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Low level detection of chemical agent simulants in meat and milk by ion trap mass spectrometry☆

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Abstract

Analytical methods for the detection of two chemical warfare agent simulants, diisopropyl methylphosphonate and chloroethylethylsulfide, in beef tissue and milk have been demonstrated to be effective to levels as low as 50–100 parts-per-billion. These methods are based upon thermal desorption into an ion trap mass spectrometer. Selective detection of the target compounds is achieved by isobutane chemical ionization in combination with collision-induced dissociation, which yields characteristic fragment ions. Rapid sample clean-up steps were also devised to reduce interferences from the sample matrix. The low detection limits achieved with this method suggest that it may be possible to take small tissue samples from livestock by needle biopsy, without requiring animal sacrifice for the analysis. In addition, because the new methods may be performed more quickly than conventional methods requiring substantial sample preparation and analysis time, more samples could be analyzed.

1. Introduction

In late 1985 [1], Congress mandated that the US stockpile of lethal unitary (single component) chemical agents and munitions be destroyed by the Department of the Army in a manner that provides maximum protection to the environment, the general public, and personnel involved in the disposal program. These unitary munitions were last manufactured in the late 1960s. The stockpiled inventory is estimated to be

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approximately 25 000–30 000 tons [2], including organophosphate ('nerve') agents, such as GB (isopropyl methylphosphorofluoridate ($C_4H_{10}O_2PF$)) (sarin) and VX (ethyl-S-2-diisopropyl aminoethyl methylphosphorethidole ($C_{11}H_{26}O_2SP$)), and vesicant ('blister') agents, such as HD ((2-chloroethyl)sulfur ($C_4H_8SC_{12}$)) (distilled sulfur mustard), and others. The method of agent destruction ('demilitarization') selected by the Department of the Army is combined high temperature and high residence time incineration at secured military installations where munitions are currently stockpiled, including eight facilities in the continental United States and one on Johnston-Atoll [3, 4]. Several of these installations are located in agricultural areas where production of livestock, pasture, and row crops is important to local economies. In the event of agent contamination outside the installation boundaries during continued storage or any stage of stockpile destruction, food and forage crops could undergo surface contamination. Meat or milk could also become contaminated from ingestion of or contact by animals with contaminated forage or other materials. This issue is especially problematic for the persistent agents VX and HD.

Reproducible methods for detecting agents or their metabolites in plant and animal tissue have not been established by regulatory authorities. The lack of rapid isolation techniques and low-level detection protocols has hindered development of control limits for ingestion and dermal contact exposure to agents for the general public. As a result, there are currently no analytical means to establish how long to restrict public access to potentially contaminated areas or agricultural materials after the accidental release of a chemical agent [5].

Previous work in our laboratory, has shown the efficacy of direct sampling ion trap mass spectrometry (DS ITMS) for the rapid, confident detection of targeted compounds in environmental samples [6]. For example, a method for detecting all 34 Environmental Protection Agency (EPA) Target Compound List (TCL) volatile organic compounds (VOC) at levels of 5 parts per billion (ppb) or less in water has been developed based on direct purge of the volatiles into the ITMS with no sample preparation or chromatographic steps. This method requires only 3 min of analysis time, compared to 30 min or longer with conventional EPA methods based on gas chromatography/mass spectrometry and is currently undergoing evaluation for adoption as EPA method for screening volatiles in water. In addition, we have also demonstrated that direct thermal desorption into an ITMS may be used for the rapid detection of nicotine, nicotine metabolites, and drugs in urine [7]. Finally, we have also employed thermal desorption ITMS for the rapid detection of phenothiazine, an anthelmintic used in animals, in milk [8]. A method for identifying agents and agent simulants in air was developed based on direct thermal desorption into an ion trap mass spectrometer [9]. This method is currently in use at Tooele Army Depot to monitor the environment around a pilot demilitarization facility. Using the thermal desorption ITMS approach, detection limits of low parts-per-billion (ppb) of chemical warfare agents and agent simulants isolated on air sampling resins have been demonstrated with analysis times of less than 2 min.

In the present study, analytical methods for detection of low levels (ppb to parts-per-million, ppm) of two agent simulants in animal tissue and milk have been developed. The analytical approach taken was to combine simple sample preparation

steps with a rapid method of detecting the targeted compounds. The simulant chemicals employed in this study were diisopropyl methylphosphonate (DIMP) for the nerve agents GB (isopropyl methylphosphonofluoridate) and VX (ethyl-S-2-diisopropyl aminoethyl methylphosphorethidole), respectively, and 2-chloroethylethyl sulfide (CEES) for the blister agent HD ((2-chloroethyl)sulfur). Verification of the developed methods will require the use of actual agent materials at certified surety facilities that are unavailable at our laboratory.

2. Experimental

Samples of beef tissue were obtained from Dr. Robert Linnaberry at the University of Tennessee College of Agriculture, Department of Veterinary Medicine (Knoxville, TN). Samples of milk (pasteurized whole and skim) were obtained commercially. The meat samples were homogenized using either an ultrasonic homogenizer (4710 Series, Cole Parmer Instrument Company, Chicago, IL) or with a Polytron homogenizer (Brinkman Instruments, Waterbury, NY). Agent simulants, diisopropyl methylphosphonate (DIMP), $C_7H_{17}PO_3$, and chloroethylethylsulfide (CEES), $C_4H_{10}SCl$, were obtained from Morton Thiokol and Aldrich Chemical Co., Inc., respectively and used as received. DIMP was used as the simulant for both of the nerve agents, VX and GB. It should be noted that dimethyl methylphosphonate (DMMP) is often used as a simulant for developing analytical methods for VX, as it more closely matches the volatility of this agent. In these studies, however, the high water solubility of DMMP was found to prohibit effective isolation of this compound from the sample matrix. Because the thermal desorption ITMS method is less dependent upon volatility than chromatographic-based analyses and because the solubility of the actual agent VX in water is more similar to DIMP than to DMMP, it was determined that DIMP would be a suitable simulant for both nerve agents. Sorbent materials evaluated in these studies include Tenax (35/60 mesh), and C-18 and C-8 bonded silica (40 μm and 30–40 μm, respectively).

To isolate the targeted compounds from the sample matrix, a combination of centrifugation, filtration and adsorption on solid phase sorbents was employed. Approximately 100 mg of tissue homogenate or 100 μl of milk were spiked with the targeted compounds (typically at levels of 500 ppb or less) and then diluted with 3 to 5 ml of distilled water. The water-insoluble particulate materials from the tissue homogenate samples were removed by centrifugation and filtration through a nylon filter; milk samples did not require this step. Nylon filters were chosen over other filters, e.g., Teflon, polyethylene and mixed cellulose nitrate and cellulose acetate, primarily because of its low retention of organics (tested using rhodamine B) and its relatively fast flow rate. Glass fiber filters were not used because of a tendency for the fibers to shed into the sample. (A note of caution is that the filter chosen for use should be tested to ensure that it does not bind the analyte under study. For example in a separate study [8], it was found that the anthelmintic drug phenothiazine bound strongly to nylon.)

Two different methods were developed to extract the targeted chemicals from the solutions onto solid-phase sorbents. In the first extraction method ('direct'), a bed of

sorbent material (50–75 mg) was made near a constricted end of a 0.4 cm ID × 7.5 cm long glass tube. This glass tube is used in the thermal desorption step with the ITMS (described below). The tube is plugged on both ends with glass wool to keep the sorbent material in place. During the direct extraction method, the sorbent trap is connected to a 10 ml syringe using a 1/8 to 1/4 inch stainless steel reducing union, producing a leak-proof seal. The particulate-free sample (5 ml volume) containing the analyte is cycled through the sorbent trap bed several times to extract the compounds. In the second extraction method ('indirect'), the prepared solution (3 ml) is added directly to a 4 ml glass vial with Teflon®-lined screw cap closures (Wheaton, Millville, NJ) to which 50–75 mg of preconditioned, dry sorbent material has been added. The sorbent material was preconditioned by washing the sorbents three to four times with two to three volumes of methanol, followed by air drying. The vials are mounted on a mechanical rotator ('Roto-torque', Cole Parmer Instrument Co., Chicago, IL) and rotated end-over-end to effect sample/sorbent contact. This device allows at least 26 samples to be processed at once. After thorough mixing, the sorbent resin, which now has adsorbed the organic materials, is quantitatively transferred by suction into an empty glass tube of the size used for thermal desorption (described above). After either of these extraction methods, the sorbent traps are washed with at least 15 bed volumes of water and then dried under a flow of helium or nitrogen at room temperature. The tubes are then ready for analysis by thermal desorption (TD) ITMS. The drying of the sorbent tubes after compound isolation was found to be necessary for the effective analysis of samples. Wet tubes gave less reproducible recoveries in the thermal desorption step than dried tubes. Also, water present in the tubes interfered in the chemical ionization step employed with the ITMS detection step.

In subsequent experiments, it was found that the indirect method of sample isolation was more reproducible than the direct method because the flow over the sorbent in the direct extraction method is difficult to control, which gave rise to difficulties in reproducible extractions. Thus, only the indirect method was used in the experiments discussed below. In addition to the meat and milk samples discussed in this paper, some preliminary tests were also conducted on application of these isolation methods on plant tissue, specifically alfalfa. In these tests, some problems were encountered with filtration of the homogenized plant tissue. An alternative approach for isolating the target compounds from plant tissue is necessary prior to analysis of this type of sample.

For development of the thermal desorption methods, stock solutions were prepared in methanol at concentrations of picograms (pg) to nanograms (ng) per microliter. One to two microliters of the stock solutions were spiked directly on the sorbent traps to evaluate the thermal desorption process and to prepare calibration curves. Quantification was performed by integrating ion counts across the desorption profile for selected product ions resulting from MS/MS fragmentation of the targeted protonated molecules for each analyte. These MS/MS experiments are described in more detail below.

The specially designed thermal desorption interface is shown in Fig. 1. In this device, a glass tube containing a small bed of sorbent resin is heated to desorb thermally the material for subsequent analysis by the ITMS. In this process, the trap is

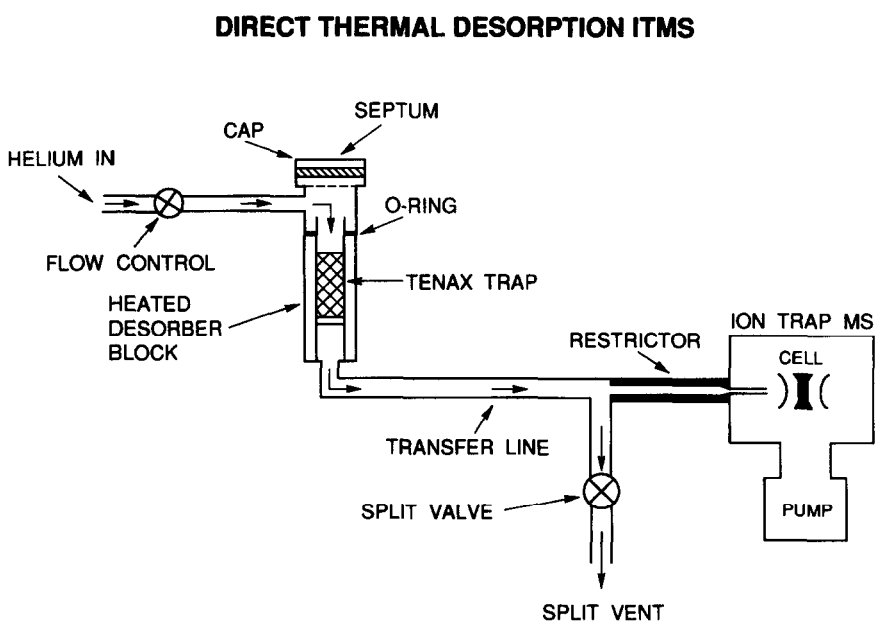

Fig. 1. Schematic diagram of specially designed thermal desorption interface used to introduce sample into ion trap mass spectrometer.

rapidly heated from ambient temperature to approximately 210 °C in about 30 s under a continuous flow of helium (approximately 30–50 ml/min). The volatilized compounds are carried into a capillary restrictor (100 μm ID uncoated fused silica) open split interface which extends directly into the ITMS analyzer cell through a heated sheath that is maintained at 250 °C. The flow through the restrictor is approximately 0.5 ml/min, which permits approximately 1–2% of the analyte effluent to enter the ITMS. The remaining part of the effluent can be diverted to another sorbent tube. This archival tube can be analyzed by another technique, if desired, to confirm results obtained by TD ITMS.

A specially modified Finnigan ion trap mass spectrometer (ITMS) (Finnigan/MAT, Inc., San Jose, CA) was used in these studies. The instrument was equipped with a custom-designed vacuum chamber which is electropolished on the inside and pumped with two 330 l/s molecular pumps. These modifications have been shown to minimize the possibility of contamination of the instrument with adsorbed materials, which might create sample-to-sample memory effects and thereby reduce the ultimate achievable detection limits and confidence of target compound identification [7–9]. The ITMS was equipped with a computer system which controls all of the instrument parameters during data acquisition. Instrument scan functions which enable the specific detection of the individual agent simulants were developed using the scan function editor program provided with the ITMS. The spectra were acquired every 3 s during the time that the materials were being desorbed.

Isobutane was used in these studies as a selective chemical ionization reagent [10]. The simulant compounds, as well as the actual agents GB, VX, and HD, are sufficiently basic that the ionized isobutane will transfer a proton to the compounds. The resulting ions, which may be represented by $(M + H)^+$, correspond to the mass of the molecule M, and the addition of a hydrogen (mass equal to one) appear at a mass to charge ratio (m/z) of $(M + 1)^+$. This selective ionization allows discrimination against less basic compounds which are commonly found in sample matrices. A second level of selectivity was afforded by employing collision-induced dissociation (MS/MS) techniques [11, 12]. Briefly, this technique may be summarized as having two steps. In the first step, the $(M + H)^+$ ions (generated by chemical ionization as described previously) from a particular target compound are isolated from other ions within the ITMS analyzer cell using specific software commands. In the second step, the selected ions are excited kinetically and collided with helium purge gas, causing the $(M + H)^+$ ions to dissociate to lower mass ions which are diagnostic of the original compound. The combination of selective chemical ionization and MS/MS techniques eliminated the need for on-line sample separation steps, such as gas chromatography. Combined gas chromatography/mass spectrometry, which is conventionally used in the analysis of mixtures [13], commonly requires 30 min or more. In contrast, the TD ITMS method employed in these studies requires less than 3 min.

3. Results and discussion

3.1. Thermal desorption studies

A typical thermal desorption profile for DIMP from Tenax is shown in Fig. 2. This profile was generated using a 1 ng standard of DIMP injected onto a bed of Tenax. The top trace is a total ion profile obtained from the desorbed material. Note that in this profile, no signal attributable to DIMP may be discerned. The lower two traces are profiles for two MS/MS fragment ions with mass to charge m/z 139 and 97, that are formed from the $(M + H)^+$ ion at m/z 181 for DIMP (which has a molecular weight M of 180). As outlined in the experimental section, these MS/MS fragment ions at m/z 139 and 97 are characteristic of DIMP, allowing these compounds to be confidently identified without interferences from other compounds that might be in the sample matrix. Note that the desorption profile of DIMP is relatively narrow, approximately 15 s in width. This feature gives enhanced analytical signal over the background, allowing for good limits of detection. For quantification, the MS/MS fragment ion intensities under the desorption profile were integrated and calibration curves were constructed. The calibration curves for DIMP standards desorbed from Tenax were linear from approximately 50 pg to at least 50 ng. The corresponding curves for CEES desorbed from Tenax were linear from 50 pg to 20 ng, although they exhibited non-linear response at higher concentrations. The thermal desorption profile for CEES is similar to that shown for DIMP in Fig. 2 (data not shown). For CEES, which has a nominal molecular of 125, the most prominent ion observed in the isobutane chemical ionization spectrum is at m/z 89, which corresponds to loss of HCl

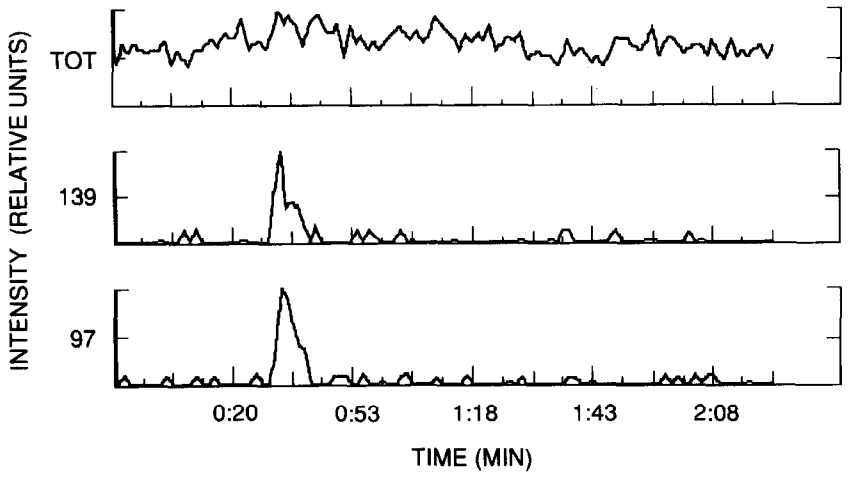

Fig. 2. Typical profile obtained for DIMP when thermally desorbed from Tenax into ITMS. Total amount of DIMP injected onto trap was 1 ng. Top trace is total ion profile and lower traces are signals for characteristic fragment ions obtained from the m/z 181 ion from DIMP, which are observed at mass to charge ratio (m/z) 139 and 97.

from the $(M + H)^+$ ion at m/z 126. This ion was isolated and fragmented under MS/MS conditions to produce a diagnostic ion with m/z 61, which was used for the determination of CEES in these studies.

Several other sorbent materials were systematically studied for suitability for thermal desorption analysis of the targeted compounds. The requirements for these materials included the ability to both extract and concentrate the agent simulants from aqueous tissue homogenates and milk and to release the compounds upon thermal desorption for subsequent analysis by ITMS. In addition to Tenax, the materials tested included C8-modified silica, C18-modified silica, and glass wool (which has no sorbent properties and was used for comparison of thermal desorption efficiencies). The C8- and C18-modified silicas are commonly used as separation media for chromatographic separations and sample clean-up steps in which adsorbed materials are removed with solvent elution. The use of these materials under thermal desorption conditions has not been widely characterized. Tenax, on the other hand, is widely used in thermal desorption analysis of organics isolated from air [14], and has also been demonstrated to be effective for removing some organics from water with subsequent analysis with thermal desorption into a gas chromatograph [15].

Studies of compound response under thermal desorption conditions clearly indicated that Tenax was more effective than C18-silica (and almost as effective as the non-sorptive glass wool) for the low-level detection of both DIMP and CEES. The C18 material yielded detection limits well up in the nanogram range for both simulants, indicating that the sorbent did not effectively release the simulants under thermal desorption conditions. In contrast, detection limits using Tenax were typically in the 50 pg range. C8-silica was included in these evaluations because it was

thought that it might bind the materials less strongly than the C18-silica and more efficiently release the targeted compounds under thermal desorption conditions. Although C8-silica did release both DIMP and CEES more efficiently than C18-modified silica, it was generally found to be no better than Tenax for thermal desorption. Moreover, a problem with reproducibility was found with the C8-silica because of its small particle size (40 μm). The small size of this material's particles sometimes allowed the sorbent bed to be too tightly packed, prohibiting the effective purging of the sorbent bed with helium during the desorption process and giving rise to irreproducible desorption of the target compounds. Recently, a source of larger particle-size C8-modified silica was identified and this material will be tested in the near future. In the present study, however, Tenax was judged to be the best overall sorbent material with respect to thermal desorption.

3.2. Sample preparation

The overall approach to the entire analytical procedure was to minimize the sample preparation steps required prior to the TD ITMS detection step. An initial attempt was made to determine if a milk sample could be analyzed with no sample preparation step. This was done by injecting two microliters of skim milk spiked with the target compounds onto a Tenax trap. The resulting spectrum demonstrated that the target compounds could indeed be detected at levels of 0.5–1 ppm (1 ng/μl). However, the desorption profiles resulting from these injections were broad and detection limits degraded after several analyses, suggesting that the thermal desorption unit or the transfer line into the ITMS was becoming fouled with higher molecular weight materials. Attempts were made to desorb thermally spiked aliquots of meat homogenates, as well. Although a response from targeted compounds was observed in these experiments, charring of the sample severely fouled the transfer line into the ITMS. Because of these observations, sample clean-up steps were developed to eliminate the macromolecular constituents in both the meat and milk samples.

Because the TD ITMS methodology described above has detection limits in the pg to ng range, this allowed smaller quantities of samples to be handled (i.e., in the milligram range), while still permitting detection limits at ppb (pg/mg) to ppm (ng/mg) levels to be achieved. Thus, in the development of sample clean-up steps, primary attention was given to processing small quantities of sample and loading all of the isolated material onto the trap. Lower detection limits could be achieved by using larger sample sizes (especially for milk, where sample quantities are virtually unlimited). However, the sensitivity of this method could potentially allow small samples of tissue to be taken from live animals without necessitating sacrifice of the animal. Further, this would allow large numbers of animals to be screened in an emergency response scenario, rather than a few animals, and give better assurance of consumer safety.

The three sorbent materials previously tested for thermal desorption were evaluated for their capacity to extract the target compounds from aqueous solution. In these tests, standard solutions of the two agent simulants were extracted onto the three sorbents, Tenax, C-18 modified silica, and C-8 modified silica. Although it was demonstrated that the C18- and C8-modified silicas had good isolation properties, as

noted above, these materials proved not to be effective as thermal desorption media. Tenax was found to efficiently adsorb both agent simulants from aqueous solutions and release the compounds under appropriate thermal desorption conditions for analysis by thermal desorption ITMS.

3.3. Detection of trace simulants in meat and milk

To demonstrate the overall detection of DIMP and CEES in meat, a beef homogenate sample (100 mg) was spiked with 5 ng of each agent simulant (corresponding to 50 ppb) and extracted onto Tenax using the indirect method. The resulting desorption profile is shown in Fig. 3. The top trace shows the total ion response, while the two lower traces show the m/z 139 fragment ion for DIMP and the m/z 61 fragment ion from CEES. Using this approach, DIMP was found to be consistently detected in beef homogenate, skim milk and whole milk at levels of 50 ppb. CEES was detected at the 50 ppb level in beef homogenates and at slightly higher levels, 100 ppb, in milk.

Even using these small sample sizes (100 mg) and low simulant concentrations (50–100 ppb), no significant interferences due to the sample matrices were observed. Overall recovery (extraction and thermal desorption) for DIMP from Tenax has been in the 20–50% range irrespective of whether beef homogenate, milk, or aqueous samples are analyzed. For CEES, the recoveries were lower and more variable, probably owing to the fact that it is more water soluble, more reactive and more volatile than DIMP. In none of the studies to date, however, have internal standards been employed to account for sample recovery in the extraction and

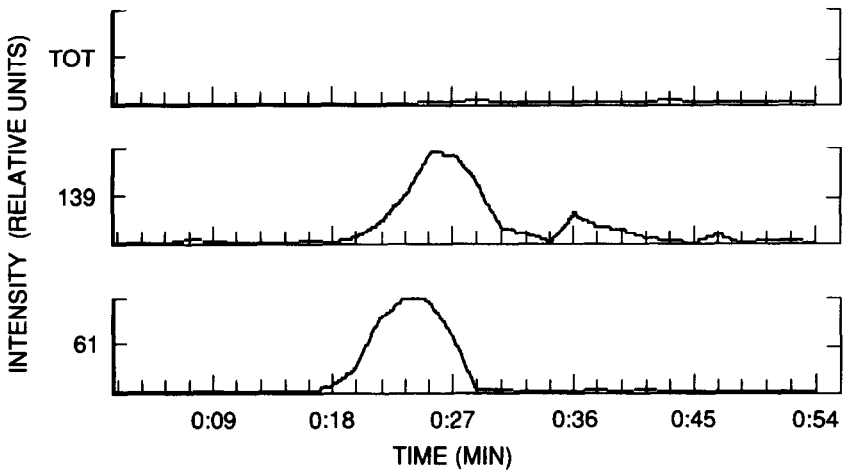

Fig. 3. Thermal desorption profile of 50 ppb of both DIMP and CEES spiked into beef homogenate and extracted onto Tenax. Ion at m/z 139 is indicative of DIMP and that at m/z 61 is indicative of CEES. Note good signal-to-noise ratios even at 50 ppb.

thermal desorption steps. This could greatly enhance the ultimate detection limits achievable with this analytical method, as well as improve the overall accuracy and precision of the method.

4. Conclusions

The use of TD ITMS for the sensitive detection of DIMP and CEES in beef tissue and milk has been demonstrated, with detection limits in the 50–100 ppb range. Because such small initial sample sizes are required to reach these detection limits, it is possible that this approach might be applicable to samples harvested by needle biopsy. This would allow livestock to be tested without sacrifice. Further, because the analyses could be performed more quickly than other more conventional approaches (such as extraction into a suitable solvent, concentration, and then analysis by combined gas chromatography/mass spectrometry) more samples could be analyzed to provide greater safety to the public. Several experiments remain to take these demonstrated techniques and develop them into validated analytical methods. First, for optimum quantification, internal standards must be used to account for sample extraction recovery and thermal desorption efficiency. The best standards would be stable-isotope labelled analogs of the materials (e.g., deuterated analogs of DIMP and CEES, which are not commercially available). It is possible when analyzing the actual agents that the simulants used in these studies could be employed as internal standards. Secondly, in these studies, only spiked tissue and milk samples were used, not actual samples from animals contaminated with the target compounds. Dosed animal studies would need to be conducted to assess the efficacy of the developed methodologies with these types of samples and to ascertain whether analytes incorporated intracellularly would be recovered using this technique.

It should be noted that the TD ITMS methods presented in this report have considerable potential for application to other situations where rapid, confident detection of targeted compounds is required. As mentioned earlier, TD ITMS techniques are being developed in our laboratory for the rapid detection of drugs and metabolites in urine and other physiological matrices and for the detection of toxic compounds in foods. For example, the sensitivity of the TD ITMS technique and the elimination of sample preparation steps have permitted urine samples as small as 1 μl have been analyzed for low part per billion levels of drugs. This has an added advantage of greatly reducing the exposure of the analyst to chemical and biological hazards. Further, the sensitivity of TD ITMS may make it possible to employ TD ITMS for monitoring drug metabolism in a single animal. Finally, reducing the time for analysis also results in reducing sample turn-around time and analytical costs when TD ITMS methods are employed.

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