Advantages of online SPE coupled with UPLC/MS/MS for determining the fate of pesticides and pharmaceutical compounds

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Abstract

Laboratory experimentation is essential for our understanding of the fate and behaviour of pollutants. Many analytical techniques exist, but they all have disadvantages either in terms of sensitivity or of selectivity. The number of samples that can be analysed, the low volume of samples available during the experiment and the need to identify different degradates are all obstacles that new techniques are able to overcome. The work presented here summarizes progress in the field of metrology as concerns on-line solid phase extraction technology coupled with liquid chromatography followed by tandem mass spectrometry detection. Recently developed analytical techniques were validated for both 18 pesticides and their degradates and 17 pharmaceuticals and their degradates. Limits of quantification from 20 to 70 ng.L^{-1} for pharmaceuticals and from 15 to 25 ng.L^{-1} for pesticides and metabolites have been obtained, with linearity range up to 1 µg.L-1.The limits of quantification of a few ng per litre, the possibility of working on less than 1 mL of sample and the simultaneous quantification of the target products and their transformation products are all advantages that are demonstrated by two environmental applications. The first application concerns the evaluation of ecotoxicological effects of pesticides on aquatic organisms exposed in mesocosms. The second application aims to determine the adsorption constants of pharmaceutical molecules on soils and river sediments. For both applications, the robustness, range of linearity and limit of quantification of the developed analytical methods satisfy the requirements for laboratory experiments conducted under controlled conditions. Specific constraints generated by this type of experiment (adding $CaCl_2$ for the adsorption study and filtration of the water coming from the mesocosms) were not found to limit the use of on-line SPE. These 2 preliminary studies show that new experimental fields are possible thanks to on-line solid phase extraction coupled with liquid chromatography.

Keywords

On-line-SPE, pesticides, pharmaceutical, experiment, monitoring

1 Introduction

Improved analytical techniques and stricter European regulations have led to an increased oversight of water in recent years. The presence in surface and groundwater of pesticides and emerging compounds has been confirmed [1-4]. This presence consequently raises several questions concerning both their toxicity for ecosystems and humans if the water resource is used as a source of drinking water, and the reasons for their presence in hydrosystems. Due to the vast number of compounds involved, the substances to be studied as a priority must be determined. Their ecotoxicological effect should be one of the criteria taken into consideration when they are ranked. At the same time, the fate of these substances must be studied and the risk of their transfer to surface- and groundwater must be assessed.

Many complex mechanisms that depend on the physicochemical properties of both the molecules and their host environment govern the fate of organic compounds in the environment. In soil, sorption and degradation processes not only govern the mobility of molecules toward groundwater, but also reduce the quantity of migrating molecules. By carrying out experiments under controlled laboratory conditions, the importance of these two processes and the key parameters affecting them can be studied.

For the adsorption of organic molecules, adsorption isotherms are therefore developed to determine the partition coefficient between the liquid and solid phases. The standard OECD (Organisation for Economic Co-operation and Development) protocol for pesticides has been the reference for many years [5] and also serves as a basis for the study of other organic substances. This guideline recommends using chromatographic techniques, which can be coupled with mass spectrometry, or liquid scintillation counting when radiolabelled substances are used. The use of ^{14}C-labelled molecules to determine adsorption isotherms is therefore fairly common. This method makes it possible to carry out precise, rapid and inexpensive analyses while working with relatively low concentrations. However, aside from the fact that this technique requires that the laboratory and personnel be certified for handling this type of products, there are few ^{14}C-labelled substances on the market vs. the number of potential organic contaminants. Custom synthesis of ^{14}C-radiolabelled compounds can be particularly expensive. Furthermore, the study of mixtures of molecules in order to determine whether they might compete with one another requires numerous experiments because several labelled molecules cannot be used simultaneously. These considerations might represent an obstacle. This is particularly crucial in environmental studies where not only the parent molecule, but also its metabolites and/or transformation products, are studied. In the same way, it is sometimes more relevant to test the behaviour of mixed rather than individual

substances either because a mixture of pesticides is registered or because several molecules are used together according to farming practices.

Unlabelled molecules can be used, but this can be more constraining because heavier extraction and analytical techniques must be employed. Moreover, the limits of quantification might be higher and require working with higher concentration ranges than with ^{14}C-labelled molecules. Last but not least, the analytical uncertainty is greater.

For toxicity, experiments that aim to determine the chronic and long-term toxic effects of compounds require working at low concentrations of mixtures of chemicals [6]. Numerous conditions must be taken into consideration, which multiplies the number of analyses that must be carried out and therefore the cost of assessments. Few ecotoxicological studies therefore use real exposure values. Most simply use theoretical values, which are, in some cases, distorted by molecular degradation and the appearance of degradation products [6]. Methods that are easy to carry out, robust and inexpensive are therefore needed in order to increase the relevance and the representativity of ecotoxicological studies.

Water samples can be analysed directly without sample pretreatment. Lin and Gan [7] injected supernatants after filtering them on Whatman 0.45-µm glass microfiber filters. Concentrations in the µg L^{-1} range can be determined for some rather sensitive molecules using these analytical methods. Despite the increased sensitivity of spectrometric methods, it is sometimes necessary to lower this limit. For that, a pre-concentration step using cartridges (Solid Phase Extraction) is usually necessary.

Classical off-line SPE techniques are therefore used but require large quantities of samples and/or high concentrations, in some cases very different from environmental conditions, e.g. 500 µg L^{-1} [8]. Drillia et al. [9], studying the adsorption of 6 pharmaceutical molecules in 2 soils, used an off-line SPE system with 50 mL of solution and initial concentrations of between 1 and 12 mg L^{-1}. Fenet et al. [10], studying the adsorption of carbamazepine and 2 of its metabolites on 2 soils, worked with concentrations ranging between 250 and 3,000 µg L^{-1}.

On-line SPE makes it possible to combine a first step that entails the loading of the sample into an extraction cartridge with a second step that couples cartridge elution and chromatographic separation, followed by detection, usually by mass spectrometry. There are various configurations for this application [11].

On-line SPE was first used to detect compounds in plasma or urine [12]. In the last decades, environmental applications have multiplied, both for monitoring compounds like organophosphorous compounds and their degradation products in rivers [13, 14] and for detecting broad ranges of chemicals in aquatic environments [15]. To our knowledge, however there are very few examples of on-line SPE coupled with liquid chromatography being used to determine the adsorption constants of organic molecules [16] and none as our knowledge to assess the ecotoxicological effects.

The aim of this study is therefore to determine to what extent the use of on-line SPE coupled with UPLC/MS-MS is suitable for environmental laboratory studies for polar organic molecules such as pesticides or emerging compounds. To do this, two environmental applications having different constraints and requirements in terms of results were considered. The first application is part of a pesticide ecotoxicity study and the second involves the assessment of the risk of leaching of pharmaceutical products by means of adsorption studies. For each application, the analytical method developed is first described and evaluated for its performance (accuracy, robustness), after which the results obtained are judged for their suitability regarding the requirements of the type of study involved.

2 Materials and Methods

2.1 Materials

Analytical standards (purity >98%) were supplied by Dr. Ehrenstorfer (VWR International, Fontenay sous Bois, France) and Sigma Aldrich (Saint Quentin Fallavier, France). HPLC-grade formic acid (98%), acetonitrile and water were supplied by Avantor Performance Materials (Deventer, Netherlands). Individual solutions containing 500 mg L^{-1} of the target compounds were prepared in methanol and stored in the dark at -18 °C. Standard mixtures were prepared – one containing 10 mg L^{-1} for each compound in methanol, and working solutions at 1 mg L^{-1} and 10 µg L^{-1} in natural water for calibrations. For pesticide analyses, D_6-mecoprop, D_6-isoproturon and D_{10}-simazine were used as surrogate standards – 30 µL of a solution mix (containing 5 mg L^{-1} of each compound) were added to each 1.5-mL water sample. For the analysis of pharmaceutical compounds, D_5-oxazepam, D_6-sulfamethoxime, D_3-ibuprofen and D_5-diazepam were used. A working solution was prepared containing 250 µg L^{-1} of each standard except for D_3-ibuprofen (2,000 µg L^{-1}). One hundred microliters of the solution were added to each 1-mL water sample.

2.2 Instrumentation and analysis

The on-line SPE system consists of a standalone 515 pump hooked up to the ACQUITY UPLC system by a Rheodyne switching valve. The sample is injected with a 2777 autosampler equipped with a 2-mL syringe and loaded through the cartridge via the 515 pump, with a water flow rate of 2 mL min^{-1}. During this loading step, the valve switches to "waste" at the cartridge outlet. During elution, the valve switches to direct the mobile phases through the cartridge, then the analytical column and the detection system. The 515 pump is off at this time (Figure 1). Analyses were done with a Waters Quattro Premier XE triple quadrupole mass spectrometer (Guyancourt, France). Waters also supplied the extraction cartridge (Oasis®HLB, 2.1 x 20 mm, 25 µm) and the HSS T3 analytical column (2.1 × 150 mm, 1.7 µm).

A sample volume of 500 µL was injected. The water for sample loading was adjusted to pH 3.4 with acetic acid. The mobile phase was composed of Solvent A (0.05 % formic acid in water) and solvent B (0.05 % formic acid in acetonitrile) at a constant flow of 0.4 $mL.min^{-1}$. The gradient was programmed to increase the amount of solvent B from an initial 0 % (maintained for 1 min) to 100 % in 7.5 min, stabilize at 100 % for 3 min, and return to the initial conditions (0 % B) in 0.3 min. These conditions were maintained for 5 min.

Mass spectrometry was done with a triple quadrupole fitted with an ESI interface and controlled by MassLynx software. Typical interface conditions were optimized for maximum intensity of the precursor ions as follows: cone gas and desolvation (drying gas) N_2 flows were set at 800 and 50 $L.h^{-1}$, respectively, and source block and desolvation temperatures were 150 and 400 °C, respectively. The ESI polarity ionisation mode was set individually for each target compound. Positive and negative polarity modes were used simultaneously during the same analytical run. Argon was used as the collision gas at a pressure of 3.7 10^{-3} mBar. MRM transitions were selected and tuned individually for each analyte. To optimize the mass spectrometer, a 500 $\mu g.L^{-1}$ standard solution of each analyte was infused directly. The specific and intense product ions of each target analyte were used for quantification, and a secondary product ion was used as a qualifier ion for confirmatory purposes. The optimal conditions for each pesticide and pharmaceutical product are summarized in tables 1 and 2.

Calibration curves were obtained by a weighted (1/x) linear least square regression. Calibration samples were treated like environmental samples. A standard curve was acquired at the beginning and at the end of each measurement series. The first measurement of standards was used for quantification and the second was used as quality control. Procedural blanks consisting of nanopure water and blank samples consisting of nanopure water with surrogate standards were used in every sequence in order to reveal any

182 analytical interference or possible carryover. Sensitivity and accuracy of the measurements
183 are controlled after each twenty-samples series by injection of quality control samples at low
184 level (limit of quantification) and intermediate level (100 ng/L).

185

186 2.3 Ecotoxicological study

187 The aim of this study was to assess and compare the structural and functional effects of
188 current and alternative wheat crop protection programs on aquatic macro invertebrates using
189 outdoor pond mesocosms. Four exposure scenarios were defined according to the type of
190 crop protection program and the geographical location of treated fields. In order to determine
191 the treatment-related effects on the structure of macro invertebrate communities and on litter
192 breakdown, researchers must characterize the exposure of the test systems to the different
193 substances. The experiment is described in detail in Auber et al. [17]. A list of the 18
194 compounds studied is given in table 1. The pesticides belong to various chemical classes
195 (ureas, azole, sulfonylureas, hydroxybenzonitriles, etc.) having different chemical properties.

196 Over a period of 18 months, samples were collected 24 h after each treatment and every
197 three weeks, regardless of the treatment, in order to obtain information on pesticide residue
198 levels. More than 700 water samples were collected (250 mL) and frozen at -20 °C until
199 extraction and analysis. One and a half millilitres of each sample was filtered (GFF, 0.45 µm)
200 and 30 µL of the surrogate solution was added before analysis.

201

202 2.4 Adsorption experiments

203 2.4.1 Molecules and solids studied

204 For this specific study, three pharmaceutical molecules that are included in the list of 17 that
205 can be analysed simultaneously with the method developed (Table 2) were tested –
206 carbamazepine, sulfamethoxazole and oxazepam. They were chosen because they are
207 frequently detected in the ground- and surface waters of the "Val d'Orléans" (the left bank of
208 the Loire River between Guilly and the confluence of the Loiret River near Orleans, France)
209 [18]. Indeed, from March 2008 until July 2010, carbamazepine, oxazepam and
210 sulfamethoxazole were quantified, respectively, in 89, 93 and 68 % of samples coming from
211 2 rivers and one well taping groundwater, with maximum concentrations of 91, 120 and 68 ng
212 L^{-1} (n = 53 for each site). These molecules are among the most quantified of the 30 that are
213 sought.

214 Three agricultural soils and two river sediments were collected in the hydrosystem. Their
215 particle size distribution and physicochemical characteristics are given in table 3. All of the
216 soils are predominantly sandy with water pH varying between 6.3 and 7.7. Soil D has the
217 highest cation exchange capacity, although it is still relatively low for a soil (10.6 meq/100 g).

218

219 **2.4.2 Adsorption isotherms**

220 Experimental isotherms were determined using the batch equilibrium method (OECD test
221 guideline 106; OECD, 2000). The liquid to solid ratio used for the sorption study was 2 - 5 g
222 of soil or sediment (air dried and sieved to 2 mm) for 10 mL of solution. The temperature was
223 set at 20 °C. Solutions of three molecules at concentrations of around 0.25, 0.64, 1.28, 6.35
224 and 25.5 µg L^{-1} were prepared in $CaCl_2$ at 0.01 M. A solution containing only carbamazepine
225 was also prepared at similar concentrations. The experiments (mixture of molecules or
226 carbamazepine alone) were done in triplicate. The experimental isotherms were fitted using
227 the Freundlich equation:

228 $$C_s = K_f \times C_e^{nF} \quad (1)$$

229 where C_s is the adsorbed concentration (mg kg^{-1}), C_e is the equilibrium concentration in the
230 solution (mg L^{-1}), K_f is the Freundlich coefficient (sorption constant in L kg^{-1}) and nF
231 (dimensionless) is the characteristic sorption coefficient. Sorption was then normalized with
232 regard to the organic carbon fraction of the soil (f_{oc} in %) by calculating the coefficient K_{oc} (L
233 kg^{-1}) using the equation:

234 $$K_{OC} = \frac{K_f}{f_{OC}}$$

235 # 3 RESULTS and DISCUSSION

236 ## 3.1 Analytical aspects and method validation

237 **3.1.1 Analytical method**

238 The chromatographic and spectrometric methods used were similar to classical ones. On the
239 other hand, the on-line SPE step needed to be optimized [19]. The main criteria to be
240 optimized were the loading time (here 1 min), the 515 pump flow rate and the nature of the
241 loading water. Due to the differences in the physicochemical properties of the molecules
242 studied, tests were run at pH 7, 3.4 and 2. Effects were evaluated in terms of signal
243 enhancement. For neutral compounds, such as azoles and strobine, there was no significant

244 impact of the pH. A distinct improvement was achieved with pH 3.4 for ureas, sulfonylureas
245 and hydroxybenzonitriles. The same assay was done for pharmaceuticals and pH 3.4 was
246 also retained because of a positive effect on ibuprofen and naproxen metabolites without any
247 negative effect on the other compounds. This improvement is also observed in off-line SPE
248 for ionic molecules where samples are acidified prior to extraction [20]. Acidifying the loading
249 water eliminates the need to acidify each individual sample prior to analysis as is done for
250 off-line SPE extractions, which is much less constraining.

251 Concerning elution conditions, the only noteworthy modification to the classical methods was
252 a shorter column rinsing time with 100 % acetonitrile (2 min vs. 5 min) in order to avoid
253 crushing the cartridge and inter-sample contamination. This robustness was verified by
254 injecting a blank after samples containing very high contents. To recondition the cartridge
255 with water at pH 3.4, the 515 pump was restarted 3 min before the end of the analysis.
256
257 The use of on-line SPE requires that there be no suspended matter in the water samples.
258 Samples from mesocosms where suspended matter appeared during the experiments were
259 therefore filtered (0.45 µm polyacrylate syringe filter). Previous laboratory tests showed that
260 the molecules under consideration did not adsorb on the filter. For analyses carried out to
261 determine adsorption isotherms, the samples were centrifuged (2,500 rpm for 20 min) before
262 surrogates were added and they were injected. The centrifuging is efficient enough to
263 eliminate any suspended matter that might alter the chromatography system. Filtration was
264 therefore not necessary.
265

266 **3.1.2 Linearity and Limits of Quantification**
267 Quantification was carried out by plotting the peak area of an analyte and its respective
268 internal standard against the corresponding analyte–internal standard concentration ratio.
269 The limit of quantification (calculated from calibration standard, with a signal to noise ratio
270 above 10:1) for 500 µL of injected sample is 20 ng L^{-1} for all of the pharmaceutical
271 substances except naproxen, o-desmethyl naproxen, diclofenac and ibuprofen, for which the
272 limit is 70 ng L^{-1}.

273 For the study of pesticide compounds, the limits of quantification (calculated from calibration
274 standard, with a signal to noise ratio above 10:1) for 500 µL of injected sample are between
275 15 and 25 ng L^{-1}, with the higher values being for hydroxybenzonitriles (bromoxynil and
276 ioxynil). The simultaneous analysis of molecules that have different physicochemical
277 properties entails compromises that affect these two molecules in particular.

Due to the preliminary on-line extraction step, the linearity ranges of these methods (Tables 1 and 2) are narrower than those of methods involving classical injections. The samples must therefore be diluted. Since the entire procedure is meant to be rapid (< 20 min), in the cases presented here, for which the measured concentrations were predictable, the dilution factors were estimated and diluted samples were injected simultaneously with the raw samples.

3.1.3 Robustness

One of the main advantages of this technique is its robustness to the aging of cartridge and matrix variability. This was evaluated based on the response (in terms of peak area) of the internal standards added to each sample. Within a given analytical series (75 to 100 samples), variability is 10 % and 11.5 % for simazine d10 and isoproturon d6, respectively. For several analytical series spread over 1 year (which corresponds to about 700 samples and more than 3,000 injections), this variability is between 15 % and 19 %, which is similar to the variability measured with off-line SPE and LC/MS/MS analyses [20].The slight variations of the concentrations of major ions in the matrix (mesocosm water) can contribute to this method reliability, together with the fact that the calibration is done in the matrix. The use of extraction tracers also makes it possible to increase the robustness of the method. Combined to quality control samples, the gravimetric adding of tracer mix guarantees the correct quantification of compounds.

Use of multiple tracers allows to enhance the range of compounds that can be measured by online SP combined to LC/MS. Huntscha et al. [15] developed a self-made mixed-bed multilayer extraction cartridge in order to increase the range of molecules that can be extracted with this technique. Combining this with the use of 50 isotope-labelled compounds as an internal standard mixture, they obtained extraction yields of between 80 and 110 %.

3.1.4 Effect of the composition of the matrix

According to OECD guidelines [5], laboratory experiments require the use of $CaCl_2$. The effect of adding calcium chloride was determined by comparing the slopes of two calibrations – one done in spring water and the other in $CaCl_2$ 0.01 M. The ratio between the two slopes is between 85 and 110 %, depending on the compound, which shows that $CaCl_2$ has little effect on analytical performance. The chromatographic peak resolution is not affected by this modification (Figure 2). The calibration ranges associated with these experiments have therefore been determined in $CaCl_2$ 0.01 M.

3.2 Results of monitoring ecotoxicological experiments

Eighteen pesticides and degradates were monitored during the experiments. As an example, figure 3 shows isoproturon dissipation and the formation of its degradates.

In our study, monitoring pesticide compound concentrations with a short time step revealed the fleeting appearance of degradation products, including those of isoproturon (Fig. 2). The replicates shown correspond to experimental replicates (3 mesocosms for each exposure scenario).

The detection of the onset, even for a relatively short period of a few weeks, of monodesmethyl-isoproturon is particularly interesting. Indeed, this substance is recognized as a major metabolite of isoproturon. Isoproturon's two metabolites are rarely quantified in water. Despite the very lengthy monitoring of a spring that is the outlet of a karstic system (476 samples collected between 1998 and 2006), rapid water circulation and exchanges between surface- and groundwater, monodesmethyl-isoproturon was detected only twice. Didesmethyl-isoproturon has never been detected [21]. In addition, European regulations recommended that particular attention should be paid to the protection of aquatic organisms [223].

Average Exposure Concentrations (AEC) were calculated for each compound and each scenario (Table 4) and could be correlated with effects on populations of exposed organisms [17]. The identification of new compounds resulting from the degradation of parent compounds is important (e.g. mono-desmethyl-isoproturon) as these can, in some cases, explain unexpected ecotoxicological effects.

3.3 Adsorption isotherms of pharmaceutical products

For all three of the molecules studied simultaneously, adsorption isotherms (Figure 4) show that the order of decreasing adsorption is the same and depends on the material: soil D > soil C > soil B ~ sediment B > sediment C.

Likewise, for a given soil, the adsorption constant decreases as follows: Oxazepam > Carbamazepine (> Sulfamethoxazole). For sulfamethoxazole, the results are unsatisfactory since the behaviour of the substance seems to be concentration-dependant (higher adsorption than the 2 others molecules for low concentrations and lower adsorption for high concentrations). A reliable estimation of the adsorption constant cannot be proposed here. Lin and Gan [7] showed, on 2 soils, that sulfamethoxazole adsorption is limited and even

considered to be negligible (concentrations in the supernatant similar to initial concentrations). As the analysis of the substance is not difficult, the inconsistencies can, a priori, be attributed to the intrinsic properties of the substance. Additional tests are needed in order to describe the fate of sulfamethoxazole. Although adsorption data are available for carbamazepine, there is little data available for the two other substances. For our soils, the average K_{oc} values are 425 +/- 58 and 1098 +/- 141 L kg^{-1} for carbamazepine and oxazepam, respectively, when considered as a mixture. The carbamazepine adsorption constant is 471 +/- 119 L kg^{-1} when the molecule was studied alone.

Drillia et al. [9], working with a soil that had an organic carbon content of 0.31 %, reported K_{oc} values of 132 +/- 2.7 kg L^{-1} for carbamazepine and 62.2 +/- 21.6 kg L^{-1} for sulfamethoxazole. Fenet et al. [10] determined carbamazepine adsorption constants of 158 and 309 kg L^{-1}, respectively, for a European "reference" soil and an agricultural soil receiving waste water effluents. Carbamazepine K_{foc} values of between 136 and 187 for 3 agricultural soils have been reported [22]. Working on a river sediment, Löffler et al. [23] demonstrated a higher adsorption of oxazepam than carbamazepine, in agreement with our results on both sediments.

The agreement of our experimental data with literature data obtained using other protocols (^{14}C molecules, off-line SPE) validates the use of on-line SPE for this type of data acquisition. For soils, the very low variability observed for the triplicates (for the mixture or for carbamazepine alone) further validates this method. The greater variability observed for sediments is not attributed to the analytical method but might be related to the heterogeneity of the material.

4 Conclusions

This work describes 2 fully-automated methods based on on-line SPE/LC/MS/MS to determine concentrations of pharmaceuticals and pesticides in the constraining context of experimental studies. Their robustness and sensitivity are adequate considering the requirements of these applications. The similarity of off- and on-line approaches makes the transfer of methodologies between the two techniques easier and opens up the field to many other method transpositions. The major role of surrogates is one of the key factors behind the effectiveness of this approach and must not be overlooked. A compromise must be found between increasing analytical performance and limiting costs, all the while considering availability issues.

The results of our preliminary applications on pesticides and pharmaceuticals and the agreement of our experimental data with those of other studies validate the use of on-line SPE for the acquisition of experimental data.

For ecotoxicological studies, monitoring enables the correlation of observed biological effects and the measured occurrence of pollutants. This approach makes it possible to determine the fate of pollutants in mesocosms, including their dissipation, bioavailability and the appearance of degradates, by accurately measuring their concentrations in systems.
Given the range of concentrations that these techniques can handle (several nanograms per litre), adsorption experiments can be carried out at concentrations much lower than those reported in the literature. The use of higher concentrations with on-line SPE would require numerous dilutions and therefore greatly increase preparation time and increase uncertainties in measurements, thus making this method less advantageous. Although the use of lower concentrations might make it more difficult to compare results with those of other studies, it enables us to work at levels that are environmentally more realistic.

The automation of the system makes it possible to treat more samples. While some time is saved on sample preparation, even more is saved by the automatic sequencing of extraction/analysis and result reprocessing. This enables us to foresee numerous future environmental applications using this approach.

Concerning the range of molecules that can be analysed with this technique, the main limitation is the small number of phases available for the on-line extraction step. This means that multi-residue extractions result, in some cases, in very low yields, partially resolved by the use of isotope-labelled compounds as internal standard, but with an important increase of the analytical cost and dependant of the availability of those standards.

For the cartridge elution system using mobile-phase solvents, it is necessary to use solvents that are compatible with the analytical column and the detector, which limits the solvent mixtures that can be used. Eluents well-suited for the elution of ionic exchange cartridges cannot therefore be used with this type of analytical set-up (sodium or ammonium hydroxide, strong acid, etc.).

A wide range of molecules can however be analysed using this methodology, including both pesticide compounds and new compounds like pharmaceuticals, hormones, polar endocrine disrupting chemicals, etc. The growing need for experimental data – both for ecotoxicological

409 studies and for studies of the fate and behaviour of emerging compounds – might be more
410 easily satisfied with this methodology.

411

412

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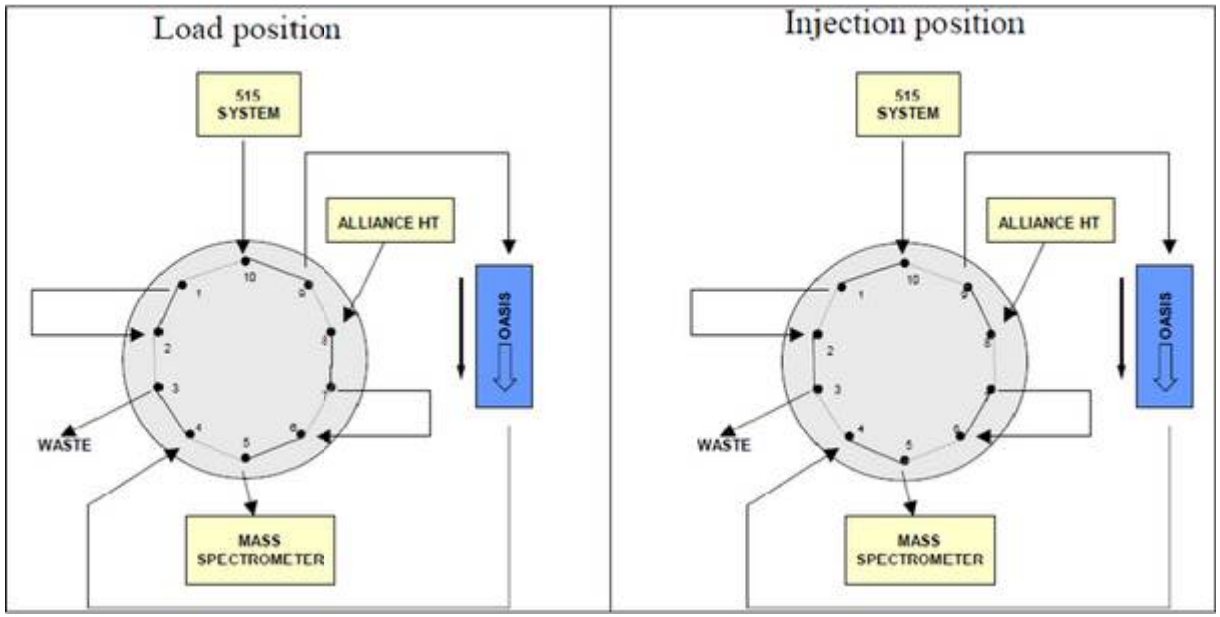

Figure 1: online SPE/UPLC/MS/MS set-up

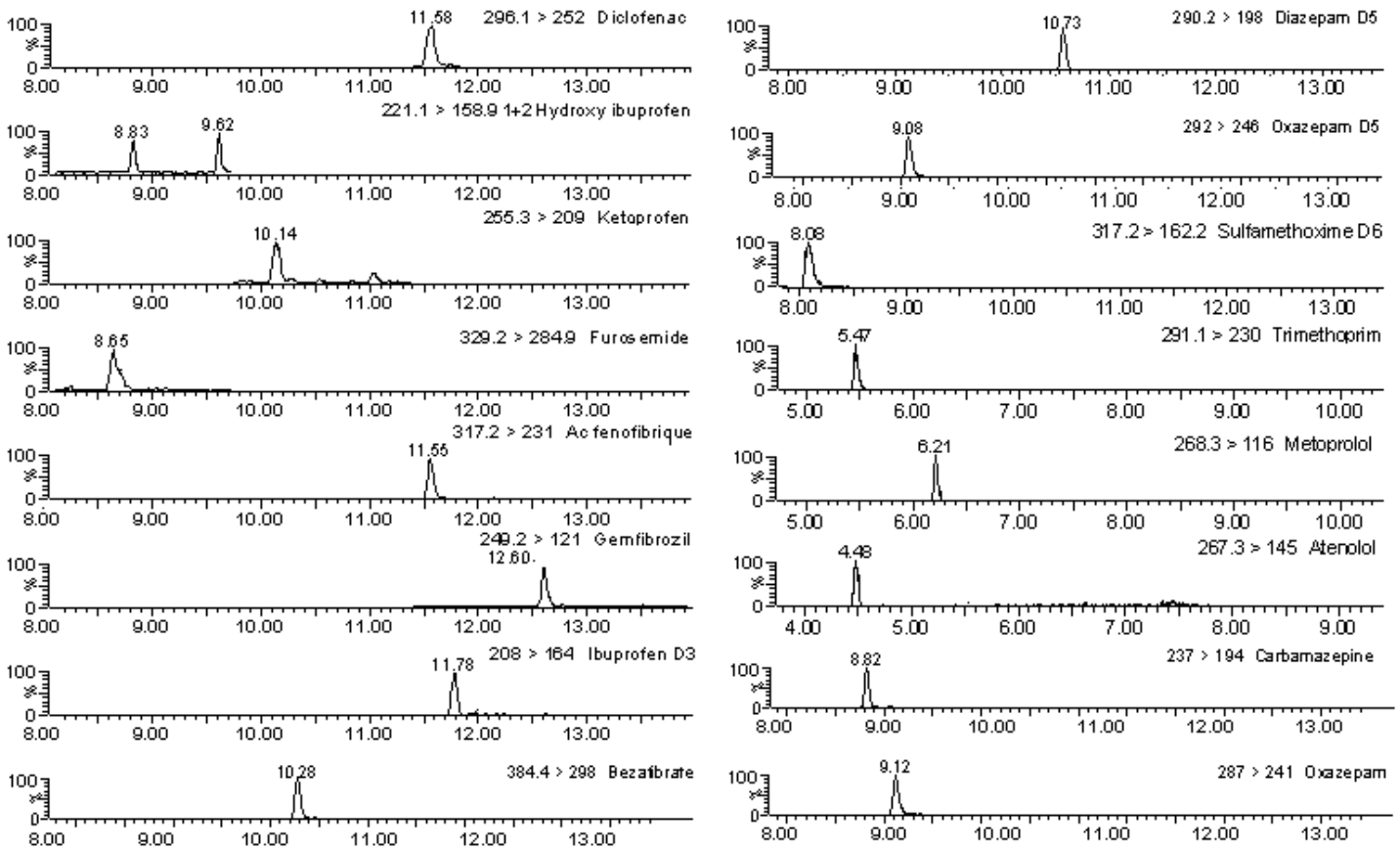
11.58 296.1 > 252 Diclofenac
221.1 > 158.9 1+2 Hydroxy ibuprofen
8.83
9.62
255.3 > 209 Ketoprofen
10.14
329.2 > 284.9 Furosemide
8.65
317.2 > 231 Acfenofibrique
11.55
249.2 > 121 Gemfibrozil
12.60
208 > 164 Ibuprofen D3
11.78
384.4 > 298 Bezafibrate
10.28
290.2 > 198 Diazepam D5
10.73
292 > 246 Oxazepam D5
9.08
317.2 > 162.2 Sulfamethoxime D6
8.08
291.1 > 230 Trimethoprim
5.47
268.3 > 116 Metoprolol
6.21
267.3 > 145 Atenolol
4.48
237 > 194 Carbamazepine
8.82
287 > 241 Oxazepam
9.12

Figure 2:

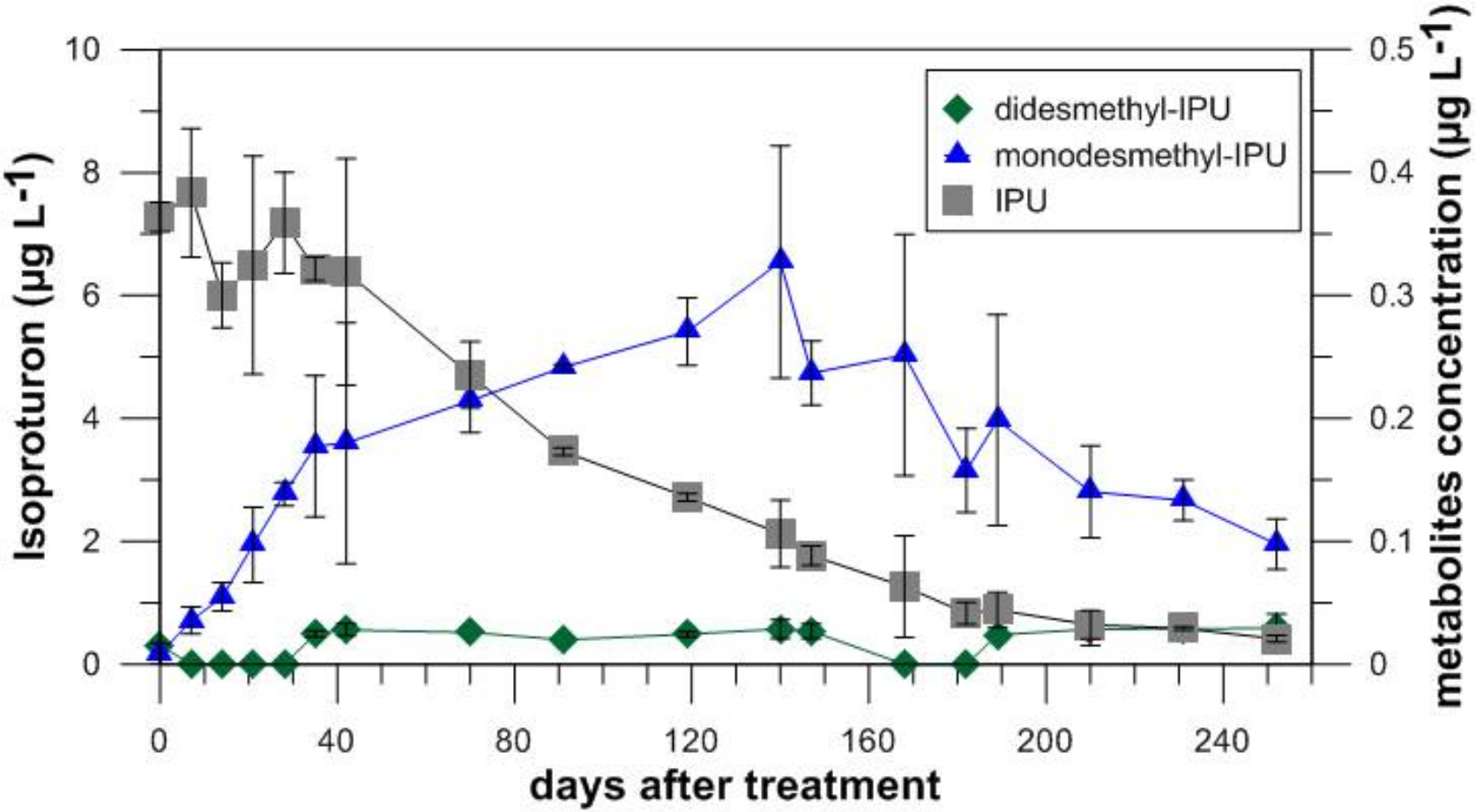

Figure 3: Monitoring of isoproturon and two degradates, concentrations in mesocosms. Results of the 3 replicates of the same scenario are shown

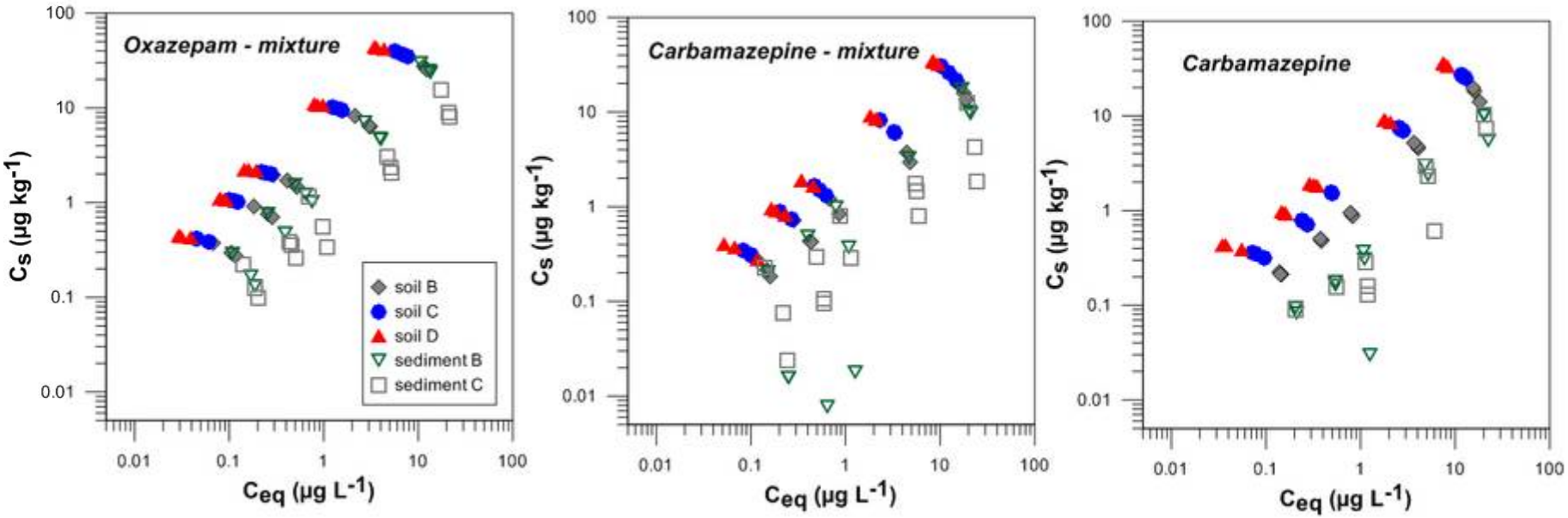

Figure 4: adsorption isotherms of oxazepam and carbamazepine studied as a mixture (with sulfamethoxazole) and carbamazepine studied alone

				Quantifier						Qualifier						
	chemical group	linear range ng.L-1	retention time (min)	Ionization	Transition			cone Voltage	Collision Energy	Ionization	Transition			cone Voltage	Collision Energy	Internal standard
Simazine D10 (SIM d10)	surrogate	250	4,08	ESI +	212,0	>	137,0	35	20	ESI +	212,0	>	104,9	35	25	
Isoproturon D6 (IPU d6)	surrogate	250	4,47	ESI +	213,1	>	77,9	30	18	ESI +	213,1	>	171,0	30	15	
Isoproturon-didesmethyl	degradate	15-500	4,11	ESI +	179,1	>	137,0	30	12	ESI +	179,1	>	93,9	30	20	IPU d6
Metsulfuron methyl	sulfonyl urea	15-500	4,17	ESI +	382,0	>	167,0	25	15	ESI -	379,9	>	139,0	25	16	IPU d6
Isoproturon-monodesmethyl	degradate	15-500	4,30	ESI +	193,1	>	93,9	25	20	ESI +	193,1	>	151,1	25	12	IPU d6
Mesosulfuron methyl	sulfonyl urea	15-500	4,37	ESI+	504,1	>	182,0	35	20	ESI -	502,1	>	347,0	30	15	IPU d6
Iodosulfuron methyl	sulfonyl urea	15-500	4,41	ESI +	507,8	>	167,0	30	18	ESI -	506,2	>	139,0	30	22	IPU d6
Isoproturon	urea	15-500	4,48	ESI +	207,0	>	71,9	30	15	ESI +	207,0	>	164,8	30	15	IPU d6
Bromoxynil	hydroxybenzonitriles	25-500	4,52	ESI -	275,8	>	79,0	40	25	ESI -	273,8	>	79,0	40	25	IPU d6
Ioxynil	hydroxybenzonitriles	25-500	4,81	ESI -	369,7	>	127,0	40	30	ESI -	369,7	>	215,0	40	25	IPU d6
Prochloraz	Azole	15-500	4,95	ESI +	378,0	>	309,9	20	10	ESI +	376,0	>	307,8	20	10	SIM d10
Cyprodinil	Pyrimidine	15-500	4,97	ESI +	226,1	>	92,8	30	35	ESI +	226,1	>	108,0	30	25	SIM d10
Azoxystrobin	Strobin	15-500	4,98	ESI +	403,9	>	372,0	30	15	ESI +	403,9	>	329,1	30	30	SIM d10
Epoxiconazole	azole	15-500	5,01	ESI +	329,9	>	120,8	33	18	ESI +	329,9	>	140,8	33	18	SIM d10
Boscalid	Anilide	15-500	5,07	ESI +	342,9	>	307,0	30	19	ESI +	342,9	>	271,5	30	32	SIM d10
Flusilazole	azole	15-500	5,15	ESI +	316,1	>	165,0	35	25	ESI +	316,1	>	247,2	35	15	SIM d10
Tebuconazole	azole	15-500	5,16	ESI +	307,9	>	70,0	33	27	ESI +	307,9	>	124,7	33	31	SIM d10
Napropamide	amide	15-500	5,19	ESI +	271,8	>	171,1	26	18	ESI +	271,8	>	198,9	26	13	SIM d10
Metconazole	azole	15-500	5,38	ESI +	320,0	>	69,9	37	20	ESI +	320,0	>	124,8	37	40	SIM d10
Prosulfocarb	thiocarbamate	15-500	5,97	ESI +	251,8	>	90,7	25	20	ESI +	251,8	>	128,0	25	12	SIM d10

511

512 Table 1 : Target pesticides and their optimized MS/MS parameters

513

514

Compounds	group	linear range ng.L-1	retention time (min)	Quantifier						Qualifier						Internal standards
				Ionization	Transition			cone Voltage	Collision Energy	Ionization	Transition			cone Voltage	Collision Energy	
Oxazepam d5 (OXZ d5)	surrogate	250	9.08	ESI +	292,0	>	246,0	30	20	ESI +	292,0	>	214,0	30	20	
Sulfamethoxime d6 (SFX d6)	surrogate	250	8.12	ESI +	317.2	>	162.2	35	22	ESI +	317.2	>	155.8	35	22	
Ibuprofen d3 (IBU d3)	surrogate	2000	11.77	ESI -	208.0	>	164.0	25	7			>				
Diazepam d5 (DZP d5)	surrogate	250	10.72	ESI +	290.2	>	262.1	35	22	ESI +	290.2	>	198,0	35	30	
O Desmethylnaproxen	degradate	70-5000	8.23	ESI -	215,0	>	170.9	25	12	ESI +						IBU d3
Fenofibric acid	hypolipemiant	20-1000	11.54	ESI -	317.2	>	231,0	25	10	ESI +	319,0	>	233.0	30	16	OXZ d5
Naproxen	AINS	70-5000	10.22	ESI -	228.9	>	184.8	25	7	ESI -	228.9	>	169.9	25	15	DZP d5
Gemfibrozil	hypolipemiant	20-1000	12.60	ESI -	249.2	>	121,0	25	13	ESI -	249.2	>	127.1	25	10	DZP d5
Ibuprofen	AINS	70-5000	11.79	ESI -	205.1	>	160.9	25	7	ESI +						IBU d3
Ketoprofen	AINS	20-1000	10.11	ESI -	252.9	>	209,0	25	8	ESI +	255.3	>	209.0	30	12	DZP d5
Furosemide	diuretics	20-5000	8.67	ESI -	329.2	>	284.9	35	15	ESI -	329.2	>	204.8	35	20	DZP d5
Bezafibrate	hypolipemiant	20-1000	10.26	ESI -	360.3	>	274,0	30	17	ESI +	384.4	>	298.0	35	17	OXZ d5
Diclofenac	AINS	20-5000	11.58	ESI -	294,0	>	250,0	25	12	ESI -	296.1	>	252,0	25	12	DZP d5
1 hydroxy ibuprofen	degradate	20-1000	8.81	ESI -	221.1	>	176.9	25	7	ESI -	221.1	>	158.9	25	12	IBU d3
2 hydroxy ibuprofen	degradate	20-1000	8.11	ESI -	221.1	>	176.9	25	8	ESI +						IBU d3
Oxazepam	antidepressant	20-1000	9.11	ESI +	287,0	>	241,0	30	20	ESI +	287,0	>	269,0	30	14	OXZ d5
Atenolol	Beta-blockers	20-5000	4.44	ESI +	267.3	>	190,0	30	18	ESI +	267.3	>	145,0	30	23	OXZ d5
Metoprolol	Beta-blockers	20-5000	6.18	ESI +	268.3	>	190.9	35	18	ESI +	268.3	>	116,0	35	18	OXZ d5
Sulfamethoxazole	antibiotic	20-1000	7.38	ESI +	253.9	>	91.8	30	26	ESI +	253.9	>	155.8	30	17	SFX d6
Carbamazepine	anti-epileptic	20-1000	8.81	ESI +	237,0	>	194,0	25	18	ESI +	237,0	>	179,0	25	33	SFX d6
Trimethoprim	antibiotic	20-5000	5.44	ESI +	291.1	>	122.9	42	24	ESI +	291.1	>	230,0	42	24	SFX d6

Table 2 : Target pharmaceuticals and their optimized MS/MS parameters

	clay (%)	silt (%)	sand %	organic carbon (%)	pH water	pH KCl	CEC (meq/100g)
sediment B	1.2	3.6	94.9	0.163	7.74	7.06	1.92
Sediment C	0.4	2.1	97.4	0.053	7.52	6.66	1.10
Soil B	4.6	9.6	85.2	0.373	6.17	5.05	2.52
Soil C	7.9	16.2	75.1	0.506	6.64	5.73	4.82
Soil D	15.1	25.3	57.8	1.055	6.33	5.46	10.65

Table 3. Soil and river sediment characteristics

521 **Table 4.** Mean (± standard error) Average Exposure Concentration (µg l^{-1}) for each active ingredient and for the different wheat crop protection programs
522 scenario 1 to 4). From [16].

523

Active ingredient	Scenario 1	2	3	4
Azoxystrobin	1.49 ± 0.13	1.60 ± 0.11		
Bifenthrin	0.046 ± 0.004	0.046 ± 0.020		
Iodosulfuron-methyl	0.25 ± 0.01	0.28 ± 0.03		
Mesosulfuron-methyl	0.47 ± 0.01	0.37 ± 0.03		
Metconazole	1.53 ± 0.16	1.71 ± 0.21		
Prochloraz	0.47 ± 0.02	0.74 ± 0.03		
Bromoxynil			0.19 ± 0.02	0.20 ± 0.03
Cyprodynil			74.20 ± 4.5	49.10 ± 4.4
Ioxynil			0.12 ± 0.02	0.12 ± 0.02
Prosulfocarb			2.87 ± 0.18	1.86 ± 0.09
Diflufenican	0.67 ± 0.01	0.57 ± 0.04	0.10 ± 0.005	0.12 ± 0.008
Isoproturon	12.90 ± 0.22	6.20 ± 0.26	4.90 ± 1.1	3.10 ± 0.06
Epoxiconazole	0.83 ± 0.07	0.89 ± 0.04	0.27 ± 0.04	0.20 ± 0.05

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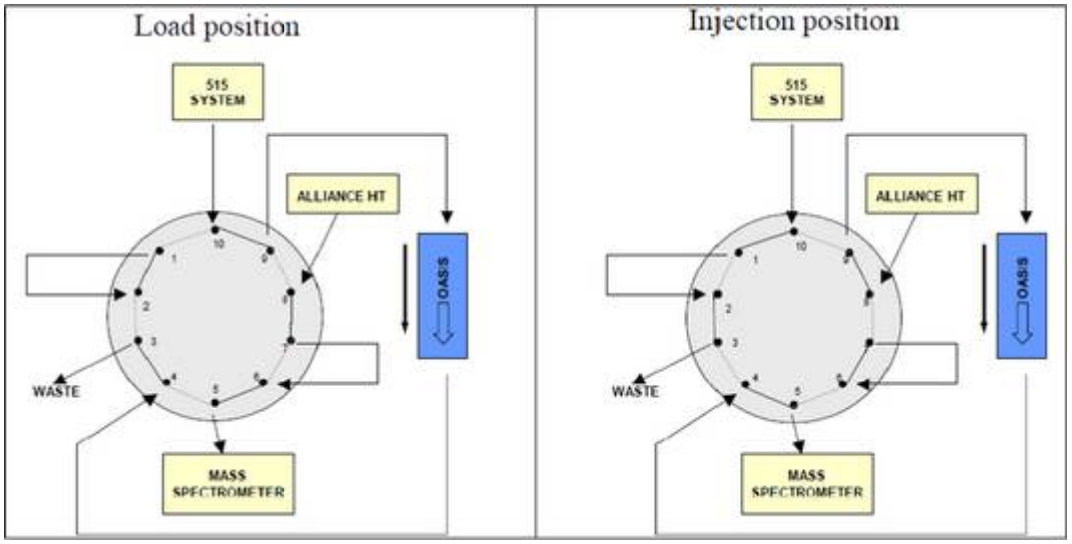

Figure 1: online SPE/UPLC/MS/MS set-up

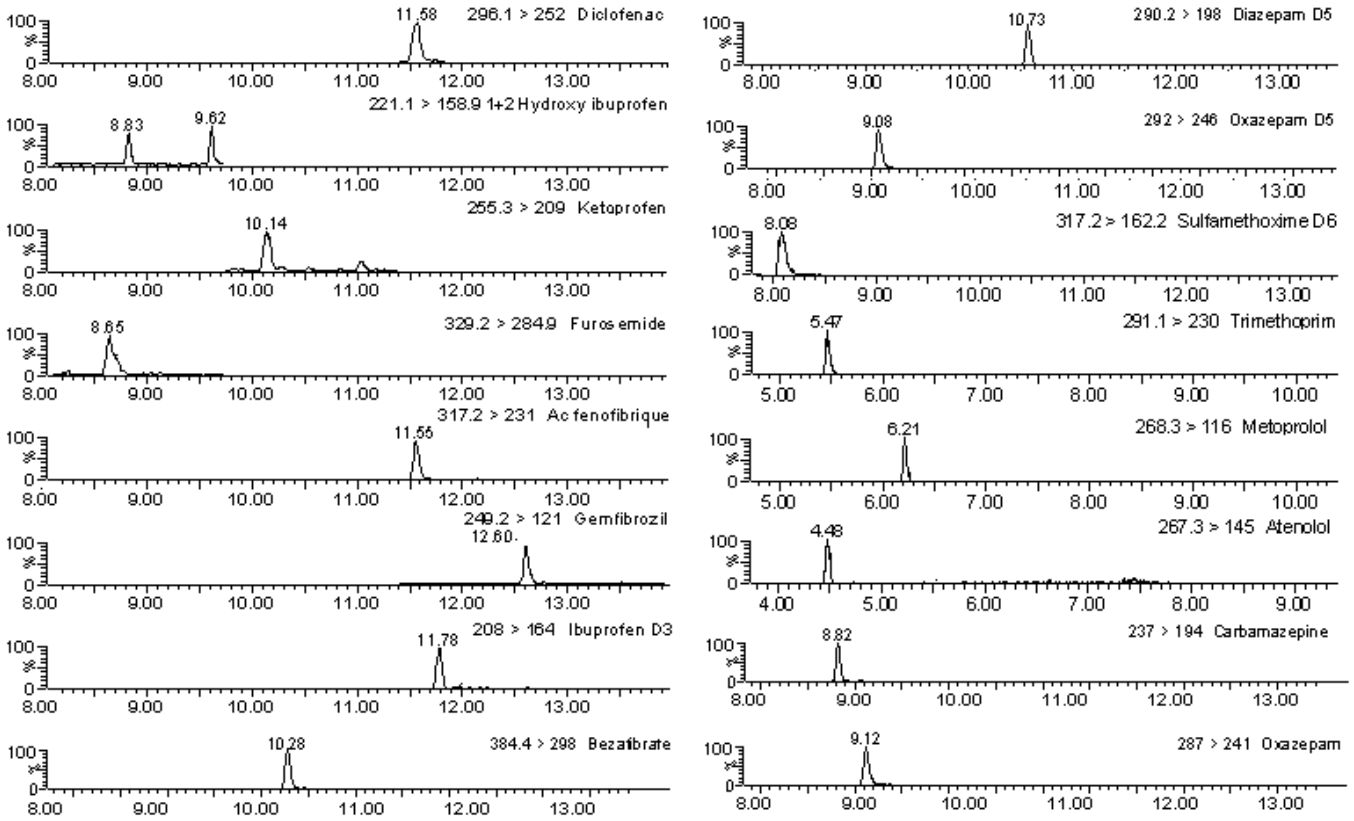

Figure 2 ; Chromatograms of pharmaceutical compounds obtained by online SPE/UPLC/MS/MS

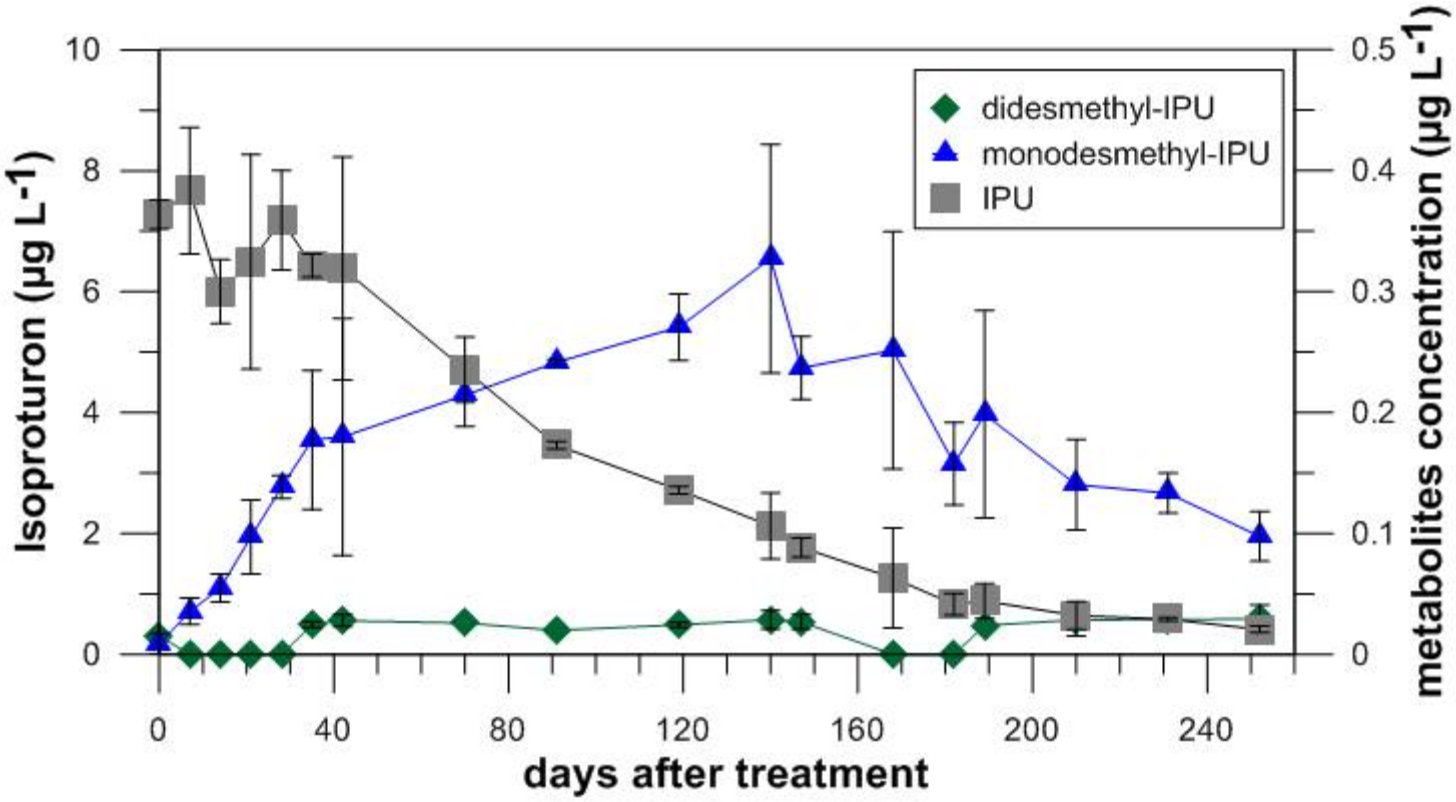

Figure 3: Monitoring of isoproturon and two degradates, concentrations in mesocosms. Results of the 3 replicates of the same scenario are shown

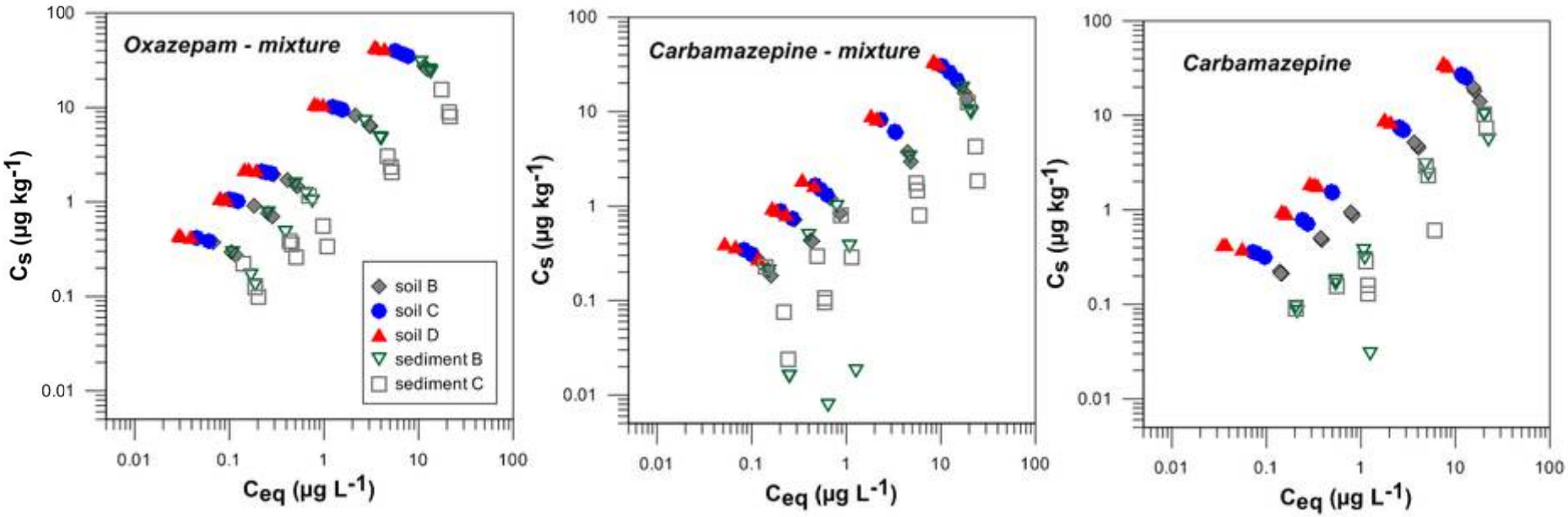

Figure 4: adsorption isotherms of oxazepam and carbamazepine studied as a mixture (with sulfamethoxazole) and carbamazepine studied alone

	chemical group	linear range ng.L^{-1}	retention time (min)	Quantifier						Qualifier						Internal standard
				Ionization	Transition			cone Voltage	Collision Energy	Ionization	Transition			cone Voltage	Collision Energy	
Simazine D10 (SIM d10)	surrogate	250	4,08	ESI +	212,0	>	137,0	35	20	ESI +	212,0	>	104,9	35	25	
Isoproturon D6 (IPU d6)	surrogate	250	4,47	ESI +	213,1	>	77,9	30	18	ESI +	213,1	>	171,0	30	15	
Isoproturon-didesmethyl	degradate	15-500	4,11	ESI +	179,1	>	137,0	30	12	ESI +	179,1	>	93,9	30	20	IPU d6
Metsulfuron methyl	sulfonyl urea	15-500	4,17	ESI +	382,0	>	167,0	25	15	ESI -	379,9	>	139,0	25	16	IPU d6
Isoproturon-monodesmethyl	degradate	15-500	4,30	ESI +	193,1	>	93,9	25	20	ESI +	193,1	>	151,1	25	12	IPU d6
Mesosulfuron methyl	sulfonyl urea	15-500	4,37	ESI+	504,1	>	182,0	35	20	ESI -	502,1	>	347,0	30	15	IPU d6
Iodosulfuron methyl	sulfonyl urea	15-500	4,41	ESI +	507,8	>	167,0	30	18	ESI -	506,2	>	139,0	30	22	IPU d6
Isoproturon	urea	15-500	4,48	ESI +	207,0	>	71,9	30	15	ESI +	207,0	>	164,8	30	15	IPU d6
Bromoxynil	hydroxybenzonitriles	25-500	4,52	ESI -	275,8	>	79,0	40	25	ESI -	273,8	>	79,0	40	25	IPU d6
Ioxynil	hydroxybenzonitriles	25-500	4,81	ESI -	369,7	>	127,0	40	30	ESI -	369,7	>	215,0	40	25	IPU d6
Prochloraz	Azole	15-500	4,95	ESI +	378,0	>	309,9	20	10	ESI +	376,0	>	307,8	20	10	SIM d10
Cyprodinil	Pyrimidine	15-500	4,97	ESI +	226,1	>	92,8	30	35	ESI +	226,1	>	108,0	30	25	SIM d10
Azoxystrobin	Strobin	15-500	4,98	ESI +	403,9	>	372,0	30	15	ESI +	403,9	>	329,1	30	30	SIM d10
Epoxiconazole	azole	15-500	5,01	ESI +	329,9	>	120,8	33	18	ESI +	329,9	>	140,8	33	18	SIM d10
Boscalid	Anilide	15-500	5,07	ESI +	342,9	>	307,0	30	19	ESI +	342,9	>	271,5	30	32	SIM d10
Flusilazole	azole	15-500	5,15	ESI +	316,1	>	165,0	35	25	ESI +	316,1	>	247,2	35	15	SIM d10
Tebuconazole	azole	15-500	5,16	ESI +	307,9	>	70,0	33	27	ESI +	307,9	>	124,7	33	31	SIM d10
Napropamide	amide	15-500	5,19	ESI +	271,8	>	171,1	26	18	ESI +	271,8	>	198,9	26	13	SIM d10
Metconazole	azole	15-500	5,38	ESI +	320,0	>	69,9	37	20	ESI +	320,0	>	124,8	37	40	SIM d10
Prosulfocarb	thiocarbamate	15-500	5,97	ESI +	251,8	>	90,7	25	20	ESI +	251,8	>	128,0	25	12	SIM d10

Table 1 : Target pesticides and their optimized MS/MS parameters

Compounds	group	linear range ng.L-1	retention time (min)	Quantifier						Qualifier						Internal standards
				Ionization	Transition			cone Voltage	Collision Energy	Ionization	Transition			cone Voltage	Collision Energy	
Oxazepam d5 (OXZ d5)	surrogate	250	9.08	ESI +	292,0	>	246,0	30	20	ESI +	292,0	>	214,0	30	20	
Sulfamethoxime d6 (SFX d6)	surrogate	250	8.12	ESI +	317.2	>	162.2	35	22	ESI +	317.2	>	155.8	35	22	
Ibuprofen d3 (IBU d3)	surrogate	2000	11.77	ESI -	208.0	>	164.0	25	7	>						
Diazepam d5 (DZP d5)	surrogate	250	10.72	ESI +	290.2	>	262.1	35	22	ESI +	290.2	>	198,0	35	30	
O Desmethylnaproxen	degradate	70-5000	8.23	ESI -	215,0	>	170.9	25	12	ESI +						IBU d3
Fenofibric acid	hypolipemiant	20-1000	11.54	ESI -	317.2	>	231,0	25	10	ESI +	319,0	>	233.0	30	16	OXZ d5
Naproxen	AINS	70-5000	10.22	ESI -	228.9	>	184.8	25	7	ESI -	228.9	>	169.9	25	15	DZP d5
Gemfibrozil	hypolipemiant	20-1000	12.60	ESI -	249.2	>	121,0	25	13	ESI -	249.2	>	127.1	25	10	DZP d5
Ibuprofen	AINS	70-5000	11.79	ESI -	205.1	>	160.9	25	7	ESI +						IBU d3
Ketoprofen	AINS	20-1000	10.11	ESI -	252.9	>	209,0	25	8	ESI +	255.3	>	209.0	30	12	DZP d5
Furosemide	diuretics	20-5000	8.67	ESI -	329.2	>	284.9	35	15	ESI -	329.2	>	204.8	35	20	DZP d5
Bezafibrate	hypolipemiant	20-1000	10.26	ESI -	360.3	>	274,0	30	17	ESI +	384.4	>	298.0	35	17	OXZ d5
Diclofenac	AINS	20-5000	11.58	ESI -	294,0	>	250,0	25	12	ESI -	296.1	>	252,0	25	12	DZP d5
1 hydroxy ibuprofen	degradate	20-1000	8.81	ESI -	221.1	>	176.9	25	7	ESI -	221.1	>	158.9	25	12	IBU d3
2 hydroxy ibuprofen	degradate	20-1000	8.11	ESI -	221.1	>	176.9	25	8	ESI +						IBU d3
Oxazepam	antidepressant	20-1000	9.11	ESI +	287,0	>	241,0	30	20	ESI +	287,0	>	269,0	30	14	OXZ d5
Atenolol	Beta-blockers	20-5000	4.44	ESI +	267.3	>	190,0	30	18	ESI +	267.3	>	145,0	30	23	OXZ d5
Metoprolol	Beta-blockers	20-5000	6.18	ESI +	268.3	>	190.9	35	18	ESI +	268.3	>	116,0	35	18	OXZ d5
Sulfamethoxazole	antibiotic	20-1000	7.38	ESI +	253.9	>	91.8	30	26	ESI +	253.9	>	155.8	30	17	SFX d6
Carbamazepine	anti-epileptic	20-1000	8.81	ESI +	237,0	>	194,0	25	18	ESI +	237,0	>	179,0	25	33	SFX d6
Trimethoprim	antibiotic	20-5000	5.44	ESI +	291.1	>	122.9	42	24	ESI +	291.1	>	230,0	42	24	SFX d6

Table 2 : Target pharmaceuticals and their optimized MS/MS parameters

	clay (%)	silt (%)	sand %	organic carbon (%)	pH water	pH KCl	CEC (meq/100g)
sediment B	1.2	3.6	94.9	0.163	7.74	7.06	1.92
Sediment C	0.4	2.1	97.4	0.053	7.52	6.66	1.10
Soil B	4.6	9.6	85.2	0.373	6.17	5.05	2.52
Soil C	7.9	16.2	75.1	0.506	6.64	5.73	4.82
Soil D	15.1	25.3	57.8	1.055	6.33	5.46	10.65

Table 3. Soil and river sediment characteristics

Active ingredient	Scenario			
	1	2	3	4
Azoxystrobin	1.49 ± 0.13	1.60 ± 0.11		
Bifenthrin	0.046 ± 0.004	0.046 ± 0.020		
Iodosulfuron-methyl	0.25 ± 0.01	0.28 ± 0.03		
Mesosulfuron-methyl	0.47 ± 0.01	0.37 ± 0.03		
Metconazole	1.53 ± 0.16	1.71 ± 0.21		
Prochloraz	0.47 ± 0.02	0.74 ± 0.03		
Bromoxynil			0.19 ± 0.02	0.20 ± 0.03
Cyprodynil			74.20 ± 4.5	49.10 ± 4.4
Ioxynil			0.12 ± 0.02	0.12 ± 0.02
Prosulfocarb			2.87 ± 0.18	1.86 ± 0.09
Diflufenican	0.67 ± 0.01	0.57 ± 0.04	0.10 ± 0.005	0.12 ± 0.008
Isoproturon	12.90 ± 0.22	6.20 ± 0.26	4.90 ± 1.1	3.10 ± 0.06
Epoxiconazole	0.83 ± 0.07	0.89 ± 0.04	0.27 ± 0.04	0.20 ± 0.05

Table 4. Mean (± standard error) Average Exposure Concentration (µg l^{-1}) for each active ingredient and for the different wheat crop protection programs scenario 1 to 4). From [16].