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Desorption electrospray ionisation mass spectrometric analysis of chemical warfare agents from solid-phase microextraction fibers

Paul A. D'Agostino*, Claude L. Chenier, James R. Hancock and Carmela R. Jackson Lepage

DRDC Suffield, P.O. Box 4000 Station Main, Medicine Hat, AB, Canada, T1A 8K6

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Desorption electrospray ionisation mass spectrometry (DESI-MS) was recently reported for the direct analysis of sample media without the need for additional sample handling. During the present study, direct analysis of solid-phase microextraction (SPME) fibers by DESI-MS/MS was evaluated with indoor office media that might be collected during a forensic investigation, including wall surfaces, office fabrics, paper products and Dacron swabs used for liquid sampling. Media spiked at the μg/g level with purified chemical warfare agents and a complex munitions grade sample of tabun, to simulate the quality of chemical warfare agent that might be used for terrorist purposes, were successfully analysed by DESI-MS/MS. Sulfur mustard, a compound that has not been successfully analysed by electrospray mass spectrometry in the past, was also sampled using a SPME fiber and analysed for the first time by DESI-MS/MS. Finally, the overall analytical approach involving SPME headspace sampling and DESI-MS analysis was evaluated during a scenario-based training live agent exercise. A sarin sample collected by the military was analysed and confirmed by DESI-MS in a mobile laboratory under realistic field conditions. Copyright © 2007 Crown in the right of Canada. Published by John Wiley & Sons, Ltd.

The ending of the Cold War and the widespread acceptance of the Chemical Weapons Convention have reduced the likelihood of battlefield chemical weapons use, but there remains a serious concern worldwide that other parties may make use of chemical warfare agents against civilian or military targets. Sarin, a well-known nerve agent, was used by the Aum Shinrikyo sect in Japan in 1995 during an attack on the Tokyo underground transit system, during which twelve people were killed and thousands more were injured. Public concern about the use of chemical or biological warfare agents reached a new peak following the al-Qaeda terrorist attacks of September 2001 and the subsequent delivery of anthrax letters in Washington DC. These events heightened security concerns within many countries and considerable resources have been expended to improve both field- and laboratory-based detection and identification methods for chemical warfare agents (CWAs).

Detection and identification methods for CWAs, their degradation products and related compounds have been thoroughly reviewed with different emphases on a number of occasions.[1–7] Many previous method developments were driven by the requirements of the military and their need to be able to detect and identify these compounds in typical battlefield samples, including, soil,[8–11] water,[10,12–15] air,[16,17] munitions or munition blocks,[9,18] and clothing.[8,9] Newer methods based on solid-phase microextraction (SPME) sampling followed by gas chromatography/mass spectrometry (GC/MS) analysis[19–23] and direct analysis by secondary ion mass spectrometry[24] have been reported for environmental analyses, but most literature methods have been based on analysis of sample extracts by GC/MS.[8–18]

Organic extracts of samples containing CWAs may be analysed directly by GC/MS, but the hydrolysis products of CWAs usually require derivatisation prior to GC/MS analysis.[6] More recently, researchers have demonstrated the value of liquid chromatography/mass spectrometry (LC/MS) as a complementary or replacement method for GC/MS, particularly for the confirmation of hydrolysis products of chemical warfare agents in aqueous extracts or samples,[25–33] as the hydrolysis products may be analysed directly without the need for additional sample handling and derivatisation. LC/MS has an additional benefit as it may also be utilised for the determination of organophosphorus CWAs and related compounds during the same analysis.[29–32]

Samples collected following a terrorist incident could be quite different from those on the battlefield and may involve the sampling of indoor office media should CWAs be used in an office environment. In a prior investigation we focused on

*Correspondence to: P. A. D'Agostino, DRDC Suffield, P.O. Box 4000 Station Main, Medicine Hat, AB, Canada, T1A 8K6.
E-mail: paul.dagostino@drdc-rddc.gc.ca

the development and application of sample handling and liquid chromatography/electrospray ionisation tandem mass spectrometry (LC/ESI-MS/MS) analytical methods for contaminated office media that might be collected for forensic purposes. Media, including flooring, wall surfaces, office fabrics and paper products, were spiked at the 4 to 20 μg/g level with sarin, cyclohexyl methylphosphonofluoridate, soman, the nerve agent simulant triethyl phosphate (TEP), or a complex munitions grade sample of tabun. Spiked samples were extracted with water using ultrasonic vibration, centrifuged to reduce the presence of fine particulates, and analysed by LC/ESI-MS and LC/ESI-MS/MS. Recoveries of the spiked CWAs varied with agent and media, ranging from 23% to 88%, sufficient for identification of all spiked compounds.[34]

Recently, a novel mass spectrometric method for sample ionisation and analysis, developed by Cooks' group and referred to as desorption electrospray ionisation (DESI), was described.[35] During the DESI experiment charged droplets in the solvent being electrosprayed impact the surface of interest, desorbing and ionising the analyte. Ionised large biomolecules and small organic molecules may then be detected by mass spectrometry, often in the tandem mode. Cooks recently reviewed ambient mass spectrometry with an emphasis on the DESI method,[36] including discussion on direct analysis in real time (DART)[37] and the atmospheric-pressure solids analysis probe,[38] two related direct analysis approaches.

DESI-MS has been used for a variety of direct analyses,[39] including the analysis of pharmaceutical products,[40–46] dyes on thin layer chromatography plates,[47] explosives on a variety of surfaces,[48] polymers,[49] alkaloids on plant tissue,[50] and CWAs on SPME fibers.[34] The DESI and DART techniques for rapid, direct sample analysis have both attracted interest in the chemical defence and public security communities due to the minimal sample handling requirements and potential for rapid sample throughput.[34,37] SPME has been applied to many sampling and analysis situations,[51] and this method of sampling has been integrated into the chemical warfare agent sampling and analysis strategy developed for counterterrorism purposes in Canada. Direct analysis of SPME fibers by DESI-MS/MS would complement existing thermal desorption GC/MS-based identification methods and might ultimately enable higher sample throughput with less sample handling. DESI-MS was first evaluated for the direct analysis of SPME fibers used to sample the headspace above office carpet spiked with TEP, and the nerve agents sarin and soman.[34] These preliminary applications were successful and led to continued investigation and application of DESI-MS/MS to more complex chemical warfare agent analyses.

During the present study, direct analysis of SPME fibers by DESI-MS/MS was evaluated with indoor office media that might be collected during a forensic investigation, including flooring, office fabrics, paper products and Dacron (polyester) swabs used for liquid sampling. Media were spiked at the μg/g level with a complex munitions grade sample of tabun, to simulate the quality of CWA that might be used for terrorist purposes, as well as with purified CWAs. The sensitivity of this direct approach to sampling and analysis was compared with a recently developed LC/ESI-MS/MS method utilising aqueous extraction.[34] Sulfur mustard (H), a compound that has not been successfully analysed by LC/ESI-MS in the past,[31] was also sampled using a SPME fiber and successfully analysed for the first time by DESI-MS/MS. Finally, the overall analytical approach involving SPME field sampling and DESI-MS analysis was evaluated during recent scenario-based training with the military under realistic field conditions.

EXPERIMENTAL

Representative indoor office media, including office carpet (100% nylon), office fabrics (56% nylon/44% polyester and 100% nylon), photocopy paper and Dacron sampling swabs, were spiked with a complex munitions grade tabun standard or CWA standards. Spiking levels were in the 5 to 25 μg/g range, consistent with levels used during Organisation for the Prohibition of Chemical Weapons proficiency testing. Blank 20 mL headspace sampling vials and office media (typically 0.5 to 1 g) placed in the same vials were spiked with 5 to 15 μL aliquots of CWA(s) or simulants in dichloromethane. The dichloromethane was allowed to evaporate and SPME sampling was conducted on the headspace above the spiked office media contained in the sampling vial for up to 10 min at 25 or 50°C. Supelco (Bellefonte, PA, USA) (65 micron film thickness) polydimethylsiloxane/divinyl benzene (PDMS/DVB) SPME fibers were used throughout the study for headspace sampling.

Mass spectrometric data were acquired in the laboratory using a Waters (Milford, MA, USA) Q-ToF Ultima tandem mass spectrometer equipped with a Z-spray electrospray interface. The electrospray capillary was operated in the 1 to 3 kV range with a sampling cone voltage of 35 V. The collision energy (CE) was maintained at 5 V for LC/ESI-MS operation and was varied from 2 to 10 V (depending on the precursor ion selected) for LC/ESI-MS/MS operation. Argon was continually flowing into the collision cell at 9 psi during both LC/ESI-MS and LC/ESI-MS/MS operation. Nitrogen desolvation gas was introduced into the interface (80°C) at a flow rate of 300 L/h and nitrogen cone gas was introduced at a flow rate of 50 L/h. ESI-MS data were typically acquired from *m/z* 70 to 300 (0.3 to 1 s). ESI-MS/MS (product ion mass spectra) data were acquired for the protonated molecules of the spiked compounds (0.3 to 1 s). All data were acquired in the continuum mode with a resolution of 8000 (V-mode, 50% valley definition).

DESI-MS and DESI-MS/MS data were initially acquired for TEP with the Z-spray interface glass sleeve removed to allow introduction of the SPME fiber into the region between the electrospray needle and the sampling cone. A laboratory stand was used to hold and position the SPME manual holder so that the fiber could be introduced into an ethanol/water (1:1) mobile phase spraying at 10 μL/min. DESI-MS experiments that vented into the laboratory (without the glass interface sleeve) were not attempted with either CWAs or the LC mobile phase for safety reasons. A replacement Plexiglass sleeve was then machined and a septum port was mounted on the inside of the sleeve to facilitate the safe

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introduction of SPME fibers contaminated with CWAs. The LC mobile phase, typically 50:50 acetonitrile/water (0.1% trifluoroacetic acid (TFA)), was sprayed at 10 μL/min during DESI analyses.

Mass spectrometric data were also collected in a field portable laboratory during a scenario-based training exercise. The headspace above a sample of sarin was sampled with an SPME fiber for 3 to 30 s at 25°C. Data were acquired on a Waters LCT mass spectrometer equipped with an earlier generation of the Z-spray interface under similar conditions to the Waters Q-ToF. Full scanning ESI-MS data were acquired for sarin using a lower sampling cone voltage of 20 V that minimised product ion formation. Complementary GC/MS data were obtained under electron ionisation conditions using an Agilent 5973 mass spectrometer (Agilent Technologies, Palo Alto, CA, USA) fitted with a RVM low thermal mass resistively heated column (RVM Scientific, Santa Barbara, CA, USA).

LC/ESI-MS/MS separations, conducted for comparative purposes, were performed with an Agilent 1100 capillary LC system using a 5% to 50%B gradient over 15 min and a flow rate of 10 μL/min. The following solvent compositions were prepared for the mobile phase: solvent A (0.1% TFA in water) and solvent B (acetonitrile). All LC separations were performed with Agilent 50 mm × 0.3 mm i.d. fused-silica capillary columns packed with Zorbax SB C18 (1.8 μm particle size). An autosampler was used to introduce 1 μL aqueous injections.

RESULTS AND DISCUSSION

SPME fiber sampling has received increased attention within the defence and public security communities since headspace or direct sampling of contaminated media may be conducted without the need for sample extraction or other steps normally associated with GC/MS or LC/MS analyses. SPME fibers contaminated with common CWAs would typically be analysed by thermal desorption GC/MS, an approach that has been successfully demonstrated in laboratory and field settings.[19–22,51] Analysis of SPME fibers using DESI-MS, a recently described direct sample ionisation and analysis technique, was investigated as it could have application within the forensic, defence and public security communities for identification of CWAs.

SPME sampling followed by direct analysis of fibers by DESI-MS/MS was first applied to the sampling and analysis of the headspace above office carpet spiked with the CWAs sarin and soman and the CWA simulant TEP. The acquired DESI-MS/MS data were identical to those obtained by LC/ESI-MS/MS, with the product mass spectrum for the $[M+H]^+$ precursor ion in most cases giving ions due to loss of the alkene(s) associated with the alkoxy groups of these compounds.

Terrorist use of CWAs may involve the use of crude products similar to munitions grade CWAs that may contain not only the toxic CWA, but also related co-synthetic, degradation or other products. Identification of these additional sample components could be helpful in establishing a link between the agent used in the incident and a source, or provide an indication of synthetic route used to prepare the CWA.

A munitions grade sample of tabun containing numerous related compounds[52] was selected in this study to evaluate the applicability of DESI-MS/MS for the identification and characterisation of CWAs and related organophosphorus compounds collected on SPME fibers. Indoor office media, including office carpet, office fabrics and Dacron sampling swabs, were placed in a headspace sampling vial and spiked with a munitions grade tabun standard at the 20 μg/g level (approximately 1 to 10 μg/g per sample component). The headspace above the spiked media was sampled for 10 min, with increased uptake being observed at the higher temperature, 50°C. Figure 1 illustrates the DESI-MS total ion current profile (*m/z* 70–300) and DESI-MS/MS product ion profiles collected during analysis of a Dacron sampling swab spiked with munitions grade tabun. Tabun and a number of related organophosphorus compounds contained in the munitions grade tabun sample were all identified by DESI-MS/MS. During DESI-MS/MS analysis, product ion data were acquired for the $[M+H]^+$ ions of tabun and eight related organophosphorus compounds previously identified during LC/ESI-MS/MS experiments.[34] Tabun, the most abundant sample component (approximately 70% of the organic content), was also easily identified on the basis of the DESI-MS data.

Figure 2 illustrates typical product ion mass spectra obtained for diethyl dimethylphosphoramidate, diisopropyl ethyl phosphate and tabun at collision energies that provided evidence of both the protonated molecule and characteristic product ions. Product ions due to the loss of the alkene associated with the alkoxy group were significant and the identities of these ions were confirmed by accurate mass measurement. Errors associated with mass measurement were typically <0.001 *m/z* units, consistent with previously acquired LC/ESI-MS/MS data.[34] Similar data were acquired for the other office media samples spiked with munitions grade tabun, with the DESI-MS and DESI-MS/MS data being identical to those obtained during LC/ESI-MS and LC/ESI-MS/MS analyses.

Signal-to-noise (S/N) ratios for SPME sampling followed by DESI-MS/MS analysis were compared with a recently described LC/ESI-MS/MS method[34] using TEP, a CWA stimulant that resists hydrolysis. A 15 μL volume of a 0.01 mg/mL TEP standard in dichloromethane was added to each of two 20 mL headspace sampling vials and the dichloromethane was allowed to evaporate. The first vial was then capped for SPME headspace sampling and DESI-MS/MS analysis. A volume of 3 mL of water was added to the second vial, the volume typically used to extract a 1 g sample prior to LC/ESI-MS/MS analysis (equivalent to a spiking level of 0.15 μg/g).

Figure 3 illustrates the LC/ESI-MS/MS product ion chromatogram obtained for *m/z* 183, the $[M+H]^+$ ion for TEP (1 μL injection volume, 50 pg). An S/N ratio exceeding 30:1 was recorded in the product ion chromatogram containing ion current associated with the detection of *m/z* 183 and its product ions. An interpretable product ion mass spectrum exhibiting product ions due to multiple losses of C_2H_4 was observed for TEP with a collision energy of 8 V.

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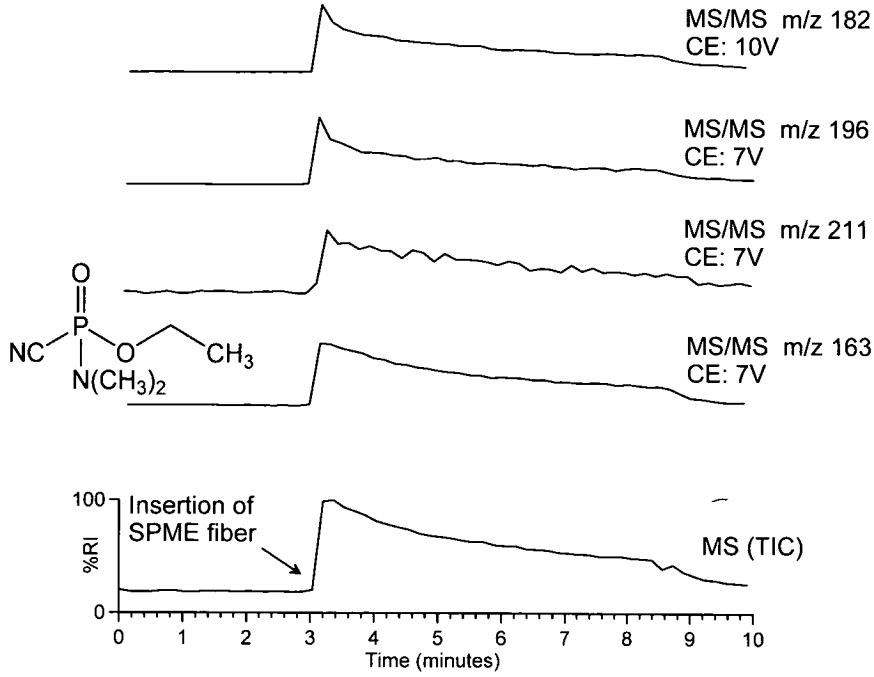

Figure 1. DESI-MS total ion current profile (*m/z* 70–300) and DESI-MS/MS product ion profiles for tabun (*m/z* 163), diisopropyl ethyl phosphate (*m/z* 211), ethyl isopropyl dimethylphosphoramidate (*m/z* 196) and diethyl dimethylphosphoramidate (*m/z* 182) obtained during analysis of a SPME fiber exposed to the headspace above a Dacron swab spiked at the 20 μg/g level with munitions grade tabun (approximately 1 to 10 μg/g per sample component).

A higher S/N level, 100:1, was recorded for the product ion profile of *m/z* 183 following DESI-MS/MS analysis (Fig. 4), as considerably more TEP was collected onto the SPME fiber during headspace sampling than was injected onto the LC column. It was estimated, based on the acquired product ion profile, that approximately 1 to 3 ng of TEP was ionised from the SPME fiber. A further experiment with an order of magnitude less TEP in the 20 mL headspace sampling vial

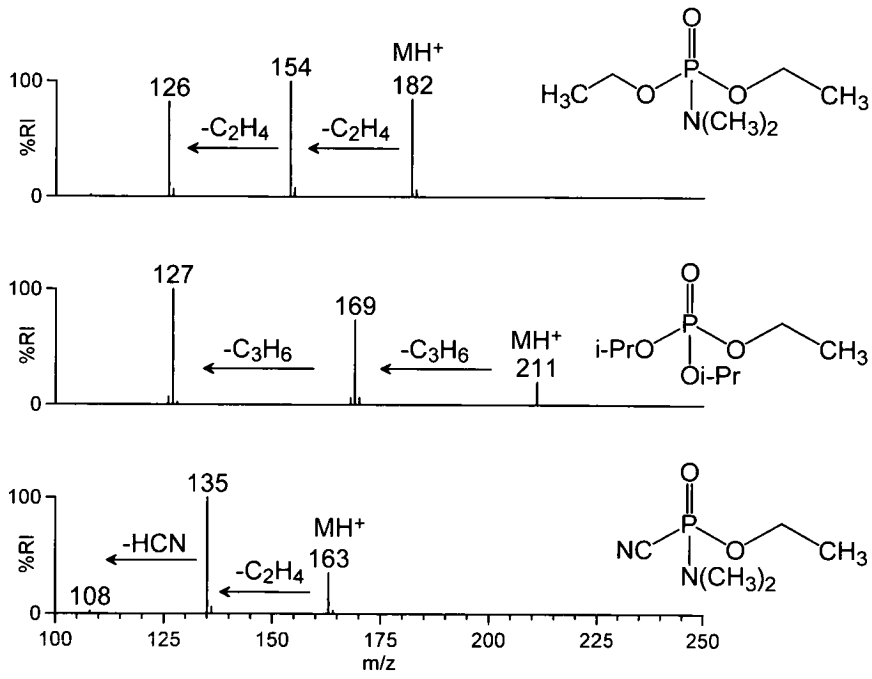

Figure 2. Product ion mass spectra obtained for (a) diethyl dimethylphosphoramidate (*m/z* 182, CE: 10 V), (b) diisopropyl ethyl phosphate (*m/z* 211, CE: 7 V), and (c) tabun (*m/z* 163, CE: 7 V) during DESI-MS/MS analysis of a SPME fiber exposed to the headspace above a Dacron swab spiked with munitions grade tabun.

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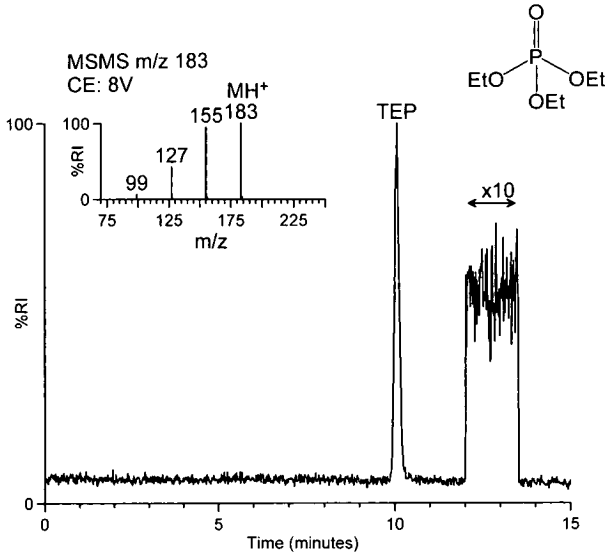

Figure 3. LC/ESI-MS/MS product ion chromatogram for *m/z* 183 obtained during analysis of an aqueous extract spiked with triethyl phosphate (50 pg injected). The product ion mass spectrum for triethyl phosphate (*m/z* 183, CE: 8 V) is inset.

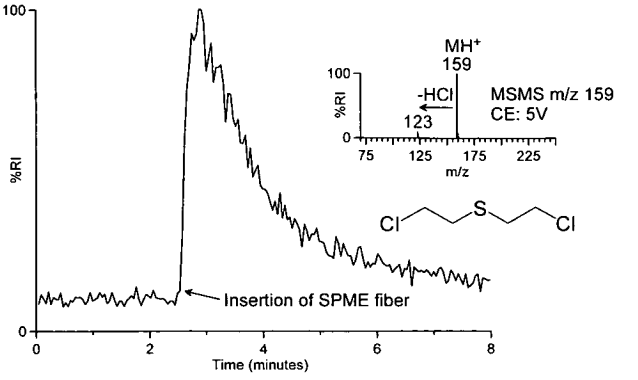

Figure 5. DESI-MS/MS product ion profile for *m/z* 159 obtained during analysis of a 20 mL SPME headspace vial spiked with 10 μg of sulfur mustard. The product ion mass spectrum for sulfur mustard (*m/z* 159, CE: 5 V) is inset.

also resulted in a detectable product ion profile for *m/z* 183 (S/N ratio >2:1). An identical, interpretable product ion mass spectrum was obtained for TEP following DESI-MS/MS analysis at this concentration, indicating detection capabilities similar to those reported for DESI-MS analysis of explosives.[35,47]

One of the shortcomings of LC/ESI-MS for CWA analysis has been the inability of this technique to analyse for the presence of the organosulfur CWA sulfur mustard, although this technique may be used for sulfur mustard hydrolysis products.[32] Sulfur mustard (10 μg) was deposited into a 20 mL headspace sampling vial and sampled with a SPME fiber to assess the potential of DESI-MS for sulfur mustard analysis. Figure 5 illustrates the DESI-MS/MS product ion profile acquired for product ions of *m/z* 159, the $[M+H]^+$ ion for sulfur mustard. The product ion mass spectrum obtained with a collision energy of 5 V contained a product ion at *m/z* 123 (due to loss of HCl), an ion that increased in relative signal intensity with increasing collision energy. Additional experiments with sulfur mustard were conducted by spiking 10 μg of sulfur mustard onto Dacron sampling swab, office carpet and photocopy paper samples. Sulfur mustard was detected following analysis of the SPME fibers but in all cases the signal recorded during DESI-MS/MS analysis was less intense than expected. Based on this finding, sulfur mustard appears to be strongly retained by the office media tested, unlike the organophosphorus CWAs and TEP which were readily sampled in the headspace above the office media using SPME fibers.

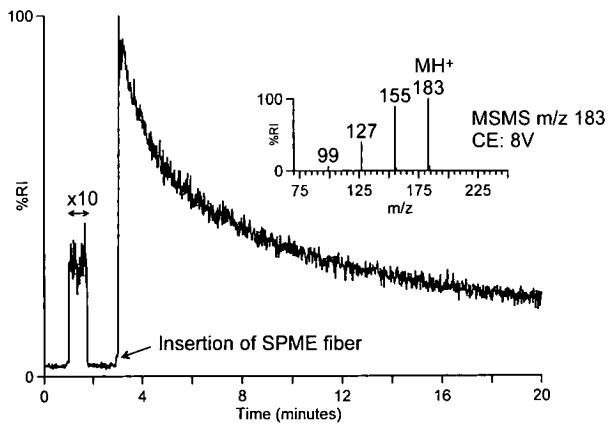

Figure 4. DESI-MS/MS product ion profile for *m/z* 183 obtained during analysis of a 20 mL SPME headspace vial spiked with triethyl phosphate (approximately 1 to 3 ng ionised from the SPME fiber). The product ion mass spectrum for triethyl phosphate (*m/z* 183, CE: 8 V) is inset.

The mobile analytical laboratory constructed for evaluation by the Canadian military forces has both a GC/MS and LC/MS capability. During the past months the laboratory has been integrated into the scenario-based training exercises being provided to the Canadian military forces and others. SPME sampling of the headspace above collected samples or of actual air samples followed by thermal desorption GC/MS analysis forms the cornerstone of the sampling and analysis strategy adopted for rapid field identification of CWAs. Additional confirmation analyses, using a second analytical technique, will be performed by LC/ESI-MS and/or DESI-MS in the same mobile laboratory. During a recent exercise a Dacron swab was used to sample an unknown liquid that was provided to the mobile analytical laboratory for CWA analysis. The headspace above the swab was initially sampled with a SPME fiber for 0.5 min (25°C) in a manner similar to that already described. The SPME fiber was thermally desorbed in the GC injection port and sarin was identified by fast (resistively heated GC column) GC/MS. Additional confirmation was provided by DESI-MS analysis of a SPME fiber used to sample the headspace above the sample again and by LC/ESI-MS analysis. Sarin was readily identified during DESI-MS analysis of the SPME fiber

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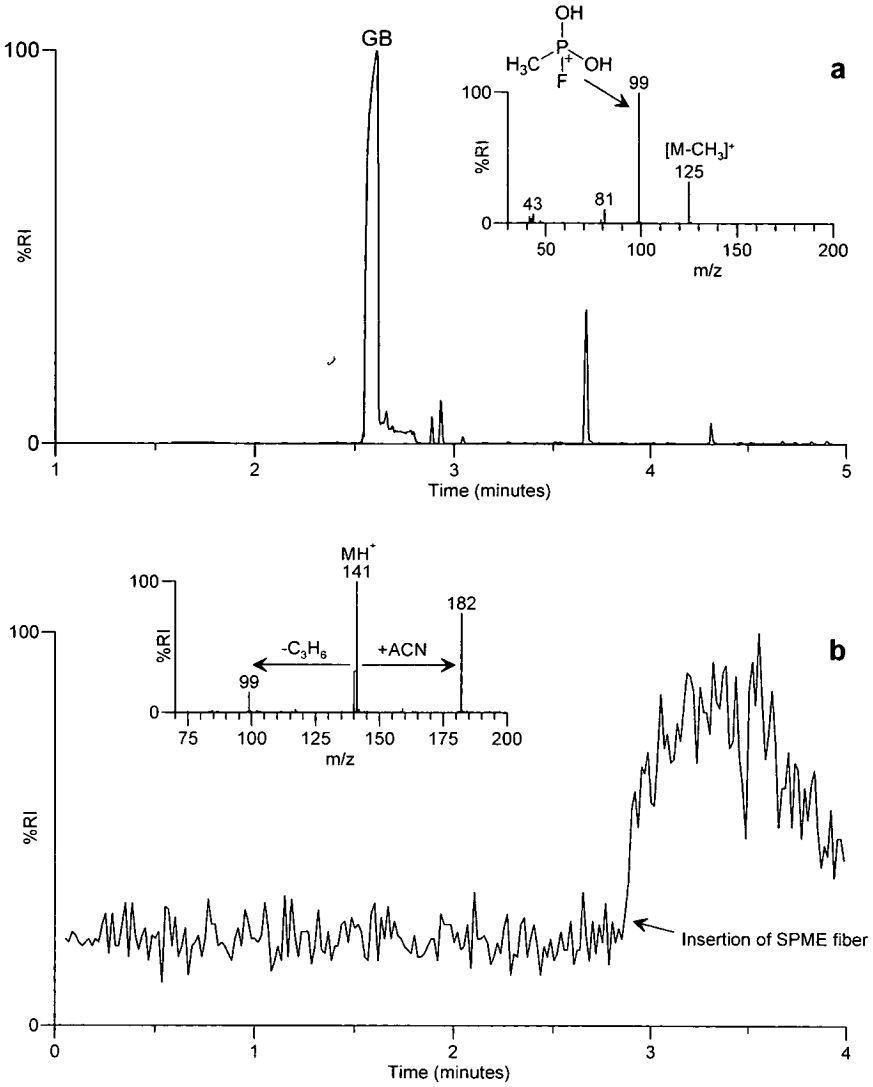

Figure 6. (a) GC/MS (EI) total ion current profile (*m/z* 40–400) and (b) DESI-MS total ion current profile (*m/z* 90 to 200) obtained from a SPME fiber exposed to the headspace above a Dacron swab used to sample during a scenario-based training exercise. Sarin was identified by the on-site mobile laboratory on the basis of the acquired mass spectra (inset).

using a lower sampling cone voltage that minimised product ion formation (Fig. 6). Ions at *m/z* 141 and 99, due to $[M+H]^+$ and $[M+H\text{-}C_3H_6]^+$, respectively, and their acetonitrile adducts at *m/z* 182 and 140, confirmed the presence of sarin in the collected field sample.

CONCLUSIONS

DESI-MS complements LC/ESI-MS methods for chemical warfare agents (CWAs). It was used for the direct analysis of SPME fibers exposed to the headspace above office media samples spiked at the μg/g level with a complex munitions grade tabun, sarin, soman or the organophosphorus CWA simulant triethyl phosphate. Tabun and a number of related organophosphorus compounds were identified in the munitions grade sample by DESI-MS/MS, with the identity of the product ions being confirmed by high-resolution analysis. Sulfur mustard was also successfully analysed for the first time from a SPME fiber exposed to the headspace above 10 μg of sulfur mustard using DESI-MS/MS. The product ion mass spectrum exhibited the $[M+H]^+$ ion at *m/z* 159 and a product ion at *m/z* 123 due to the loss of HCl.

The developed SPME headspace sampling and DESI-MS/MS analysis method was also used during a recent scenario-based training exercise. The on-site mobile laboratory used this technique and others to confirm the presence of sarin collected on a Dacron swab by the military participants. It is expected that this approach will be applied within the defence and public security communities during future investigations where evidence of the use of CWAs is required for forensic purposes or to assess remediation/restoration efforts following a chemical incident.

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