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# Determination of O-ethyl S-2-diisopropylaminoethyl methylphosphonothioate (VX) by thermospray liquid chromatography–mass spectrometry

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## ABSTRACT

The determination of the nerve agent O-ethyl S-2-diisopropylaminoethyl methylphosphonothioate (VX) by thermospray liquid chromatography–mass spectrometry was studied. The solvent system acetonitrile–methanol–0.25 *M* ammonium acetate was used on a reversed-phase $C_{18}$ column. By selected ion monitoring at the protonated molecular ion of VX (*m/z* 268), the predominant peak in its thermospray mass spectrum, an amount of 200 pg could be detected. For the determination of VX in water at levels below 1 ng/ml, preconcentration by $C_{18}$ cartridges was investigated. The applicability of the method was demonstrated by the determination of VX in spiked river waters. A concentration of 0.1 ng/ml could be detected starting from a water sample of 50 ml. A second application concerned the analysis of water extracts of spiked soil samples.

## INTRODUCTION

Owing to its acetylcholinesterase-inhibiting properties O-ethyl S-2-diisopropylaminoethyl methylphosphonothioate (VX) is considered as a chemical warfare agent [1], the use of which is forbidden by the Geneva Protocol of 1925. The confirmed use of chemical weapons in the Iran–Iraq conflict [2] and their presumed proliferation [2,3] emphasizes the need for specific detection and identification methods for all compounds which are considered as chemical warfare agents. Unequivocal proof of the use of chemical weapons can only be based on spectrometric analyses. Owing to its sensitivity and selectivity, mass spectrometry is at present the most suitable technique for this purpose, especially if environmental samples need to be analysed.

The determination of VX and a number of its impurities have been studied in detail by gas chromatography–mass spectrometry (GC–MS) [4]. Using electron impact and chemical ionization, over twenty compounds were identified in an aged VX sample. VX is a fairly involatile compound which, after dispersion in the environment, will be retained in soil and surface water. The fate of VX in several types of soil has been studied [5,6]. In humic sand, humic loam and clayey peat, 90% of VX degraded within 2 days. VX is more stable in water. Below pH 8.0 the hydrolysis is fairly slow at 25°C ($t_{\frac{1}{2}}$ = 184 h at pH 8.0) [7]. In contrast to other organophosphorus nerve agents, no

determination of VX in water samples has been reported so far. Verweij *et al.* [8] isolated the nerve agents isopropyl methylphosphonofluoridate (sarin), 1,2,2-trimethylpropyl methylphosphonofluoridate (soman) and ethyl N,N-dimethylphosphoramidocyanidate (tabun) from water by adsorption on XAD-4 resin, followed by desorption with ethyl acetate and transfer of the ethyl acetate solution to a Tenax tube, which was analysed by a thermal desorption method. However, an attempt to determine VX by thermal desorption from Tenax proved to be unsuccessful [9]. Owing to the tendency of VX to adsorb strongly on any surface, Fowler and Smith [10] converted VX into the more volatile ethyl methylphosphonofluoridate in front of an adsorption tube filled with Chromosorb 106 in a procedure for the determination of VX in air at low concentrations by thermal desorption.

Instead of isolating VX from the aqueous phase, direct analysis of water samples by reversed-phase high-performance liquid chromatography (HPLC) may be performed. Sipponen [11] reported the determination of the nerve agents sarin, tabun and soman by HPLC using a detector based on the cholinesterase inhibition reaction. Detection limits in the range 10–200 pg were obtained. However, VX was not investigated and the described application concerned the analysis of urban air samples. As VX exhibits a relatively weak non-selective absorbance with a maximum at *ca.* 210 nm, the use of ultraviolet detectors is limited. Recently, a number of papers have been published describing the determination of VX-related organophosphorus pesticides [12–15] and hydrolysis products of pesticides and nerve agents in water [16] by thermospray liquid chromatography–mass spectrometry (TSP–LC–MS).

The determination of VX by TSP–LC–MS is described in this paper. In principle, no isolation step is necessary for the determination of compounds in aqueous samples by TSP–LC–MS. However, in order to obtain a low detection level, preconcentration will be necessary. Recently, the use of Sep-Pak $C_{18}$ cartridges for the isolation and concentration of organophosphorus pesticides from water was demonstrated [17]. This was also investigated for VX.

## EXPERIMENTAL

### *Materials*

Ammonium acetate and ammonium formate (both analytical-reagent grade) were obtained from Aldrich (Milwaukee, WI, U.S.A.). Ammonia solution (25% in water), used to adjust the pH of the eluent, acetonitrile (gradient grade) and methanol (analytical-reagent grade) were purchased from Merck (Darmstadt, F.R.G.). Polyethylene glycols (PEG-200 and PEG-400) used for tuning and mass axis calibration were supplied by Fluka (Buchs, Switzerland). Tri-*n*-butyl phosphate was obtained from UCB (Leuven, Belgium).

Sep-Pak and Bond Elut $C_{18}$ cartridges were purchased from Waters Assoc. (Milford, MA, U.S.A.) and Analytichem International (Harbor City, CA, U.S.A.), respectively.

VX was prepared in the laboratory and gave, in addition to a satisfactory elemental analysis, correct spectral (IR, NMR and mass) data. A stock solution of VX in water was prepared at a concentration of 4 μg/ml. At a pH of *ca.* 6 and when stored in a refrigerator at 4°C, no noticeable hydrolysis was observed over a period of 2 weeks. More dilute solutions were prepared freshly from this stock solution.

For all purposes water was purified in a Milli-Q water-purification system (Millipore, Bedford, MA, U.S.A.). Use of plastic tubes, containers, etc., with a high content of plasticizer was avoided as much as possible. Samples from the rivers Rhine and Meuse were taken in The Netherlands at Lobith and Keizersveer, respectively.

Soil samples were prepared as part of an international round-robin exercise coordinated by the Finnish Research Project for Chemical Warfare Verification [18]. The samples were spiked with VX (purity 94%) and some of its degradation products at a level of 100 mg/kg. The samples were prepared on September 21, 1989, stored at 5°C until September 25, 1989, and arrived at this laboratory on September 28, 1989. They were stored in a freezer at −25°C till the start of the analysis on October 13, 1989. The soil samples had the following chemical and physical characteristics: granulation, clay $<2$ μm 49.2%, silt 2–50 μm 16.5% and sand $>50$ μm 34.3%; moisture content at 105°C, 4.5%; pH, 6.8; and organic matter content, 3.2%.

*Liquid chromatography*

The LC system was assembled from a Waters Assoc. Model 510 solvent-delivery system, a Valco injector (Bester, Amsterdam, The Netherlands) with a 40-μl sample loop and a stainless-steel column (250 mm × 5 mm I.D.) which was packed in the laboratory with 7-μm LiChrosorb $C_{18}$ particles (Merck). The connection between the column and the TSP interface consisted of a low-dead-volume tee, a Valco injector with a 5-μl sample loop for flow injections and a 2-μm screen filter (Waters Assoc.). A second solvent-delivery system (Waters Model 590) combined with a pulse damper (Touzart et Matignon, Vitry sur Seine, France) was connected to the low-dead-volume tee for post-column addition of an ammonium acetate solution or for the introduction of the calibration mixture.

TSP–LC–MS analyses were performed with mobile phases consisting of methanol–0.1 *M* ammonium acetate (80:20) or acetonitrile–methanol–0.25 *M* ammonium acetate (70:20:10) at a flow-rate of 1.2 ml/min. In both instances 0.05 *M* ammonium acetate was added post-column at a flow-rate of 0.5 ml/min. Injections directly into the TSP interface were carried out in a flow (1.2 ml/min) of 0.05 *M* ammonium acetate.

*Mass spectrometry*

A Nermag (Argenteuil, France) R 10-10 C quadrupole instrument, equipped with a TSP ion source (Nermag), was coupled with the LC system via a Vestec (Houston, TX, U.S.A.) TSP interface. The TSP source was equipped with a repeller and discharge ionization, whereas the mass spectrometer was fitted with the CONIPHOT detection system. Tuning and mass axis ($m/z$) calibration in the positive ion mode from $m/z$ 60 to 800 were performed with a mixture of PEG-200 and PEG-400. Mass spectra were scanned over the mass range $m/z$ 100–350 at a scan rate of 0.6 s. Single-ion detection experiments were carried out by monitoring the protonated molecular ion of VX at $m/z$ 268 using an integration time of 0.6 s.

The temperature of the capillary tip was optimized before each set of experiments using background ions in the $m/z$ 200–300 region. The ion block temperature was maintained at 250°C and the repeller voltage was adjusted between 120 and 200 V.

*Determination of breakthrough volumes*

Breakthrough volumes were measured by successively pressing portions of 20 ml of VX solution (4 μg/ml) through $C_{18}$ cartridges by means of a syringe at a flow-rate of *ca.* 10 ml/min. After each portion, the effluent was analysed for VX using flow injections. Cartridges were prewetted by passing 5 ml of methanol and 10 ml of water through the cartridges.

## RESULTS AND DISCUSSION

*Thermospray mass spectrum of VX*

The TSP mass spectrum of VX depends on the liquid composition. The protonated molecular ion at *m/z* 268 was obtained almost exclusively (Fig. 1A) by using ionization by the ammonium acetate buffer in mixtures with high contents of methanol or acetonitrile. No ammonium adduct ion could be observed, indicating that the proton affinity of VX is higher than that of ammonia (858 kJ/mol) [19]. Small fragments were observed at *m/z* 145, 146 and 188. In Table I the most probable

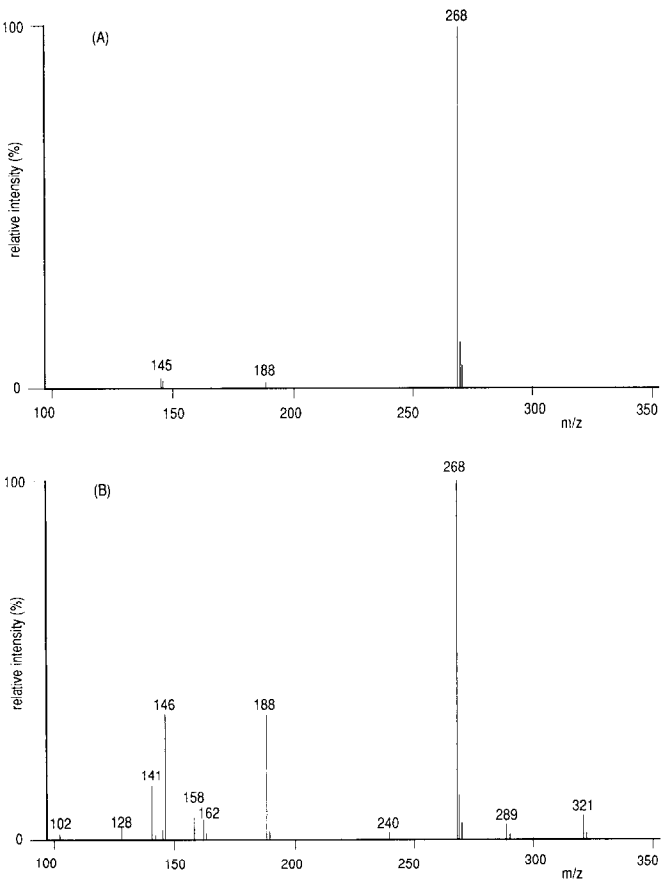
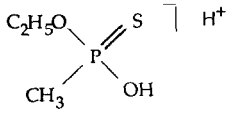
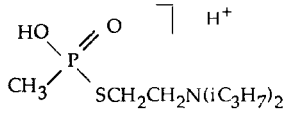
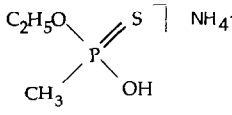
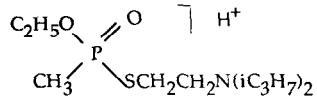



Fig. 1. Thermospray mass spectrum of VX (A) in a liquid composition consisting of acetonitrile–methanol–0.089 *M* ammonium acetate (50:14:36) and (B) in 0.1 *M* ammonium acetate.

TABLE I

STRUCTURES OF FRAGMENTS FOUND IN THE TSP MASS SPECTRA OF VX

i = Iso-.

| *m/z* | Fragment | *m/z* | Fragment |
|---|---|---|---|
| 102 | $(iC_3H_7)_2NH$ ⌉ $H^+$ | 162 | $(iC_3H_7)_2NCH_2CH_2SH$ ⌉ $H^+$ |
| 128 | $(iC_3H_7)_2NCH{=}CH_2$ ⌉ $H^+$ | | |
| | | 188 | $(iC_3H_7)_2NCH_2CH_2OC(=O)CH_3$ ⌉ $H^+$ |
| 141 |  ⌉ $H^+$ | | |
| 145 | | | |
| | | |  ⌉ $H^+$ |
| 146 | $(iC_3H_7)_2NCH_2CH_2NH_2$ ⌉ $H^+$ | 240 | |
| 158 | $(iC_3H_7)_2NCH_2CH_2OH$ ⌉ $H^+$ | | |
| |  ⌉ $NH_4^+$ | 268 |  ⌉ $H^+$ |
| | | 289 | $(iC_3H_7)_2NCH_2CH_2SCH_2CH_2N(iC_3H_7)_2$ ⌉ $H^+$ |
| | | 321 | $(iC_3H_7)_2NCH_2CH_2SSCH_2CH_2N(iC_3H_7)_2$ ⌉ $H^+$ |

structures of the ions are presented. The ion at *m/z* 188 cannot be readily explained from simple bond cleavages, or attributed to VX hydrolysis products. Using ammonium formate this ion shifted to *m/z* 174, indicating the formation of an ester between 2-diisopropylaminoethanol and either acetic or formic acid. Except for this unexpected ion, the spectra obtained by using both buffers were identical. In accordance with the results published by Voyksner and Haney [12] and Barceló [20], no enhancement of the sensitivity was observed by using ammonium formate.

More ions were observed in 0.1 *M* ammonium acetate solution (Fig. 1B). They correspond to the protonated molecular ions or ammonium adduct ions of known VX decomposition products [5–7] (see Table I). The relative intensities of the ions depended strongly on the experimental conditions, so the spectrum presented has to be regarded as an example. As already demonstrated by McFadden and Lammert [21], discharge ionization and variation of the repeller voltage may lead to fragmentation of analytes. This was also observed for VX. Using discharge ionization, the intensities of some ions (*m/z* 128, 146 and 162) became enhanced. The ion at *m/z* 128 may be derived from those at *m/z* 146 and 162 by the elimination of water and hydrogen sulphide, respectively. Unfortunately, analysis in a 100% aqueous solution can only be performed when VX is directly introduced by flow injection. This type of analysis will be limited to those samples in which the concentration of VX is sufficiently high in comparison with other constituents.

*Liquid chromatography of VX*

Water with a high content of organic modifier was used for the described determination of the organophosphorus nerve agents or pesticides by reversed-phase HPLC [11–15]. Similar conditions were chosen for VX. Owing to the basic diisopropylaminoethyl moiety, adjustment of the pH was necessary. At a pH of *ca.* 5, a broad, tailing peak was observed using a $C_{18}$ column and methanol–0.1 *M* ammonium acetate (50:50) as the eluent, probably owing to an exchange reaction between VX and its protonated form. Increasing the pH led to longer retention times, so the methanol content was raised to 80%. A reasonably sharp peak was obtained when the pH of the eluent corresponded with the $pK_a$ of VX (*ca.* 8.5) [7]. However, it was necessary to change the eluent composition owing to the co-elution of VX with the well known plasticizer tri-*n*-butyl phosphate (MW 266). Under the conditions used its TSP mass spectrum consisted mainly of the protonated molecular ion at *m/z* 267. This spectrum differed from that published by Barceló [13], which gave in addition to the ion at *m/z* 267 (relative intensity 40%) the ammonium adduct ion as the base peak. However, both spectra gave an isotope peak of the protonated molecular ion at *m/z* 268, which interfered with the protonated molecular ion of VX. Because tri-*n*-butyl phosphate is a water pollutant which has been found at relatively high levels (up to 10 ng/ml) in European rivers [22,23] chromatographic separation has to be achieved. In addition to its appearance in the environment, tri-*n*-butyl phosphate may also be considered as an analytical artifact [24] which is difficult to eliminate. Inspection of the mass spectrometer background at high multiplier gain revealed the presence of ions at *m/z* 267 and 268, probably due to tri-*n*-butyl phosphate originating from organic solvents, plastic tubing, etc. Therefore, another eluent composition was evaluated, consisting of acetonitrile, methanol and water. The eluent composition was optimized for the separation between tri-*n*-butyl phosphate and VX, leading to the mixture acetonitrile–methanol–0.25 *M* ammonium acetate (70:20:10). Because of the low water content, a relatively high ammonium acetate concentration was used, giving a good shielding of the acidic silanol groups of the column. The combination used also gave a short retention time, providing fast analyses. No adjustment of the pH with ammonia proved to be necessary when using such a high acetonitrile content. A typical chromatogram is presented in Fig. 2A.

In agreement with a recent paper [25], the chromatographic conditions described here may be used for several weeks without a noticeable decrease in efficiency, provided that the top of the column is repacked regularly. However, it must be noted that dissolution of silica material occurs under these conditions, which may ultimately lead to blocking of the TSP interface. During several weeks of operation a gradual increase in the optimum tip temperature occurred, caused by deposition of silica material at the heated capillary tip. This process could be reduced by setting the vaporizer temperature *ca.* 2°C below the optimum temperature.

*Sensitivity*

The sensitivity of the system was determined by single ion monitoring (SIM) at *m/z* 268 using ionization by the ammonium acetate buffer. Although VX could be determined using the above-described eluent composition, the high content of the organic modifier is a less preferential situation in TSP ionization [26]. In order to achieve a lower detection limit, the water content of the liquid in the TSP interface was

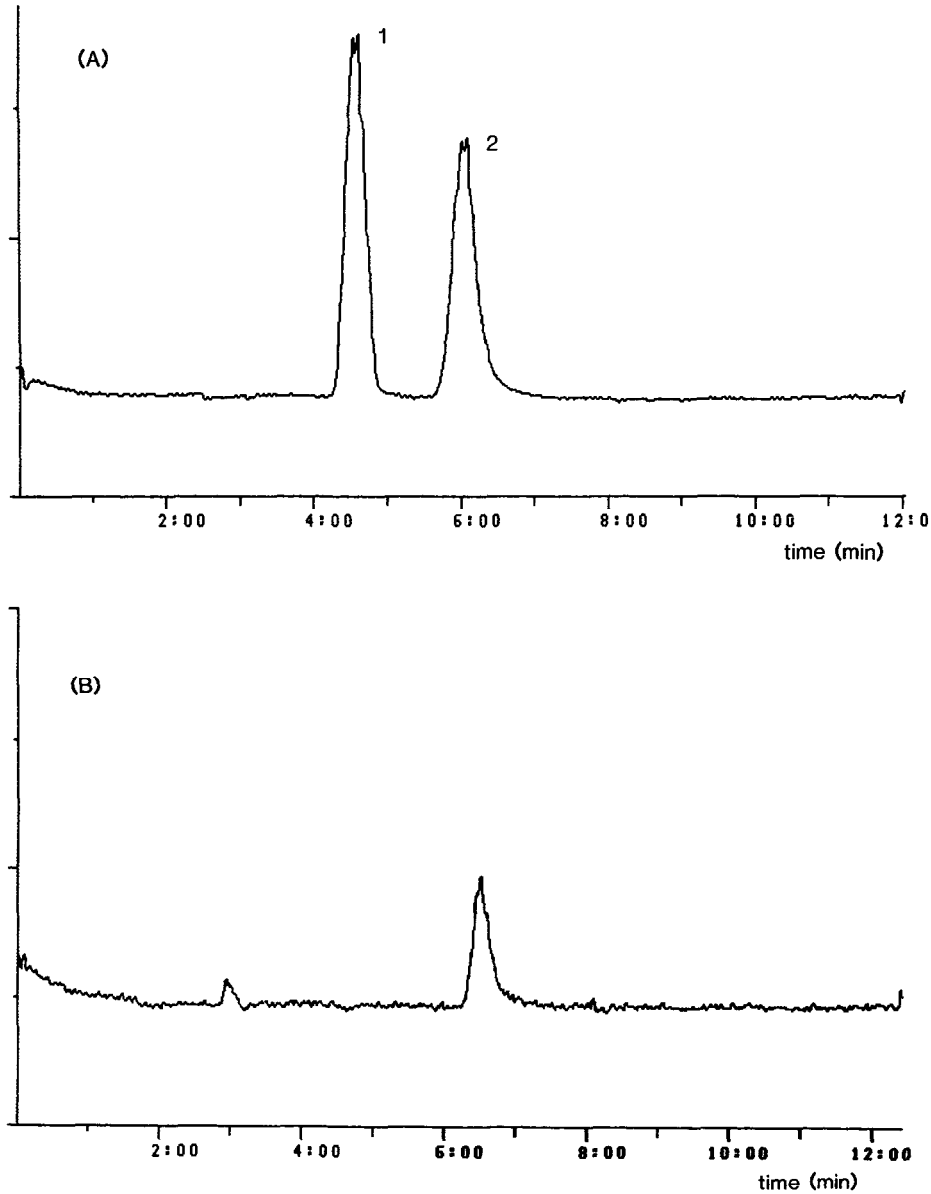



Fig. 2. Chromatographic behaviour of VX on a $C_{18}$ column using acetonitrile–methanol–0.25 *M* ammonium acetate (70:20:10). (A) Separation between (1) tri-*n*-butyl phosphate and (2) VX. (B) Signal-to-noise ratio obtained after injecting 200 pg of VX.

increased by post-column addition of 0.05 *M* ammonium acetate, leading to acetonitrile–methanol–0.089 *M* ammonium acetate solution (50:14:36). Using an injection loop of 40 μl, an amount of 200 pg of VX dissolved in methanol could be detected with a signal-to-noise ratio above 10 (see Fig. 2B). The noise was partly

determined by the height of the mass spectrometer background signal at $m/z$ 268. However, the result could be readily repeated on a day-to-day basis. Owing to the high percentage of organic solvents in the eluent, the degree of contamination of the ion source block increased daily, resulting in a gradual decrease in the signal-to-noise ratio after 1 week.

*Preconcentration*

The above-described sensitivity allows the determination of VX in water at concentrations down to 5 ng/ml. In order to detect VX in water below this level, preconcentration has to be carried out. The breakthrough volume of VX on Sep-Pak $C_{18}$ cartridge was measured in demineralized water at pH 6.0 using a concentration of 4 $\mu$g/ml. After passing 60 ml through the cartridge, 1% of the original VX concentration was found in the effluent. A similar experiment was carried out with Rhine water (pH 7.5) spiked with VX at the same concentration. After 180 ml still no VX was observed in the effluent, indicating that the breakthrough volume is strongly dependent on the nature of the water. Based on these experiments, 50 ml was chosen as the maximum volume of water used for preconcentration experiments. The desorption of the Sep-Pak $C_{18}$ cartridges with isopropanol and methanol was investigated. Methanol gave slightly better results. However, 2 ml of methanol were necessary to achieve an extraction efficiency above 80%. In order to reduce the volume of methanol to 1 ml, the cartridge was eluted in the reverse direction. In this way, recovery efficiencies of the procedure higher than 80% were normally obtained.

The possibility of sampling water in the field by $C_{18}$ cartridges instead of transporting the water samples to a laboratory was investigated. Therefore, some preservation experiments were carried out. Decomposition of VX on Sep-Pak $C_{18}$ cartridges was observed. The recovery efficiency decreased when the time between adsorption of VX and elution with methanol became longer than 15 min. After 1 day VX could no longer be detected. This was observed for a wide range of VX concentrations. Analysis by TSP–LC–MS showed that the following seven compounds were formed: ethylmethylphosphonic acid, ethylmethylthiophosphonic acid, S-2-diisopropylaminoethylmethylphosphonothioic acid, 2-diisopropylaminoethanol, 2-diisopropylaminoethanethiol, bis(2-diisopropylaminoethyl) sulphide and bis(2-diisopropylaminoethyl) disulphide. These decomposition products, due to the cleavage of the P–S, S–C and C–O bonds of VX, were also found during the hydrolysis of VX in the pH range 7–10 [7].

The preconcentration and preservation of VX were also investigated using Bond Elut $C_{18}$ cartridges. Comparable adsorption and desorption efficiencies were obtained, but in contrast to Sep-Pak $C_{18}$, no decomposition was observed after storage overnight (18 h). Apparently Sep-Pak $C_{18}$ cartridges contain active sites which catalyse the hydrolysis of VX. According to information given by the manufacturers, the difference between these two types of cartridges must be due to the procedures used for linking the $C_{18}$ group to the silica surface. This led to a better shielding of the silanol groups in the case of the Bond Elut cartridges.

*Applications*

In order to investigate the applicability of the procedure, water samples from two major European rivers (Rhine and Meuse) were spiked with VX. In Fig. 3A the

chromatogram obtained using SIM at $m/z$ 268 after concentration of 50 ml of Rhine water to 1 ml of methanol with a Bond Elut $C_{18}$ cartridge is presented. Three peaks were observed, of which the middle one corresponded to tri-*n*-butyl phosphate. In Fig. 3B the result of the same experiment is presented after spiking Rhine water with VX at a level of 0.1 ng/ml. The contact time was *ca.* 15 min, in which hardly any hydrolysis of

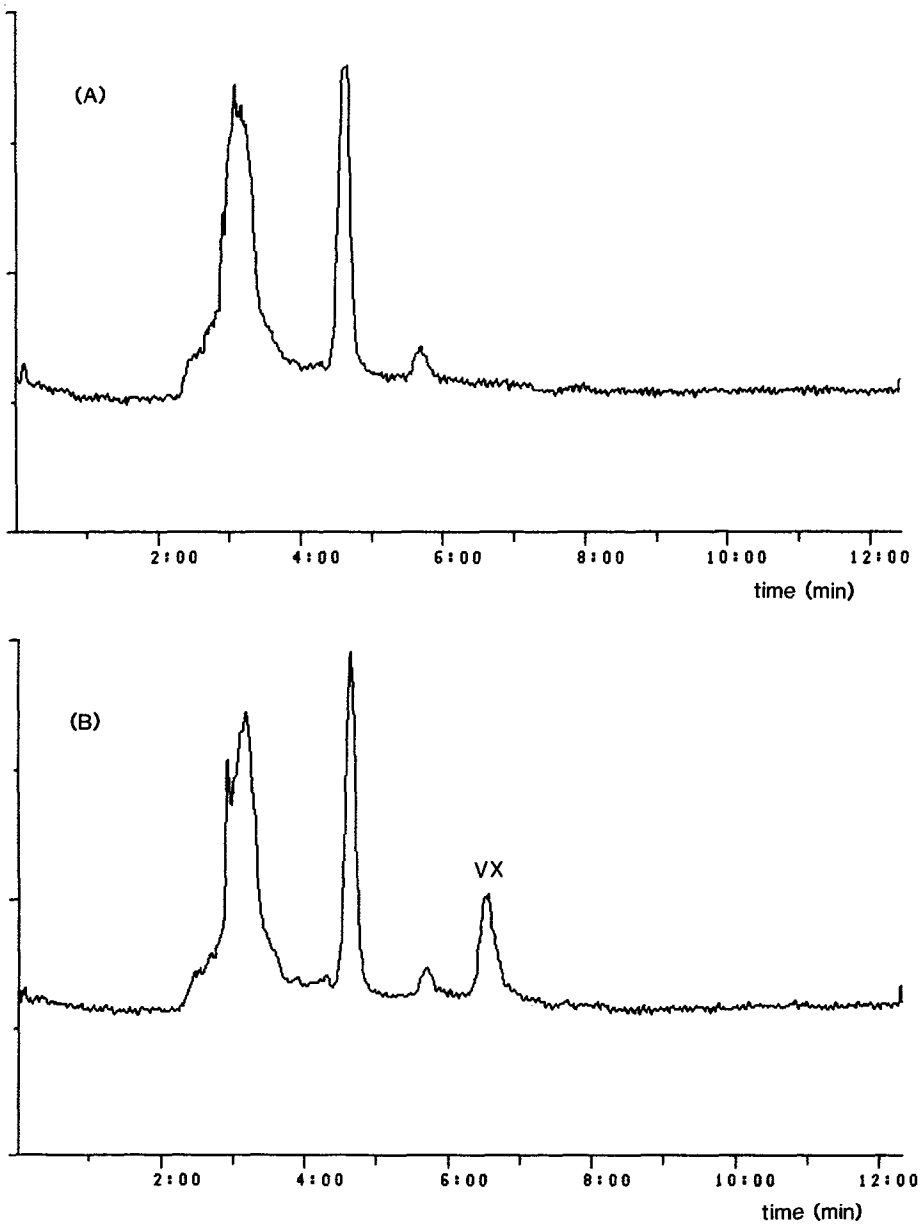



Fig. 3. Determination of VX in a 50-ml Rhine water sample. (A) Unspiked Rhine water; (B) Rhine water spiked with 0.1 ng/ml of VX.

the added VX took place. Based on the applied concentration step with an efficiency of 80% and the sample loop volume of 40 $\mu$l, the amount of VX injected corresponded to 160 pg. Similar results were obtained with water from the river Meuse. Both results demonstrate that it is possible to detect the presence of VX by TSP–LC–MS at a level of 0.1 ng/ml in *ca.* 15 min. Perhaps this level could be reduced even further by increasing the amount of water and/or further concentration of the methanol solution by evaporation. However, at lower levels problems with the selectivity are to be expected and more extensive clean-up procedures or techniques such as TSP–LC–MS–MS will be necessary.

VX has also determined successfully in water extracts of soil samples. Clayey soil samples spiked with VX were extracted as described by Verweij and Boter [5] by shaking at room temperature for 1 h either with an organic solvent mixture (chloroform–methanol) or with demineralized water. Extraction of the soil samples with water and determination of VX by TSP–LC–MS led to better quantitative results compared with the extraction with the organic solvent mixture and determination of VX by GC techniques (GC–MS and GC combined with a thermionic nitrogen–phosphorus detector). In three soil samples an average concentration of 3 mg/kg of VX was found in the water extracts, whereas in the organic solvent mixtures only 0.4 mg/kg of VX was found. Because also no interferences of soil constituents were observed, the analysis based on TSP–LC MS provided a good alternative to the analysis based on GC techniques.

## CONCLUSIONS

A rapid and simple procedure based on TSP–LC–MS was developed for the determination of the nerve agent VX. Combined with preconcentration, the procedure shows promise for the detection of VX in environmental samples at a relatively low level.

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