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Low-Level Quantification of NDMA and Non-Targeted Contaminants Screening in Drinking Water Using GC-Orbitrap MS

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ABSTRACT

N-nitrosodimethylamine (NDMA) is an emerging drinking water contaminant known to induce tumors following administration by either ingestion or inhalation. NDMA is considered a priority pollutant and various countries around the world have already introduced maximum acceptable levels. Traditional analytical methodology used for NDMA detection and quantification are often lacking enough selectivity and sensitivity and lead to false positive detection and erroneous quantification of NDMA. This is due to poor selectivity through insufficient resolving power of such instrumentation. The Thermo Scientific™ Exactive™ GC Orbitrap™ mass spectrometer was evaluated for NDMA sensitivity, mass accuracy, repeatability, and linearity of response. Moreover, additional contaminants were detected and identified in the drinking water samples without the need for separate sample injections or complicated experimental setup.

INTRODUCTON

N-nitrosodimethylamine (NDMA) is a semivolatile organic compound that belongs to nitrosamines, an emerging class of drinking water contaminants. NDMA is the main nitrosamine of concern and is classified as a potent carcinogen by the U.S. Environmental Protection Agency as it is known to induce tumors following administration by either ingestion or inhalation.[1] NDMA is formed as a by-product during industrial processes such as chloramination of wastewater and drinking water.[2] NDMA is considered a priority pollutant and various countries around the world have already introduced maximum acceptable concentrations of 9 ng/L[6] and action levels of 10 ng/L.[7] It is particularly important that NDMA is detected and accurately quantified in drinking water as even low levels of this chemical (e.g., 10 ng/L) can pose human cancer risks, being especially toxic to the liver.[1]
Traditionally, the analytical methodology used for NDMA detection and quantification employs single or triple quadrupole gas chromatography mass spectrometry (GC-MS), or magnetic sectors and high-resolution time-of-flight mass spectrometers. With these analytical instruments it is difficult to obtain high selectivity and high sensitivity at the same time. Reduced selectivity can lead to interferences with the matrix and background chemical ions and can result in false positive detection and erroneous quantification of NDMA.[8] This is due to poor selectivity through insufficient resolving power of such instrumentation. In this work, a sensitive and selective method for NDMA detection and quantification using high-resolution, accurate-mass GC Orbitrap™ technology is described. Test samples were subjected to GC-MS analysis using an Exactive GC Orbitrap mass spectrometer and the quantitative performance of this novel analytical platform was evaluated for sensitivity, mass accuracy, repeatability, and linearity of response. In addition to targeted quantification of NDMA, acquiring the data using full-scan high-resolution mode allowed for additional contaminants screening and identification in the drinking water samples without the need for separate sample injections or complicated experimental setup.

MATERIALS AND METHODS

The solvent standards were prepared in dichloromethane and were spiked with native NDMA in DCM in a similar manner as for real water samples. The final concentration levels in the standards were: 0.1, 1.0, 10, and 100 µg/L (ppb). Each solvent standard was spiked with 20 µg/L deuterated NDMA in DCM, which was used as internal standard. In addition to these calibration standards, a procedural blank was used. Validation of the results was done using three drinking water samples collected in duplicate from the local ICRA facility and spiked with native NDMA prior to SPE extraction at three concentration levels: 0.96, 4.8, and 9.6 ng/L. A drinking water sample that was not spiked with NDMA was used as a matrix blank. Samples were analyzed using an Exactive GC Orbitrap instrument. Details of the analytical conditions are given in Table 1.

Data was acquired and processed using the Thermo Scientific™ TraceFinder™ software application, which allows for easy set-up and complete quantitative and qualitative analysis workflows. This includes peak integration, calculation of compound concentration and recoveries as well as easy data review and reporting. In addition, for qualitative analysis, TraceFinder automatically generates clean mass spectra following automated peak deconvolution and, compound identification (by searching a custom made, NIST compatible accurate mass library and commercially available spectral libraries).

Table 1. Gas chromatography and mass spectrometers analytical parameters.

TRACE 1310 GC Parameters	
Injection Volume(µL):	2.0
Liner	Single gooseneck (P/N:4530924-UI)
Inlet (°C):	220
Inlet Module and Mode:	Surged Splitless
Surge pressure (kPa)	385
Surge duration (min)	1.0
Oven Temperature Program:	
Temperature 1 (°C):	35
Hold Time (min):	1
Temperature 2 (°C):	130
Rate (°C/min)	25
Temperature 3 (°C):	230
Rate (°C/min)	125
Hold Time (min):	6

Exactive parameters	
Transfer line (°C):	260
Ionization type:	EI
Ion source(°C):	230
Electron energy (eV):	70
Acquisition Mode:	full scan
Mass range (*m/z*):	50-650
Mass resolution (FWHM at *m/z* 200):	60,000
Lockmass (*m/z*):	207.03235

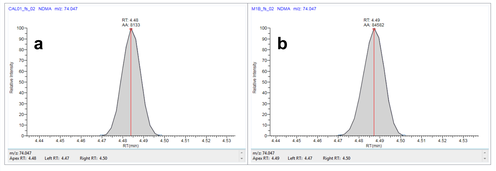
RESULTS

The objective of the analysis was to assess the use of GC Orbitrap technology for the analysis of NDMA in drinking water samples at a very low concentration level and for a broad scope non-targeted screening of the samples for the detection and identification of additional contaminants. NDMA chromatography, sensitivity, linearity, and peak area repeatability were evaluated using solvent based standards. This was followed by validation of the method using drinking water samples that were spiked with NDMA at low levels prior to SPE extraction and concentration. In addition to NDMA quantification, the water samples were also screened, using a non-targeted approach, for the presence of additional chemical contaminants. Putative identifications based on NIST library matches, fragment ion rationalization, and accurate mass information were made.[4]

Chromatography and Resolution

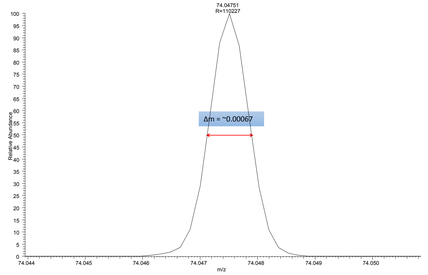
Using the GC conditions stated in Table 1, fast GC separation (total GC run time 11 min), with good chromatographic separation was obtained, allowing for a high sample throughput. An example of chromatography for NDMA in the lowest calibration solvent standard (0.1 µg/L) and in the lowest level spiked drinking water sample (0.96 ng/L) is shown in Figure 1.

Figure 1. Extracted ion chromatogram (XIC, EI at 70 eV) of the *m/z* 74.04747 corresponding to NDMA molecular ion at 0.1 µg/L in the lowest calibration solvent standard (A) and at 1.0 ng/L in a drinking water sample (B). The absolute amount on column is shown as pg of NDMA on column.



Accurate detection of the NDMA molecular ion (*m/z* 74.04747) can be affected by background ions. In all experiments, the instrument resolving power was set to 60,000 (FWHM at *m/z* 200) and this corresponded to a mass resolution of >100,000 when measured at *m/z* 74, sufficient to achieve selective detection of NDMA target ions in matrix (Figure 2).

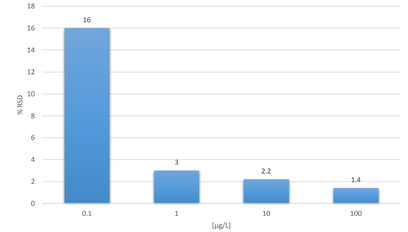
Figure 2. NDMA in a drinking water sample showing a mass resolution R > 110,000 (FWHM) measured at *m/z* 74.04747. Data acquired in full-scan using electron ionization at 70 eV.



Estimated Instrument Detection Limit (IDL) and Peak Area Repeatability

System sensitivity was assessed by calculating the minimum quantifiable limit or the instrument detection limit (IDL) for NDMA. This was done by using the peak area %RSD derived from n=9 repeat injections of the lowest calibration standard 0.1 µg/L and taking into account the Student's *t* distribution critical values for the corresponding degrees of freedom (at 99% confidence). The results of this experiment showed that the IDL derived from the Exactive GC system data was 0.09 µg/L, a value similar to the lowest calibration standard detectable. For reliable quantification, robust instrumental response is important, and this was demonstrated by assessing the peak area repeatability of the NDMA quantification ion (*m/z* 74.04747). To achieve this, each solvent standard was injected five times except for the 1.0 µg/L standard, which was injected nine times. Absolute peak area repeatability was evaluated by looking at %RSD at each concentration level and the results obtained are shown in Figure 3.

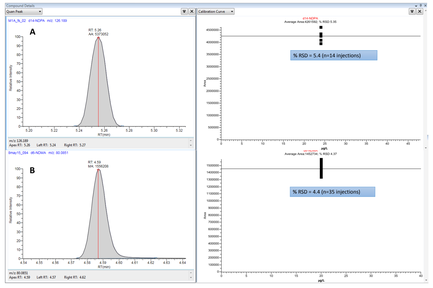
Figure 3. Absolute peak area repeatability of NDMA at various concentration levels (n=5 for 0.1, 10, and 100 µg/L and n=9 for 1.0 µg/L). The average %RSD values at each level are indicated above each bar.



** n=5 injections per calibration standard were used except 1.0 µg/L level; where n=9 inj. were used*

Excellent peak area repeatability was demonstrated using the two batches of samples. For the experiment using solvent standards, across a total number of injections of n=35 the %RSD calculated from the peak area response of the d6-NDMA internal standard was < 4.5%, whereas the %RSD peak area response of the d14-NDPA across n=14 injections (including water samples) was ~5% (Figure 4).

Figure 4. Peak area repeatability (as %RSD) demonstrated for two internal standards corresponding to two different experimental batches: d14-NDPA internal standard across n=14 injections (A), and d6-NDMA internal standard across n= 35 injections (B).



Mass Accuracy and Linearity of Response

Excellent linearity and mass accuracy for NDMA *m/z* 74.04747 was always < 1 ppm at low and high levels in both solvent standards and in extracted drinking water samples (Figures 5 and 6, Table 2).

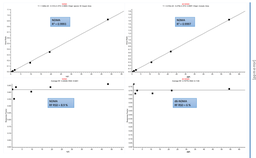


Figure 5. Linearity of NDMA (left) and d6-NDMA (right) internal standard corrected with d14-NDPA over a 7-point calibration curve (0.1-50 µg/L) showing the corresponding %RSD RF <9% for NDMA and 6% for the d6-NDMA surrogate.

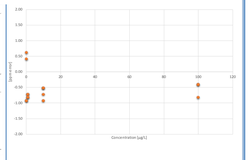


Figure 6. Mass accuracy measurements for NDMA *m/z* 74.04747. Concentration levels (µg/L, X-axis) as well as the corresponding mass error (ppm, Y-axis) are shown. Each dot represents a separate injection.

Quantification of NDMA in Drinking Water Samples

Calculated NDMA concentrations in the drinking water samples show good accuracy of the method (Table 2). Surrogate d6-NDMA recovery was monitored throughout the entire sample sequence with the recovery values obtained in very good agreement with EPA Method 521, which requires that surrogate recovery should be within 70–130% (Table 4). Overall, these results indicate that the Exactive GC mass spectrometer delivers excellent results and is highly suitable for routine laboratory use.

Table 2. Quantification results in drinking water

Sample	% recovery d6-NDMA	Calculated NDMA concentration (ng/L)	Mass error [ppm]
M1A	107	1.1	0.7
M1B	105	0.96	0.01
M5A	111	4.7	0.01
M5B	104	4.3	0.01
M10a	88	8.4	0.2
M10b	99	8.1	0.1

Non-Targeted Screening of Drinking Water Samples for Additional Contaminants

A significant advantage of Exactive GC technology is that, due to its full-scan, high-resolution mode of operation, the analyst can screen the raw data used for the quantitation experiment for additional, potentially harmful chemical contaminants. This was demonstrated in this work using the data acquired from the drinking water samples, which was subjected to a non-targeted screening workflow with TraceFinder software. This resulted in the detection of 220 additional chemicals not present in the procedural DCM solvent blank. A detailed description of this workflow is described elsewhere.[4] An example of the TraceFinder software deconvolution browser is shown for tetrachloroethylene identified in the drinking water sample with an excellent library match (Figure 7).

Figure 7. TraceFinder software deconvolution browser highlighting tetrachloroethylene with the corresponding deconvoluted mass spectra, the total identification confidence score, NIST library match (forward SI) and accurate mass measurements for each of the measured ions.

CONCLUSIONS

- With the Exactive GC system in full-scan operation at 60,000 resolving power (FWHM at 200 m/z), NDMA was detected at the 0.1 µg/L level in the lowest calibration level, which, assuming 100% recovery, translates to an NDMA limit of detection (LOD) of 0.1 ng/L.
- In addition, NDMA was easily detected and accurately quantified at 1.0 ng/L in the drinking water samples with excellent recovery values.
- Full-scan acquisition enabled the detection and putative identification of additional harmful contaminants in the drinking water samples. Halogenic organic compounds were predominantly detected and their presence is most probably related to the disinfection processes that involves chloramination and chlorination reactions. Putative identifications require further confirmation using analytical standards.
- In addition to very high sensitivity, excellent linear response across 0.1–50 µg/L was observed for both NDMA (R^2 >0.999 and residuals <9 %RSD RF) and for its corresponding d6-NDMA surrogate (R^2 > 0.999 and residuals < 6 %RSD RF).
- Moreover, consistently low (sub ppm) mass deviation from the theoretical NDMA mass was observed at all concentration levels and in all analyzed samples.

Taken together, these results described demonstrate excellent quantitative and qualitative performance of the Exactive GC system for the analysis of trace levels of NDMA.

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TRADEMARKS/LICENSING

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