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Headspace Solid-Phase Microextraction of Pesticide Residues in *Cannabis* Samples

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Abstract: A headspace solid-phase microextraction method combined with gas chromatography–mass spectrometry was evaluated for the extraction and analysis of selected pesticides, namely alachlor, β-hexachlorocyclohexane, bromopropylate, carbaryl, diazinon, linuron, polychlorobiphenyl 209, permethrine and simazine in *cannabis* samples. Using a 100 μm PDMS fibre, compounds were directly extracted in the headspace mode at 150 °C for 5 min and desorption was performed in the GC injector in the splitless mode at 280 °C for 3 min. Pesticide analysis was achieved and method repeatability, given as the coefficient of variation, ranged between 2.4% for bromopropylate and 12.6% for linuron. The limits of detection obtained using single ion monitoring (SIM) were between 0.014 and 0.83 mg/kg, depending on the pesticide.

Keywords: *Cannabis* · Headspace solid-phase microextraction · Pesticides

1. Introduction

Even if pesticides are widely used, they are associated with important health and environmental risks. Because of the persistence and potential toxicity of some compounds, pesticide residue analysis has received increasing attention in the last few years. Thus, environmental, food and biological samples are analysed regularly to obtain qualitative and quantitative information on their pesticide content. Due to the extensive number of pesticides and significant matrix diversity, chromatographic separations using either gas chromatography (GC) or high-performance liquid chromatography (HPLC), coupled with different detectors, are generally used. However, prior to these analyses, a sample preparation step, including extraction, clean-up and pre-concentration, is often mandatory. For plant material, extraction is often performed by Soxhlet, solvent maceration or percolation [1]. These procedures offer good performance, but can be tedious and consume a large amount of solvent. Thus, the sample preparation often constitutes the limiting step of the analytical procedure and alternative methods have been developed to overcome these disadvantages. In particular, recent techniques have been evaluated for the extraction of pesticides, such as microwave-assisted extraction (MAE) [2][3] and supercritical fluid extraction (SFE) [4][5]. After extracting drugs from plants, different conventional techniques are available for sample purification and concentration such as liquid–liquid extraction (LLE) and solid-phase extraction (SPE) [6–8].

New sample preparation strategies prior to GC analysis have appeared in the literature in order to reduce the above-mentioned disadvantages. Solid-phase microextraction (SPME), a solvent-free technique, was introduced in 1990 by Arthur and Pawliszyn [9] and has gained a large interest due to its simplicity, sensitivity, ease of automation and relatively low cost. This technique is performed in two steps with a modified syringe containing the extraction fibre, as previously described in the literature [10]. In the first step, analytes are extracted from the matrix and retained on the stationary phase impregnated on the fibre. In the second step, compounds are desorbed in the GC injector. According to both the physico-chemical properties of the compounds of interest and to the matrix complexity, there are mainly two modes of extraction: direct SPME (DI-SPME) in which the fibre is dipped into a liquid sample, and headspace-SPME (HS-SPME) with extraction of the compounds from the sample's headspace. The number of applications of SPME is increasing and includes environmental [11][12], biomedical [13–15], food [16][17] and pharmaceutical [15][18] fields. A number of reviews have been published that describe the use of this technique for pesticide monitoring [11][19–21].

In Switzerland, for several years, there have been numerous discussions on the legalization of the culture and consumption of *cannabis* and derivatives, in which case a strict quality control would become mandatory for *cannabis* material. For this purpose, a method was developed in our laboratory to perform the *cannabis* profiling by a simple HS-SPME combined with GC-MS [22]. The aim of the present study was to evaluate this HS-SPME method also for the extraction of pesticides from *cannabis*, with the ultimate objective of performing simultaneous analyses of cannabinoids and pesticide residues in plant material. It should be noted that, since *cannabis* is considered as a drug of abuse in almost all countries, there are few publications in the scientific literature concerning pesticide residues in *cannabis* [23][24]. But according to its popularity, *cannabis* cultivation is largely documented. Information collected from the internet as well as from authorities (*e.g.* Service de Protection de la Consommation, Geneva) showed that the following pesticides have been frequently observed and thus selected for this study: alachlor (herbicide), β-hexachlorocyclohexane (β-HCH) (insecticide), bromopropylate (acaricide), carbaryl (insecticide), diazinon (insecticide), linuron (herbicide), polychlorobiphenyl 209 (PCB) (environmental contaminant), permethrine (insecticide),

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simazine (herbicide). The chemical structures of these compounds are presented in Fig. 1. Numerous SPME methods have already been reported in the literature for the analysis of these substances. They included extractions from different matrices, such as water [25–27], soils [28][29], foodstuff [30-32], biological fluids [19][33][34] and plants [35–38], using both types of SPME modes and several fibres.

2. Experimental

2.1. *Chemicals and Standards*

Analytical grade solvents were purchased from Panreac Quimica SA (Barcelona, Spain). Standard pesticides were from Riedel-de-Haën (Seelze, Germany). It should be noted that permethrine contained both *cis* and *trans* isomers. Depending on each compound's solubility, standard stock solutions were prepared in methanol at different concentrations (Table 1). Stock solutions were used to prepare a methanolic mixture containing all compounds except the internal standard (IS) fenthion (see concentrations in Table 1).

2.2. *Plant Material*

In this study, two different plant materials were used. The first was employed for the method development, and the second consisted of home-cultivated plants subjected to pesticide treatment (see conditions below) for real case analyses.

It should be noted that a special authorization (Decision AB-8/5-BetmG-222) from the federal authorities (Bundesamt für Gesundheit, Switzerland) was attributed to our laboratory for projects on *cannabis*. Thus, the laboratory can acquire, keep in stock, use and produce *cannabis*.

2.2.1. *Method Development*

As previously reported [22], Swiss marijuana samples from the Geneva area and without pesticides were used for the method development. Method suitability and evaluation of quantitative performance were carried out by spiking the samples with the pesticide mixture.

2.2.2. *Cannabis Cultivation*

Twenty-one-month old plantlets (two per pesticide and two untreated samples) of certified origin were purchased in Geneva. They were transferred into 13 cm i.d. pots filled with commercial potting mixes (pH = 7). Before repotting the plantlets, herbicides, *i.e.* alachlor, linuron and simazine, as well as the environmental contaminant PCB 209, were added in methanolic solutions at 1% to the soils. The remaining pesticides were applied twice (one month apart) by spraying 10 ml of a 1% methanolic solutions on plants. This concentration corresponded to the average concentration recommended for pesticide applications on *cannabis*.

Plants were grown from June until the end of September in a room equipped with large windows without artificial light. The ambient temperature varied between 20 and 25 °C during the day and 12 and 15 °C during the night. The room was aerated twice daily for 15 min. Watering was done once a week. Flowering took place at the end of September and flowering tops were distributed all along the plant. Plants were cut at 2 cm above soil level, hung upside-down in the same room and allowed to dry for two weeks. Finally, each dried plant was cut into three parts and flowering tops were separated from leaves.

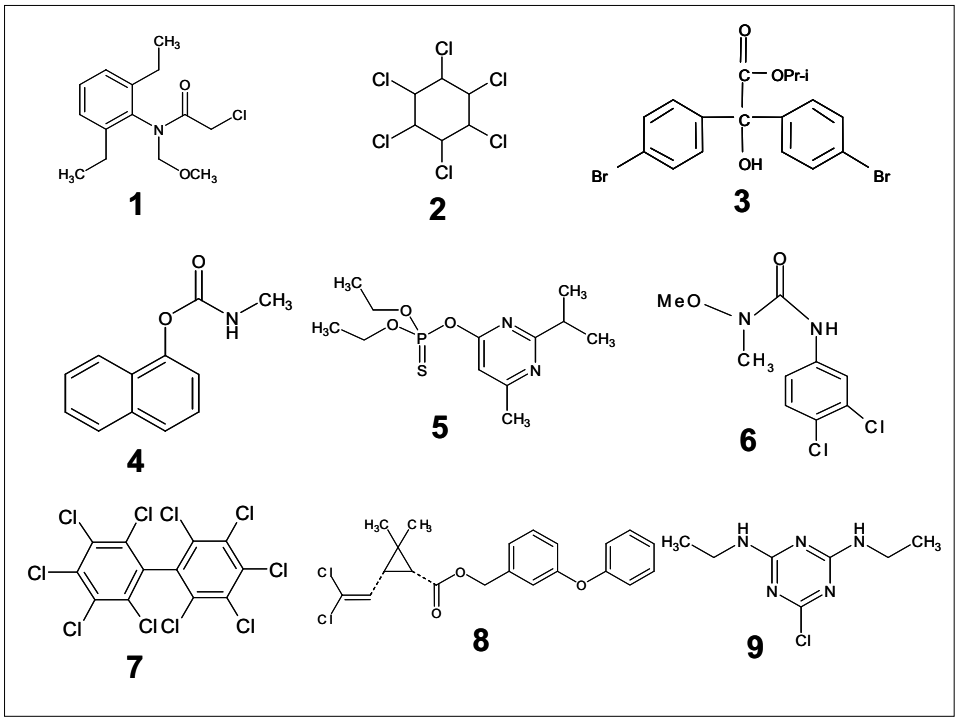

Fig. 1. Chemical structures of the selected pesticides. **1**: alachlor; **2**: β-HCH; **3**: bromopropylate; **4**: carbaryl; **5**: diazinon; **6**: linuron; **7**: PCB 209; **8**: permethrine; **9**: simazine

Table 1. Concentrations of pesticides [ppm] in standard stock solutions and in the mixture

Compound	Stock solution	Mixture
Diazinon	1500	150
Alachlor	1000	100
Bromopropylate	1000	100
Carbaryl	1000	100
β-HCH	1000	100
Linuron	1000	100
Permethrine	1000	100
Fenthion (IS)	1000	–
Simazine	100	10
PCB 209	50	15

2.3. *SPME Procedure*

A 100 μm polydimethylsiloxane (PDMS) fibre, purchased from Supelco (Bellefonte, PA, USA) was used and conditioned according to the instructions given by the supplier.

2.3.1. *Standard Solution Analysis*

Standard methanolic solutions containing the pesticide mixture were introduced into 2 ml glass vials and solvent evaporated to dryness at ambient temperature under a gentle stream of nitrogen (Techne Concentrator, Witeg AG, Littau-Luzern, Switzerland) for 2 min. As reported elsewhere [22], vials sealed with silicone/PTFE septa were placed in a thermostated bath at 150 °C. Solid-phase microextractions were

performed without agitation in the headspace mode for 5 min. After extraction, the fibre was removed and directly inserted into the injection port of the GC and analytes were desorbed at 280 °C for 3 min.

2.3.2. *Spiked Plant Analysis*

Marijuana samples were powdered with a ball-mill (MM Retsch, Switzerland) and sieved to an average particle size between 100 and 150 µm. Powdered marijuana (60 mg per analysis) was placed in 2 ml glass vials and pesticides in solution were added on the plant material. After 5 min, the solvent was evaporated under a nitrogen steam and HS-SPME was performed as described above. Before introducing the pesticide solutions, a blank analysis was performed on the plant material to determine the cannabinoid profile and to confirm the absence of pesticides. All analyses were carried out in triplicate.

2.3.3. *Cultivated Plant Analysis*

Dried cultivated marijuana samples were powdered and analysed in triplicate by HS-SPME in the same conditions described above.

2.4. *Focused Microwave-assisted Extraction of Cultivated Plants*

Focused microwave-assisted extractions (FMAE) were performed to extract all putative pesticides and compare the results with those obtained by HS-SPME. Samples containing 60 mg of dried and powdered marijuana were immersed in 5 ml methanol and exposed for 30 s to microwave irradiation (125 W) [39]. Extractions were performed at atmospheric pressure at a standard frequency of 2450 MHz using a 3.6 FMAE apparatus (Prolabo, France). Methanolic extracts were filtered over a 0.45 µm PTFE filter and aliquots of 1 µl were directly analysed by GC/MS.

2.5. *GC/MS Conditions*

GC/MS analyses were performed on an HP 5890 series II gas chromatograph (Agilent Technologies, Waldbronn, Germany) coupled with an HP 5972 mass spectrometer. A HP-5MS capillary column (30 m × 0.25 mm i.d., 0.25 µm phase thickness) was used. The injection was performed in the splitless mode (3 min) at 280 °C. The oven temperature was: 50 °C for 1 min, to 190 °C at 10 °C/min, to 200 °C at 1 °C/min, to 290 °C at 45 °C/min, held for 3 min. Helium was used as carrier gas at constant flow rate (1 ml /min). The transfer line temperature was set at 280 °C. For qualitative analysis, the mass spectrometer was operated using electron impact (EI) ionisation at 70 eV, in the scan range *m/z* 30–400. For quantification of the different pesticides, single ion monitoring (SIM) was employed (see Table 2 for the monitored ions for each compound).

Table 2. Monitored ions for the quantification of the selected pesticides

Compound	Retention time [min]	Quantification ion [Th]	Confirmation ion [Th]
Aromatic isocyanate	10.40	124	187
Dichloroaniline	12.04	161	163
Naphthalenol	13.23	115	144
Simazine	15.81	201	68
β-HCH	15.96	181	183
Diazinon	16.66	137	304
Alachlor	18.29	160	188
Linuron	19.14	61	160
Fenthion	19.80	278	125
Bromopropylate	27.50	341	183
***Cis*-permethrine**	28.66	183	163
***Trans*-permethrine**	28.76	183	163
PCB 209	29.90	497	428

3. Results and Discussion

3.1. *Qualitative Analysis*

In a previous study [22], a straightforward SPME/GC-MS method was developed for profiling cannabinoids from plant material. Compounds were directly extracted from the plant's headspace for 5 min with a 100 µm PDMS fibre. The extraction temperature was 150 °C and desorption was directly performed in the GC injection port at 280 °C for 3 min in the splitless mode.

In order to evaluate the applicability of this method to the extraction of the selected pesticides, first experiments were performed on standard pesticide solutions dried under nitrogen and extracted by HS-SPME. Fig. 2 presents a typical chromatogram obtained for the mixture of the nine selected pesticides.

From a qualitative point of view, all pesticides were extracted and detected. In addition, MS detection allowed the identification of three supplementary peaks corresponding to degradation products of carbaryl (peak 3) and linuron (peaks 1 and 2). Müller and Stan [38] reported the degradation of carbamates (carbaryl) into the corresponding phenols and methyl-isocyanate (Fig. 3). This degradation was dependent on the GC injection mode. In the case of on-column injection, no degradation was observed by the authors. On the other hand, a total degradation was obtained when a

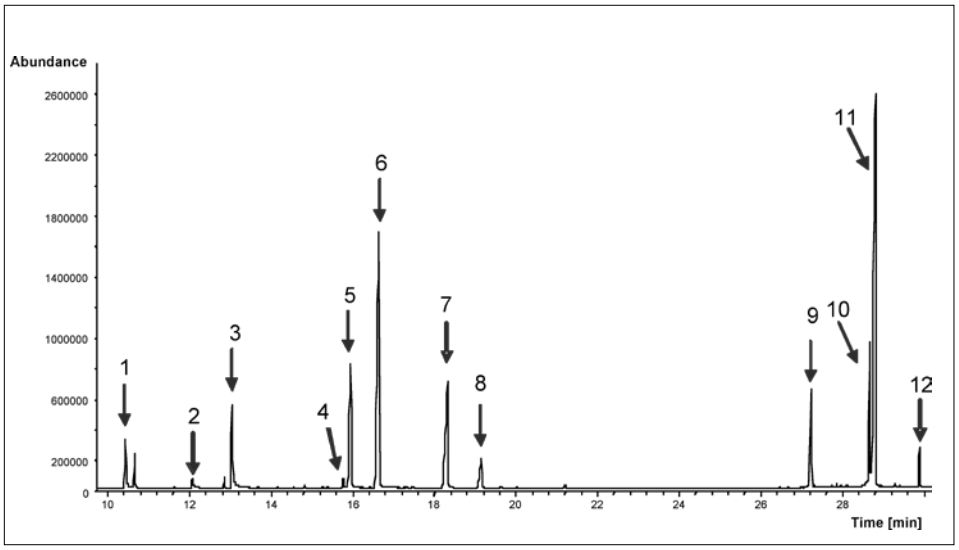

Fig. 2. GC-MS chromatogram of the pesticide mixture extracted by HS-SPME. Compounds: **1**: aromatic isocyanate; **2**: dichloroaniline; **3**: naphthalenol; **4**: simazine; **5**: β-HCH; **6**: diazinon; **7**: alachlor; **8**: linuron; **9**: bromopropylate; **10**: *cis*-permethrine; **11**: *trans*-permethrine; **12**: PCB 209.

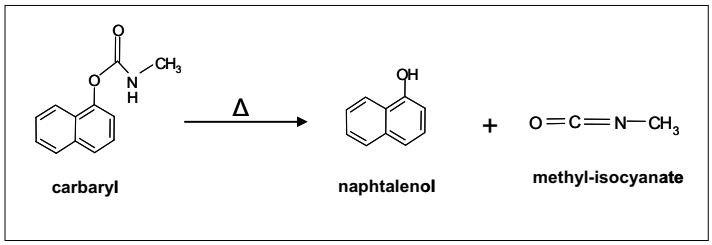

Fig. 3. Degradation scheme of carbaryl [38]

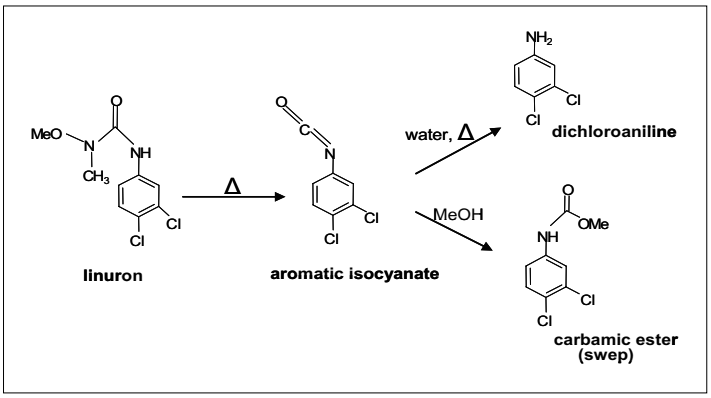

Fig. 4. Degradation scheme of linuron

splitless injection was performed at 220 °C, whereas only partial decomposition was noted in the case of a programmable temperature vaporization (PTV) injection. In our method, since desorption was accomplished in the splitless mode at 280 °C, carbaryl was entirely degraded and only naphthalenol was detected.

Concerning linuron, the degradation scheme is more complex (Fig. 4). Indeed, not only the temperature but also the injection solvent can influence the degradation process, as discussed by Carabias-Martinez *et al.* [40]. In our case, only aromatic isocyanate and dichloroaniline were observed in addition to the original compound peak, since methanol was completely evaporated prior to SPME. For the following investigations, peak area of naphthalenol was monitored for carbaryl, whereas the sum of isocyanate, dichloroaniline and linuron was reported for linuron.

In addition, an analysis on blank plant material was performed and the chromatogram, showing the cannabinoid profile, is presented in Fig. 5. The window between 10 and 16 min contains volatile compounds of *cannabis* [22], whereas cannabinoids elute between 26 and 28.5 min.

Moreover, by spiking plant material with the solution containing all pesticides, simultaneous analysis of the cannabinoids and the selected pesticides was achieved with the same procedure. The chromatographic profile is presented in Fig. 6. Compounds with retention times below 16 min, *i.e.* aromatic isocyanate (1), dichloroaniline (2) and naphthalenol (3), cannot be determined on the chromatogram, since they appeared in the *cannabis* volatiles window (see Fig. 5).

3.2. *Quantitative Aspects*

In order to evaluate the quantification of pesticides using the HS-SPME/GC-MS method, preliminary experiments were performed.

Calibration curves were established by spiking *cannabis* samples with standard solutions at increasing concentrations (with fenthion as internal standard at 20 ppm). Five concentrations were used with three independent analyses at each calibration level. After evaporating the solvent, analyses were performed to establish calibration

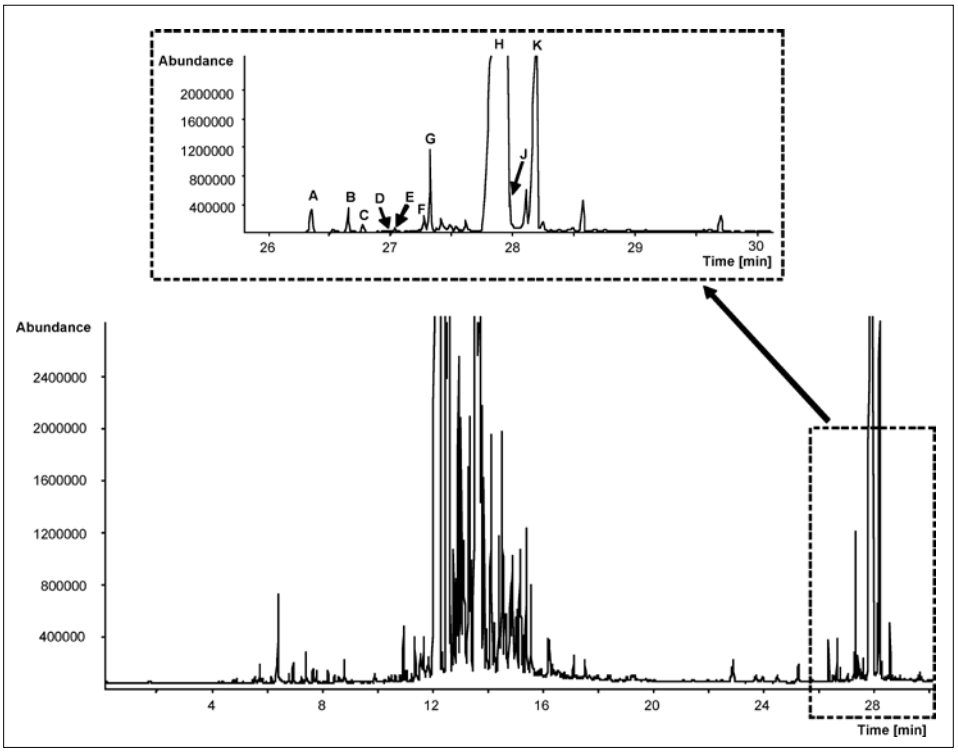

Fig. 5. GC-MS chromatogram of a plant without pesticides extracted by HS-SPME. **Cannabinoids** [22]: **A**: cannabinoid 1; **B**: tetrahydrocannabivarine; **C**: cannabinoid 2; **D**: cannabicyclol; **E**: cannabivarine; **F**: cannabidiol; **G**: cannabichromene; **H**: Δ^9-tetrahydrocannabinol; **J**: cannabigerol; **K**: cannabinol.

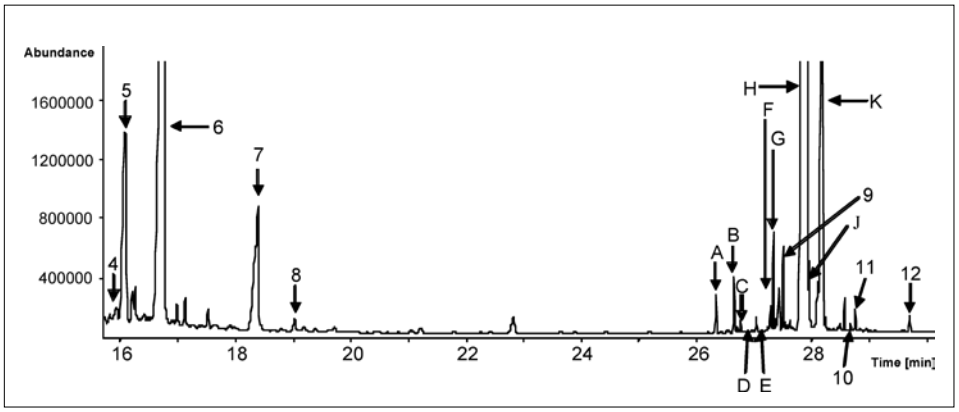

Fig. 6. GC-MS chromatogram of a spiked plant extracted by HS-SPME. **Pesticides**: compounds 1 to 3 are not shown on this chromatogram (see explanations in the text). **4**: simazine; **5**: β-HCH; **6**: diazinon; **7**: alachlor; **8**: linuron; **9**: bromopropylate; **10**: *cis*-permethrine; **11**: *trans*-permethrine; **12**: PCB 209. **Cannabinoids** [22]: **A**: cannabinoid 1; **B**: tetrahydrocannabivarine; **C**: cannabinoid 2; **D**: cannabicyclol; **E**: cannabivarine; **F**: cannabidiol; **G**: cannabichromene; **H**: Δ^9-tetrahydrocannabinol; **J**: cannabigerol; **K**: cannabinol.

parameters based on conventional least-squared regression (Table 3). The determination of the limits of detection (LOD) was carried out by spiking the plants with decreasing concentrations of the standard solutions. In order to evaluate the method sensitivity, when available, reference values indicated for tobacco [41] were taken as targets and listed in Table 3.

As reported in Table 3, satisfactory results were achieved with the applied HS-SPME/GC-MS method. The simplest linear model exhibited coefficients of determination (R^2) between 0.96 and 0.99. LODs obtained in the SIM acquisition mode demonstrated that the method was sensitive enough to allow quantification of pesticide residues in plant material.

Furthermore, results concerning repeatability and method trueness were studied by performing six analyses on plant material spiked with the pesticide mixture solution at a concentration level situated in the centre of the investigation range. As listed in Table 4, coefficients of variation (CVs) of the peak area ratios (compound/IS) ranged from 2.4% for bromopropylate to 12.6% for linuron. Finally, the method trueness, expressed as recoveries (measured amount/applied amount), ranged from 96.1% to 104.8% (Table 4).

Table 3. Quantitative evaluation of the HS-SPME/GC-MS method

Compound	Calibration range [mg/kg]	Coefficient of determination (R^2)	LOD[a] [mg/kg]	Recommended maximum amounts [mg/kg]
Naphthalenol	0.83–165	0.9754	0.17	3
Simazine	0.86–16.5	0.9694	0.17	*n.i.*[b]
β-HCH	0.85–165	0.9632	0.17	1
Diazinon	0.13–165	0.9776	0.025	1
Alachlor	0.87–165	0.9701	0.017	0.1
Linuron	3.65–165	0.9630	0.83	5
Bromopropylate	0.08–165	0.9725	0.017	*n.i.*
***Cis*-permethrine**	0.06–12.07	0.9604	0.014	*n.i.*
***Trans*-permethrine**	0.08–165	0.9625	0.014	*n.i.*
PCB 209	0.37–50	0.9884	0.083	*n.i.*

[a]Determined at a signal-to-noise ratio of 3; [b]not indicated. For these compounds, a limit of 1 mg/kg was fixed as a reference value

Table 4. Estimation of the method repeatability and trueness (n=6)

Compound	CV [%]	Trueness [%]
Naphtalenol	5.4	97.2
Simazine	4.9	98.8
β-HCH	3.2	96.6
Diazinon	6.3	97.7
Alachlor	7.2	101.5
Linuron	12.6	96.4
Bromopropylate	2.4	101.9
***Cis*-permethrine**	10.3	96.1
***Trans*-permethrine**	8.2	98.6
PCB 209	4.9	104.8

3.3. *Application on Cultivated Cannabis*

The HS-SPME/GC-MS method provided suitable qualitative and quantitative performance for the analysis of *cannabis* previously spiked with pesticides. Final investigations were conducted to test the analysis of pesticides in real cases, *i.e.* in cultivated samples treated with such compounds. Therefore, *cannabis* plants were cultivated at the University of Geneva, including regular treatments with the different pesticides.

HS-SPME and GC-MS analyses were performed on flowering tops as well as on leaves in triplicate, in both acquisition modes (scan and SIM). For all plants, cannabinoids were detected, but none of the screened pesticides were found.

Different explanations for these results can be proposed. Firstly, residues could be at lower concentrations than determined LODs. Secondly, a loss of pesticides could occur either by natural removal (*e.g.* washing, evaporation and photolysis) or by metabolization in the plant. The latter, also described as the detoxification process, is the major route of elimination of pesticides by plants and is mainly based on enzymatic transformations [42], involving cytochromes P450, peroxidases and other oxidoreductases, hydrolytic enzymes, *etc*. These various and complex metabolic pathways are generally classified in a three-phase process, as described by Roberts [43] and Hoagland *et al.* [44]. The final hypothesis to explain the absence of pesticides on the chromatograms could be their strong matrix linkage, hindering their extraction by HS-SPME.

Therefore, plants were submitted to more drastic extraction conditions, using microwave irradiation. In this case, the penetration of solvent molecules into the matrix is enhanced by two phenomena: disruption of hydrogen bonds together with migration of dissolved ions [45]. As a result, a better solvation of the components can be obtained, particularly in the case of solid matrices. Thus, a FMAE method previously developed for cocaine extraction [39] was applied to the spiked *cannabis* samples. Under these conditions, all pesticides were extracted (data not shown). FMAE extracts of cultivated plants were finally analysed by GC-MS. No pesticides were found on the chromatograms. This confirmed the absence of pesticide residues in cultivated plant material and supported the results obtained by the HS-SPME procedure.

4. Conclusion

Headspace solid-phase microextraction combined with GC-MS can be used for the determination of pesticide residues in plant material. The highly efficient PDMS fibre allowed several compounds of different chemical structures and physicochemical properties to be simultaneously extracted. Indeed, the same method was performed for the extraction of cannabinoids and pesticide residues from *cannabis*. Moreover, satisfactory quantitative performance was obtained with LODs lower than targeted concentrations and repeatability ranging from 2.4% to 12.6%. Thus, the HS-SPME/GC-MS method provides the possibility of a simple

and rapid quality control of plant material based on cannabinoid profiling (qualitative analysis, scan mode) and pesticide residue determination (quantitative analysis, SIM mode).

Finally, the developed method was applied to the analysis of plants treated with the selected pesticides at usual concentrations. No pesticide residues were observed, even when samples were submitted to microwave extraction.

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