in all tap water samples five out of the six relative ion abundances met the criterion compared with the mean relative ion abundances of the standards. The exception was the intensity of the peak representing the transition 199→157 which was much too high, i.e., 28–47 compared to 10, in six samples (which explains the high mean value of 26). With all spiked surface water samples, the criterion was met for at least four out of the six relative ion abundances. The intensity of the peak representing the 199→157 transition now was out of bounds for 13 out of the 20 samples (and the mean value consequently, was even higher than before). In addition, the peak intensity representing the 198→86 transition was not in the proper range in five instances. In these cases the relative ion abundances were 67–69 as against a criterion threshold of 65. Obviously, analysis according to the criterion of four correct transitions was possible for all samples.

For hydroxysimazine, for which only three transitions could be acquired, the relative ion abundances were correct for all tapwater samples. For surface water, however, the transition 184→97 had a rather high relative ion abundance, 34, as against 23 for the standard solutions and maximum value of 36 according to the criterion. In addition, the RSD of this transition in the 20 surface water samples was high, i.e. 32%.

Scrutiny of the individual data revealed that 16 out of these 20 samples met the criterion for all three transitions. The same result was obtained when the real-life relative ion abundances for the 184→97 transition were compared with those of the abundances for standards within a sample series rather than all standards. In other words only 80% of the surface water samples met the criterion for three transitions. As will be argued below, these three transitions can be considered sufficient for confirmation purposes.

For desethylatrazine, all but one relative ion abundance (190→148) met the criterion for all spiked samples. That is, there were seven transitions that could be used to confirm the identity of the compound.

3.5.3. Selection

The experimental results presented above show that for all but one test analyte, 4–9 SRM transitions could be found which met the confirmation criterion for all samples that were analysed. Therefore, it seems justified to recommend as an FIA–MS–MS criterion that ''at least four SRM transitions per compound should meet the criterion of $\pm(0.1 \cdot I_{std} + 10\%)$''.

Since several LC–MS criteria [6, 11, 12] state that, next to the retention time, ''at least two and preferably three ions'' should be included, the FIA criterion is slightly more severe. This may well lead some analysts to decide that, in exceptional situations, the use of only three transitions will be acceptable. The results for hydroxysimazine show that such a case can indeed be made, but that it is a borderline case.

As regards the four transitions finally selected for the test analytes (printed in bold type in Table 2), the considerations made for atrazine may serve as an example. For atrazine, every diagnostic ion can be, in principle, selected. The results of the spiked surface water samples showed that essentially the same results were obtained for all relative ion abundances, and that most RSDs were the same. Because the chlorine ratio is an important additional aspect, one ^{37}Cl transition was selected (218→176) with the corresponding ^{35}Cl transition, 216→174. In addition, m/z 68 is important in triazine analysis and is often used as the diagnostic ion in the parent scan mode to search for 1,3,5-triazines, whereas m/z 69 is used as the diagnostic ion in the parent scan mode to search for hydroxylated triazines. From the other transitions, the transition with the highest m/z value will give the highest selectivity.

3.6. Comparison of FIA–MS–MS and other analytical procedures

The Institute for Inland Water Management and Waste Water Treatment (RIZA) frequently monitors the presence of pesticides in water samples. Various

Table 3
Comparison of river water sample data of some test analytes determined by LC–DAD, LC–MS–MS, GC–MS and FIA–MS–MS[a]

Procedure	Analyte	Concentration (μg/l) in sample:										
		1	2	3	4	5	6	7	8	9	10	10**
LC–DAD	Atrazine	0.18	0.28	0.17	0.09	0.30	0.11	0.47	0.54	0.40	0.66	0.69
	Simazine	[0.11]	[0.10]	[0.09]	[0.06]	0.13	[0.10]	[0.39]	0.18	0.16	0.68	0.94
LC–MS–MS	Atrazine	0.17	0.28	–	–	–	0.12	0.32	0.49	0.39	0.69	0.69
	Simazine	[0.08]	0.09	–	–	–	0.13	0.12	0.22	0.18	0.94	0.94
	Desethylatrazine	–	0.12	0.07	–	0.05	–	0.09	–	0.06	0.68	0.69
GC–MS	Atrazine	0.22	0.25	0.20	0.21	0.35	0.32	0.38	0.43	0.34	0.13	0.13
	Simazine	0.04	0.03	0.04	*	0.16	*	0.12	0.18	0.15	0.11	0.11
	Desethylatrazine	0.04	0.04	*	*	*	*	0.05	0.11	0.10	*	*
FIA–MS–MS	Atrazine	0.19	0.32	0.22	0.13	0.31	0.22	0.44	0.50	0.44	0.84	0.69
	Simazine	0.13	0.13	0.07	0.09	0.15	0.22	0.13	0.21	0.15	0.85	0.94
	Desethylatrazine	0.08	0.10	0.16	*	*	0.27	0.10	0.10	0.06	0.88	0.69
	Hydroxyatrazine	*	*	0.05	0.05	0.06	0.04	0.03	0.10	0.07	*	*

[a] [], low spectrum quality or problems with duplicate sample; –, not determined; *, below detection limit; **, spiked concentration (control sample).

analytical methods are used to that end, which include LC–diode array UV (DAD), LC–MS–MS and GC–MS. Table 3 compares results from some such exercises with FIA–MS–MS. The analyte recoveries for the spiked surface water samples were good: atrazine (80%), simazine (81%), hydroxyatrazine (89%), hydroxysimazine (95%) and desethylatrazine (94%). If one takes into account that the precision of most of the analytical procedures was on the order of ±0.05 μg/l, it becomes clear that a majority of the data show a fully satisfactory agreement, even at concentration levels as low as 0.1–0.3 μg/l. Whereas one might argue, on the basis of the reported data, that GC–MS is a more suitable technique in the case of simazine than is FIA–MS–MS, it is much more obvious that the reverse is true for desethylatrazine.

The combined results show that FIA–MS–MS is an interesting and efficient alternative to established LC- and GC-based procedures for trace-level analyses, and that the confirmation criterion used is, indeed, relevant.

4. Conclusions

A confirmation criterion for FIA–MS–MS, based on the use of four diagnostic transitions for an analyte and related to the relative ion abundance of the same transitions of that analyte in a standard solution, was proposed and tested at the sub-μg/l level. Several triazines and triazine transformation products in surface and tap water were used as targets. In all but one instance, 4–9 transitions were found to meet the criterion; even with hydroxysimazine where only three transitions were available, quite acceptable results were obtained.

Comparison of the FIA–MS–MS and several LC- and GC-based procedures for twenty surface water samples illustrated the practical usefulness of the proposed alternative.

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