Application Note: 52146

High-Throughput Food Safety Control Employing Real Time Ionization (DART) Coupled to Orbitrap High-Resolution Mass Spectrometry

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Key Words
- Exactive
- DART
- Melamine
- Mycotoxins

Introduction

In recent years, substantial developments have taken place in the field of mass spectrometry, enabling the introduction of a number of novel ambient desorption ionization techniques[1] such as direct analysis in real time (DART®),[2] desorption electrospray ionization (DESI),[3] surface desorption atmospheric pressure chemical ionization (DAPCI)[4] and atmospheric solids analysis probe (ASAP™).[5] These novel ion sources are characterized by remarkably high throughput of analyses which can be carried out under ambient conditions without (chromatographic) separation of sample components prior to desorption/ionization or the need for complicated and time demanding sample pre-treatment procedures. The DART technology employed in this study relies upon fundamental principles of atmospheric pressure chemical ionization (APCI). Excited-state helium atoms produce reactive species for analyte ionization.[2] Numerous applications of the DART ion source coupled to various types of mass spectrometers have been reported.[6-16] DART found its use in many areas of analytical chemistry as a tool for rapid qualitative analysis of numerous compounds. Due to the relatively high signal fluctuation of ion intensities obtained by repeated DART measurements, an internal standard usually has to be employed for compensation during quantitative analysis. However, implementation of Vapur® gas ion separator and automatic sampling systems were reported to significantly improve the repeatability for some analytes.[15]

Due to the absence of separation, the whole sample is introduced into a mass spectrometer. This unavoidably leads to a significant number of spectral interferences. In order to correctly determine the masses of relevant compounds and potential unknowns in the case of fingerprinting analysis, it is essential to separate them from the matrix ions. A mass spectrometer based on Orbitrap technology routinely achieves the mass resolving power of up to 100,000 FWHM (full width half maximum) while maintaining excellent mass accuracy of < 5 ppm, without the use of internal mass correction.[17] Those features make it an ideal tool to complement DART ionization for the analysis of complex samples.

This application note shows the possibilities using the DART ion source coupled with the ultra high-resolution Thermo Scientific Exactive mass spectrometer for rapid detection and quantitation of a wide range of food contamin - ants like mycotoxins and food adulterants (melamine).

Experimental

DART-Exactive MS

DART-Exactive MS system used in this study consisted of a new commercial model of DART ion source (DART-SVP) with a 12 Dip-It™ tip scanner autosampler coupled to the Exactive™ benchtop mass spectrometer – see Figure 1. Vapur interface was employed to hyphenate the ion source and the mass spectrometer, low vacuum in the interface chamber

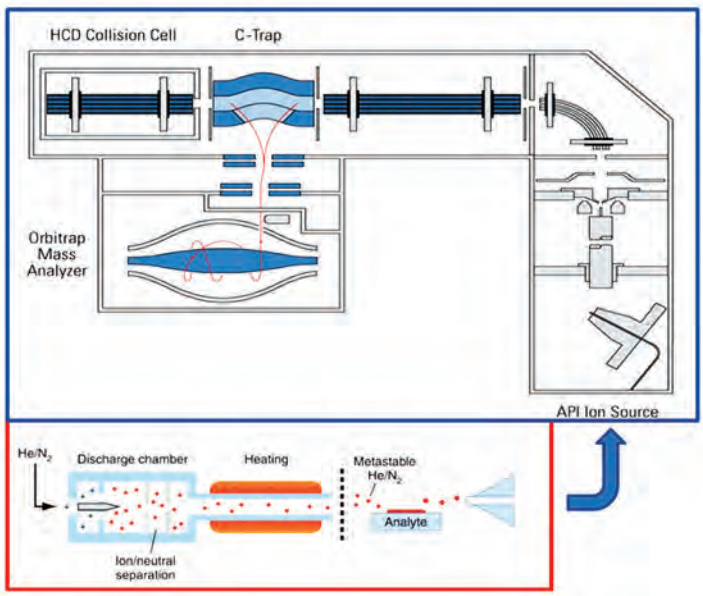

Figure 1: Schematics of a DART-Exactive system (source: *www.ionsense.com*). DART ionization source (bottom), Exactive MS (top).

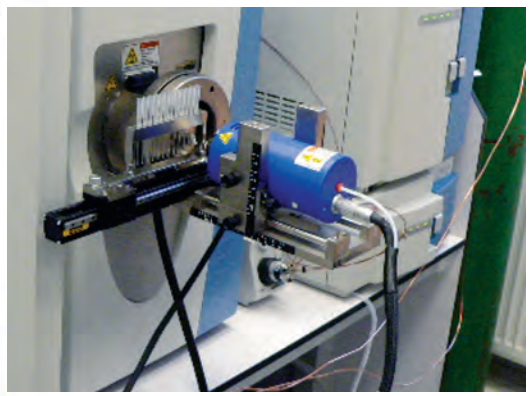

Figure 2: The DART ionization source coupled to Exactive MS

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was maintained by a membrane pump (Vacuubrand, Wertheim, Germany). The use of Vapur gas ion separator during DART ionization was essential in order to maintain stable vacuum within the operating pressure limits of the Exactive instrument. Vapur interface also improved transport efficiency of ions from the sampling area to the atmospheric-pressure interface inlet of the mass spectrometer, thus enhancing both sensitivity and reproducibility of the measurement. The distance between the exit of the DART gun and the ceramic transfer tube of the Vapur was set to 10 mm, the gap between the ceramic tube and the inlet to the heated capillary of the Exactive was 2 mm.

DART-MS instrument was operated either in positive or negative ionization mode; optimized settings of the system parameters were as follows: *(i)* DART positive ionization: helium flow: 2.5 L min^{-1}; gas temperature: 350 °C; discharge needle voltage: -5000 V; grid electrode: +200 V. *(ii)* DART ionization negative ionization: helium flow: 2.5 L min^{-1}; gas temperature: 350 °C; discharge needle voltage: -5000 V; grid electrode: +350 V. *(iii)* Mass spectrometric detection: capillary voltage: ±55 V; tube lens voltage: ±130 V; capillary temperature: 250 °C. Sheath, auxiliary and sweep gases were disabled during DART-MS analysis. The acquisition rate was set according to desired resolving power of the Exactive mass analyzer, and was 10 spectra s^{-1} at 10,000 FWHM (full width at half maximum), 4 spectra s^{-1} at 25,000 FWHM and 2 spectra s^{-1} at 50,000 FWHM. In all cases, the mass resolving power was calculated for *m/z* 200.

Semi-automatic analysis of liquid samples was carried out with the use of 12 Dip-It tip scanner autosampler. Dip-It tips were inserted into a holder and immersed in sample extracts placed in deepwell micro-plate (Life Systems Design, Merenschwand, Switzerland). The holder was mounted on the body of the autosampler. Subsequently, the Dip-It tips automatically moved at a constant speed of 0.5 mm s^{-1} through the helium gas beam in perpendicular direction to the axis leading from DART gun exit to the mass spectrometers inlet. Using the above moving speed, the time of desorption from the surface of each tip was 9 s; total run time of 12 analyses was approx. 4.2 min. To enable and/or enhance ionization of certain analytes, 2 mL autosampler vial containing dopant solution was placed in the distance of 20 mm from the DART gun exit. Aqueous solution of ammonia (25%, *w/w*, Penta, Chrudim, Czech Republic) and neat dichloromethane (Scharlau, Barcelona, Spain) were used as dopants in positive and negative ionization mode, respectively.

Mycotoxin Analysis

Chemicals and standards

Standards of 3-acetyldeoxynivalenol (3-ADON), deoxynivalenol (DON), deoxynivalenol-3-glucoside (DON-3-Glc), fusarenon-X (FUS-X), nivalenol (NIV), HT-2 toxin (HT-2), T-2 toxin (T-2), diacetoxyscirpenol (DAS), aflatoxin B1 (AFB1), aflatoxin B2 (AFB2), aflatoxin G1 (AFG1), aflatoxin B2 (AFG2), ochratoxin A (OTA), fumonisin B1 (FB1), fumonisin B2 (FB2), sterigmatocystin, zearalenone (ZEA), $^{13}C_{15}$-deoxynivalenol ($^{13}C_{15}$-DON), $^{13}C_{15}$-nivalenol ($^{13}C_{15}$-NIV) and $^{13}C_{18}$-zearalenone ($^{13}C_{18}$-ZEA) were supplied by Biopure (Tulln, Austria). Standards of deepoxy-deoxynivalenol (deepoxy-DON), altenuene, alternariol, alternariolmethylether (alternariol-met), ergocornine, ergocrystine and ergosine were obtained from Sigma-Aldrich (Steinheim, Germany).

Composite standard was prepared in acetonitrile containing each of analytes (isotope-labeled compounds not included) at concentration level of 5000 ng mL^{-1} and further diluted to obtain solvent standards at 500 ng mL^{-1}. Individual solvent solutions of ^{13}C-labeled internal standards were prepared at 5000 µg mL^{-1} in acetonitrile. Matrix-matched standards in the concentration range 10 to 1000 ng mL^{-1} (corresponding to 50 to 5000 µg kg^{-1} in matrix) were obtained by spiking of blank wheat and maize extracts (prepared by procedures described below), additionally, isotopically labelled compounds were added at level 100 ng mL^{-1} (500 µg kg^{-1} in matrix).

Acetonitrile and methanol, both of HPLC-grade, were supplied by Merck (Darmstadt, Germany). Pure water was obtained from Milli-Q® purification system. Anhydrous magnesium sulphate, sodium chloride and ammonium formate (≥ 99% purity), were from Sigma-Aldrich. Primary secondary amine (PSA) sorbent was obtained from Varian (Harbor City, CA, USA), formic acid (≥ 98% purity) was from AppliChem GmbH (Darmstadt, Germany).

Samples and sample preparation

Modified QuEChERS procedure[18] was employed to extract target analytes from the examined matrices (wheat, maize and millet). 2 g of homogenized sample were weighed into a 50 mL polypropylene (PP) centrifuge tube, 7.5 mL of deionized water and 10 mL of acetonitrile were added. Vigorous shaking of the mixture (4 min) was followed by the addition of 4 g $MgSO_4$, 1 g NaCl, further shaking for 3 min and centrifugation (5 min, 10,000 rpm, 20 °C). 4 mL aliquot of the upper organic phase was transferred into a 15 mL PP tube containing 200 mg of PSA and 600 mg $MgSO_4$ and shaken for 3 min to perform solid phase extraction (SPE) clean-up of the extract. After centrifugation (3 min, 10,000 rpm, 20 °C), approx. 600 µL were taken for DART-Exactive MS analysis.

Analysis of Melamine

Chemicals and standards

Solid standard of melamine (MEL, ≥ 99.0%) was supplied by Sigma-Aldrich; isotopically labeled $^{13}C_3$-melamine ($^{13}C_3$-MEL, ≥ 98.0%) was from Witega (Berlin, Germany). Individual stock solutions of MEL and $^{13}C_3$-MEL were prepared at 1000 µg mL^{-1} in water. By further dilution, aqueous solutions at 100 and 10 µg mL^{-1} were obtained and used for preparation of matrix matched standards and spiking experiments. Matrix-matched calibration was prepared by spiking of blank raw milk, standards containing MEL in the range from 25 to 2500 ppb and fixed amount of $^{13}C_3$-MEL at 250 ppb were obtained this way. Water used in this study was purified with the use of Milli-Q purification system.

Samples and sample preparation

Raw milk samples were analyzed without any pre-treatment. Prior to DART-MS analyses, blank milk was spiked with MEL at 100 and 500 ppb and with $^{13}C_3$-MEL at 250 ppb. Additionally real-life samples (n = 2) representing contaminated powdered milk were, according to producers instructions, reconstituted in water (1:10, *w/v*), spiked with $^{13}C_3$-MEL and subjected to instrumental analysis.

Results and Discussion

DART-Exactive Analysis of Mycotoxins

The efficiency and practical applicability of DART technology for ionization of aflatoxins, fusarium toxins, alternaria toxins, ochratoxins, ergot alkaloids, and sterigmatocystin (analytes possessing relatively largely differing physico-chemical properties) was evaluated in this part of the study. For this purpose, solvent standards containing respective mycotoxin at level 500 ng mL^{-1} were analyzed. Various settings (100 – 400 °C) of ionization gas temperature and grid electrode voltage were tested in order to obtain best sensitivity and best efficiency of analyte's thermo-desorption. As shown below, most mycotoxins could be transferred into gaseous phase at temperature 350 °C which was found as an optimal compromise between signal intensity and analytes' thermal desorption speed. While the use of lower grid voltage (200 V) in positive ionization mode enabled approx. 50% intensity increase compared to 350 V setting, 350 V potential was optimal for analytes ionized in negative mode. It was also found that ionization of some mycotoxins is improved by introducing dopant vapours (dichloromethane or ammonia) into the region between the ion source exit and Vapur interface ceramic tube inlet.

The list of ions generated by DART, when analyzing mycotoxin standard solutions, is provided in Table 1. As it can be seen, most of the examined mycotoxins could be effectively ionized in positive or negative ion mode, either as pseudomolecular ions or forming charged adducts supposing dichloromethane or ammonia vapors were present in the ionization region. Relatively poor ionization efficiencies were obtained for aflatoxins where electrospray ionization (ESI)[19, 20] was documented to be option for their control at ultra trace levels which are of regulatory interest.

				Detected Ions		
Compound	**Elemental Formula**	**Exact MW**	**Ionization Mode**	**Ion**	**Elemental Composition**	**Exact Mass**
ADON	$C_{17}H_{22}O_7$	338.1360	Negative	$[M+Cl]^-$	$C_{17}H_{22}O_7Cl$	373.1049
DON	$C_{15}H_{20}O_6$	296,1254	Negative	$[M+Cl]^-$	$C_{15}H_{20}O_6Cl$	331.0943
Deepoxy-DON	$C_{15}H_{20}O_5$	280,1305	Negative	$[M+Cl]^-$	$C_{15}H_{20}O_5Cl$	315.0993
FUS-X	$C_{17}H_{22}O_8$	354,1309	Negative	$[M+Cl]^-$	$C_{17}H_{22}O_8Cl$	389.0998
NIV	$C_{15}H_{20}O_7$	312,1204	Negative	$[M+Cl]^-$	$C_{15}H_{20}O_7Cl$	347.0903
ZEA	$C_{18}H_{22}O_5$	318,1462	Negative	$[M-H]^-$	$C_{18}H_{21}O_5$	317.1394
				$[M+Cl]^-$	$C_{18}H_{22}O_5Cl$	353.1150
HT-2	$C_{22}H_{32}O_8$	424,2092	Positive	$[M+NH_4]^+$	$C_{22}H_{36}NO_8$	442.2435
T-2	$C_{24}H_{34}O_9$	466,2197	Positive	$[M+NH_4]^+$	$C_{24}H_{38}NO_9$	484.2541
DAS	$C_{19}H_{26}O_7$	366,1673	Positive	$[M+H]^+$	$C_{19}H_{27}O_7$	367.1750
				$[M+NH_4]^+$	$C_{19}H_{30}NO_7$	384.2017
Altenuene	$C_{15}H_{16}O_6$	292,0941	Negative	$[M-H]^-$	$C_{15}H_{15}O_6$	291.0874
				$[M+Cl]^-$	$C_{15}H_{16}O_6Cl$	327.0630
Alternariol	$C_{14}H_{10}O_5$	258,0523	Negative	$[M-H]^-$	$C_{14}H_9O_5$	257.0455
				$[M+Cl]^-$	$C_{14}H_{10}O_5Cl$	293.0211
Alternariol-met	$C_{15}H_{12}O_5$	272,0679	Negative	$[M-H]^-$	$C_{15}H_{11}O_5$	271.0612
				$[M+Cl]^-$	$C_{15}H_{12}O_5Cl$	307.0368
AFB1	$C_{17}H_{12}O_6$	312,0628	Positive	$[M+H]^+$	$C_{17}H_{13}O_6$	313.0712
AFB2	$C_{17}H_{14}O_6$	314,0785	Positive	$[M+H]^+$	$C_{17}H15O_6$	315.0868
AFG1	$C_{17}H_{12}O_7$	328,0578	Positive	$[M+H]^+$	$C_{17}H_{13}O_7$	329.0661
AFG2	$C_{17}H_{14}O_7$	330,0734	Positive	$[M+H]^+$	$C_{17}H_{15}O_7$	331.0712
Sterigmatocystin	$C_{18}H_{12}O_6$	324,0628	Positive	$[M+H]^+$	$C_{18}H_{13}O_6$	325.0707
OTA	$C_{20}H_{18}ClNO_6$	403,0817	n.d.	n.d.	–	–
FB1	$C_{34}H_{59}NO_{15}$	721,3879	n.d.	n.d.	–	–
FB2	$C_{34}H_{59}NO_{14}$	705,3930	n.d.	n.d.	–	–
Ergocornine	$C_{31}H_{39}N_5O_5$	561,2946	n.d.	n.d.	–	–
Ergocristine	$C_{39}H_{39}N_5O_5$	657,2946	n.d.	n.d.	–	–
Ergosine	$C_{30}H_{37}N_5O_5$	547,2789	n.d.	n.d.	–	–

n.d. - signal not detected

Table 1: Overview of most intensive mycotoxins ions detected under optimized DART-Exactive MS conditions in solvent standard (500 ng mL^{-1})

Material Description	Analyte (Assigned/Certified Value)	DART-Exactive MS External Calibration/Isotope Dilution	
		Mean (µg kg^{-1})	RSD (%)[a]
CRM, maize flour	DON (474 ± 30 µg kg^{-1})	459/486	9.0/5.9
CRM, wheat flour	DON (2800 ± 200 µg kg^{-1})	2608/2819	6.7/5.4
CRM, ground millet	ZEA (648 ± 140 µg kg^{-1})	583/613	7.5/6.0
CRM, maize flour	ZEA (60 ± 9 µg kg^{-1})	< LCL[b]	– / –

a Relative standard deviation (RSD) calculated from 3 analyses.
b The concentration of analyte was below LCL of the method.

Table 2: Trueness of data obtained by DART-Exactive MS analysis of certified reference materials

No ions were obtained under tested conditions for a few other mycotoxins, such as ochratoxin A, fumonisins or ergocornine, ergocrystine and ergosine. These compounds are rather polar, and especially in case of fumonisins and ergot alkaloids, have relatively high molecular weight (MW). Both of these properties are associated with low volatility that hampers the transfer of such analytes into gaseous phase. To facilitate and/or enhance DART ionization of troublesome mycotoxins, derivatization of polar functional groups, which enables avoiding hydrogen bonding, may represent a conceivable strategy.[21]

Quantitative Analysis

For quantitative purposes, the most abundant ions yielded by respective mycotoxins (see Table 1) were used and narrow isolation window of 4 ppm was employed to extract ion records (chronograms) of target analytes with high selectivity. The quantitative parameters of the method for DON and ZEA, demonstrated by analysis of available certified reference materials containing incurred *Fusarium* toxins, are presented in Table 2. For evaluation of repeatability, peak areas were preferred since they were shown to give better results compared to calculations based on peak heights. Typical RSDs for cereals spiked by mycotoxins at 500 µg mL^{-1} level ranged from 8.1 to 14.3%. Further decrease of RSDs (4.7–8.7%) and improved linearity of calibration plots compared to external calibration, was obtained when isotopically labelled internal standards were employed for compensation of absolute signal fluctuation. In case of regulated mycotoxins (DON, ZEA) DART-MS method lowest calibration levels allowed a reliable control of maximum limits established for tested matrices.[22] The recoveries of all target mycotoxins at both tested spiking levels 150 and 500 µg kg^{-1} were in the range 82–120% when external calibration based on matrix matched standards was employed for quantification. Regarding the requirements for performance characteristics in analysis of regulated analytes,[23] these were reliably met for both target toxins.

Melamine Analysis

Under experimental conditions, both MEL and $^{13}C_3$-MEL were detected as $[M+H]^+$ ions in positive DART ionization mode. The efficiency of ionization was comparable for both compounds. Very good mass accuracy, with mass error less than 3 ppm was achievable with Exactive mass analyzer (operated under mass resolving power setting 50,000 FWHM) within all measurements in this study; analyte confirmation based on elemental composition estimation could be performed. As shown in Figure 3, abundant spectral interference observed at *m/z* 127.04 was detected both in blank and spiked samples (in contrast to solvent standards). At mass resolving power ~3,500 FWHM obtained by time-of-flight mass analyzer it was not possible to resolve signals of analyte and interference. Especially at low concentration levels of MEL, the signal of analyte was completely overlapped by the interference making its detection impossible. On the other hand, employing high mass resolving power of DART-Exactive MS, reliable detection of MEL in milk, was feasible even at low concentration levels. Using

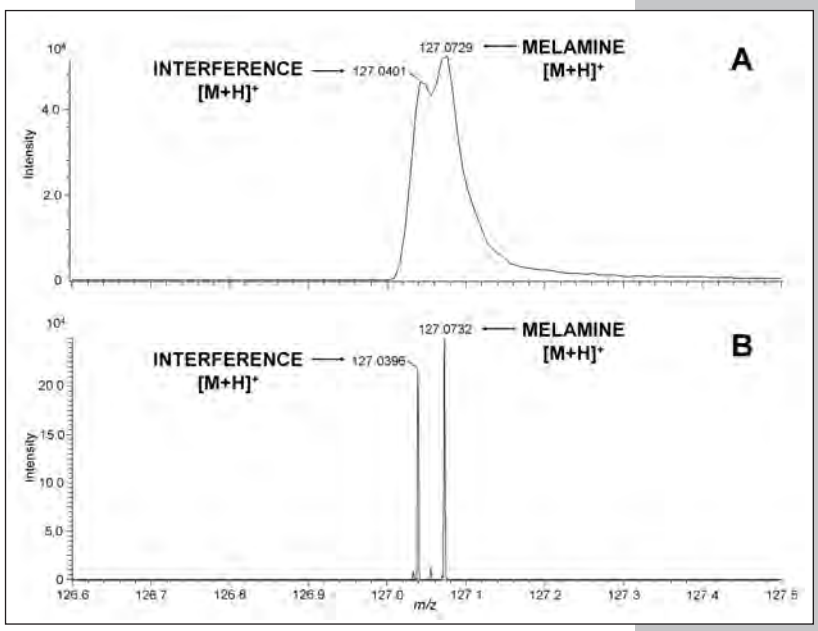

Figure 3: The improvement of mass separation by applying high mass resolution during analysis of melamine in milk sample at 2.5 mg/kg.
(A) DART-TOFMS (mass resolving power 3,500 FWHM);
(B) DART-Exactive MS (mass resolving mass power 50,000 FWHM).

Sample	DART-Exactive MS		LC-MS/MS	
	Mean (ppb)	RSD (%)	Mean (ppb)	RSD (%)
Milk powder 1	501	8.2	530	5.1
Milk powder 1	2496	6.4	2612	2.1

Table 3: Concentration of MEL in real-life samples as measured by DART-Exactive MS and LC-MS/MS

accurate mass of interference ion, elemental composition $C_6H_7O_3$ was estimated. This value corresponds to protonated molecule of hydroxymethyl furfural (HMF) which is typically formed during thermal processing of sugars containing foods.

The detectability of the method was characterized as lowest calibration level (LCL). Generally used limit of detection could not be calculated due to absence of noise in obtained records. LCL for melamine in milk was 25 ppb. For quantification purpose, isotope dilution technique was used. Figure 4 shows record of calibration standards analysis of which can be completed within 4.2 min (duplicate of each standard), Figure 5 documents acceptable linearity obtained for calibration curve in the range 25 to 2500 ppb ($R^2 \geq 0.99$). The LCL for melamine in milk was determined at 25 ppb and recoveries calculated at 100 and 500 ppb were in the range 98–119% and 101–109%. Repeatability at 100 ppb (n = 5) was 7.2%.

The results of real life samples analyses were compared to those obtained by validated LC–MS/MS method. Good agreement between respective values was observed (see Table 3).

Conclusions

The results presented in this application note demonstrate the feasibility of DART ionization source in combination with Exactive mass spectrometer for the rapid detection and quantification of various food contaminants, including set of priority mycotoxins and melamine selected as an example. Comparable trueness of generated results was achieved by applying isotope dilution-based quantification and matrix-matched calibration to compensate for signal suppression and other matrix effects that unavoidably occur during direct analysis of real matrix samples.

The major advantages of the combination of ambient ionization technique with Exactive mass spectrometry are the simplicity of operation, day-to-day robustness and broad application range. In addition, ultra high-resolution provided by Exactive mass analyzer helps to solve some of the problems caused by isobaric interferences from matrix components. The choice of ultra high-resolution mass spectrometer such as Exactive is one of the key requirements when considering the application of DART ionization as a reliable tool in the food laboratory.

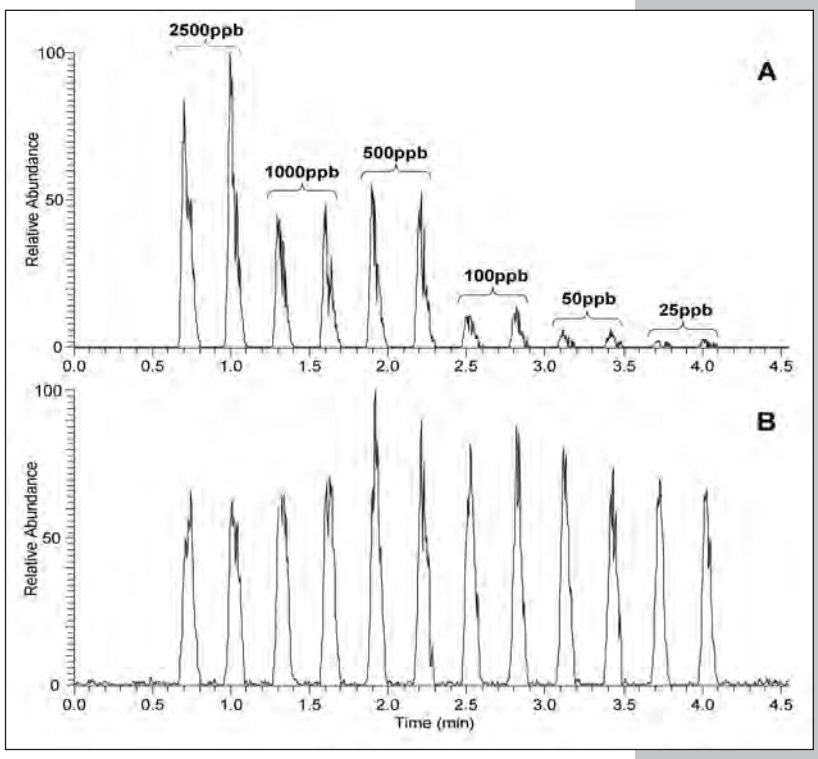

Figure 4: DART-Exactive MS record of milk spiked with MEL in the range 25 to 2500 ppb. (A) MEL (m/z 127.0726 ± 3 ppm); (B) $^{13}C_3$-MEL (m/z 130.0827 ± 3 ppm).

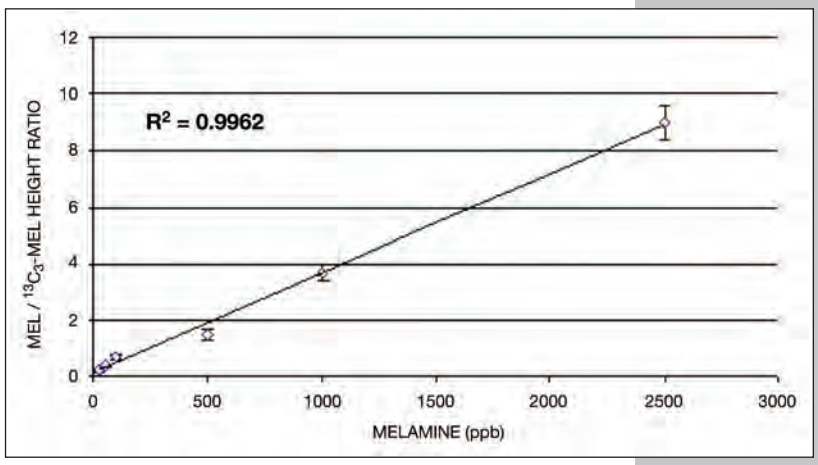

Figure 5: Calibration curve of melamine obtained by DART-Exactive MS analysis of matrix-matched standards constructed by plotting analyte-to-internal standard peak height ratio. Error bars are standard deviation (n = 3).

Acknowledgements

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