Low Level Determination of N-nitrosodimethylamine (NDMA) by Chemical Ionization GC/MS with Large Volume Injection

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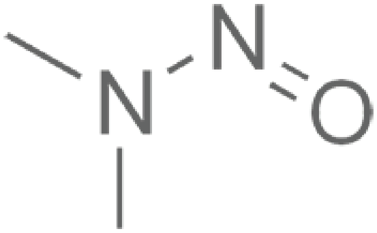


Abstract

Prior to 1976 NDMA was used as an additive in the production of liquid rocket fuel. Today it is primarily used as a research chemical. NDMA has been recognized as an emergent chemical of concern due to the U.S. Environmental Protection Agency's (EPA) classification as a probable human carcinogen. NDMA has been found to be a disinfection byproduct in water systems using chloramination and has also been detected in wastewater effluents. A method has been developed to detect NDMA at low part per trillion levels using a continuous extraction designed to minimize analytical interference. The extracts are subsequently analyzed using a large volume injector in conjunction with chemical ionization (CI) gas chromatography and mass spectroscopy (GC/MS) running in the selected ion monitoring mode (SIM), and quantified by isotope dilution techniques. The U.S. EPA has yet to set a Maximum Contaminant Level (MCL) while The California Department of Health Services (DHS) has established an action level of 10 ng/L.

Introduction

Traditional methods to detect low levels of NDMA have used modifications to EPA Method 1625 or Method 8270. These involve using standard extraction techniques of neutral or basic separatory funnel shakeouts or continuous liquid-liquid extractions. The sample extract is then analyzed by GC/MS with electron impact ionization (EI) and quantitated using an isotope dilution model1. While this approach can achieve reporting limits at a 2ng/L level, it pushes the limit of the analytical technique. Matrix and background interferences can lead to difficulty in quantification, low recovery and false positives. As the action levels for NDMA continue to drop, a more reliable and sensitive analytical method is needed.

Positive chemical ionization (PCI) using ammonia reagent gas is a soft ionization technique that increases both sensitivity and selectivity over electron impact ionization methods. Background interferences seen with EI are not ionized in this mode, producing a very clean background2. The primary reactions that yield the distinct NDMA spectrum are:

Ammonium ion is generated by

$$NH_{3\,(g)} + e^- \rightarrow NH_4{}^+{}_{(g)} + 2e^-$$

The ammonium ion is then available for the ion-molecule reaction with NDMA, where M is NDMA

1. $NH_4{}^+ + M \rightarrow NH_3 + [M+H]^+$
2. $NH_4{}^+ + M \rightarrow [M + NH_4{}^+]$

In the first process, a proton is transferred from the ammonium ion to the molecule to form a protonated molecule, while the second process involves the formation of an ammonium ion adduct.

This analytical method is designed for low level analysis of N-nitrosodimethylamine in water. Samples are extracted by EPA Method 3520C and then analyzed using large volume injection with GC/MS -SIM using positive chemical ionization. All quantitation is performed by isotope dilution against NDMA-d6. N-nitroso-di-n-propylamine-d14 is used as an internal standard to evaluate the recovery of NDMA-d6.

Materials & Methods

Reagents and Standards

- VWR OmniSolv Dichloromethane, Gas Chromatography/Residual Analysis grade
- NDMA at 5.0 mg/ml in methanol from Supelco
- NDMA at 5.0 mg/ml in methanol from AccuStandard
- NDMA-d6 at 1.0 mg/ml in methanol from Cambridge Isotope Laboratories, Inc.
- N-nitroso-di-n-propylamine-d14 at 1000 µg/ml from Cambridge Isotope Laboratories, Inc.

Calibration

- A calibration curve was prepared using a 0.2 µg/ml stock standard.
- Concentration levels were 0.5,1,2,10,20,50 and 100 ng/ml.
- NDMA was quanitiated using an isotope dilution model against NDMA-d6 at 50 ng/ml.
- N-nitroso-di-n-propylamine-d14 was added to each standard and sample at a concentration of 50 ng/ml as an internal standard.

Sample Preparation

- Samples extracted by EPA Method 3520C, continuous liquid-liquid extraction.
- Base side only at pH 11 shielded from light at all times.
- 1 L sample size
- Brought to a final volume of 2 ml in dichloromethane.
- Reagent water must undergo UV treatment prior to use.
- A Method Detection Limit (MDL) study was prepared by extracting eight replicates spiked with 100 µl of a 10 ng/ml NDMA standard.
- Two Lab Control Samples were prepared and spiked at a solution concentration of 20 ng/L.

Instrument Conditions

System Configuration

- Agilent 6890 gas chromatograph
- ATAS Optic 2 Programmable injector
- 5973 Mass Selective Detector (MSD)
- Chemical Ionization (CI) source
- 7683 Automatic Liquid Sampler (ALS) tray and autoinjector

Injector Parameters:

- ATAS Optic 2 Programmable Capillary Injector
- 20ul injection volume

Split State:

Time (Min)	Split State
Initial	Vent
0.40	Closed/Splitless
2.00	Open/Split
13.00	Vent

Temperature Profile:

Ramp	Rate(°C)	Final Temp(°C)	Isothermal Time (Min)
1	0	5	0.40
2	6	305	14.73
Initial temperature: 5°C			

Pressure Ramps:

Ramp	Start Pressure (PSI)	Step Time (Min)	Target (PSI)
1	5.00	0.40	5.00
2	20.00	1.6	20.00
3	9.08	2.00	9.08
4	9.08	12.00	33.70

GC/MS Run Conditions

Column:	Phenomenex ZB-5 (5% phenyl, 95% dimethyl polysiloxane)
Length:	30m
Diameter:	0.25mm
Film Thickness:	0.25µm
Oven:	Agilent 6890 45°C initial temp for 4.0min 25°C/min to 145°C for 0.0min 35°C/min to 320°C for 0.0min Run Time – 13.00 minutes
Detector:	Agilent 5973 MSD with PCI Source
Ionization Gas:	Ammonia run at 10% - 12% to achieve higher abundance for the adduct ion over the molecular ion.
Transfer Line:	300°C
Quad Temp:	150°C
Source Temp:	250°C
Solvent Delay:	4.00 minutes

SIM Parameters:

Group 1			
Start time:	4.00 minutes		
Ions/Dwell:	Mass, Dwell	Mass, Dwell	Mass, Dwell
	75.0, 40	81.0, 40	92.0, 40
	98.0, 40		
Group 2			
Start time:	6.00 minutes		
Ions/Dwell:	Mass, Dwell	Mass, Dwell	
	145.0, 100	162.0, 100	

Figure 1a. EICPs of NDMA of a 0.5ng/ml calibration standard
Electron Impact Ionization

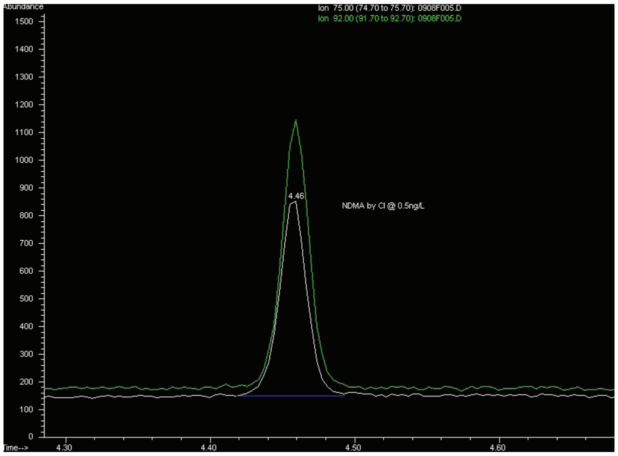
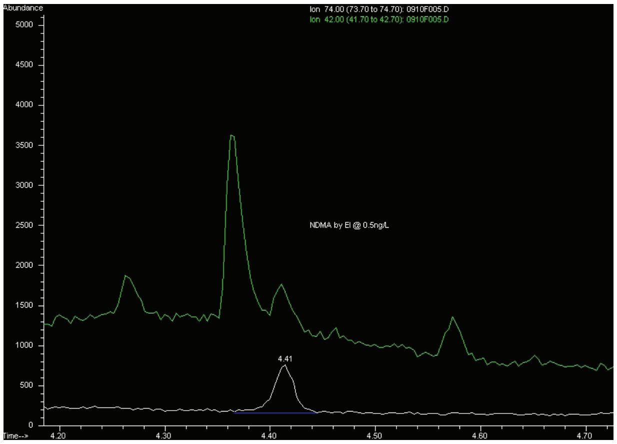


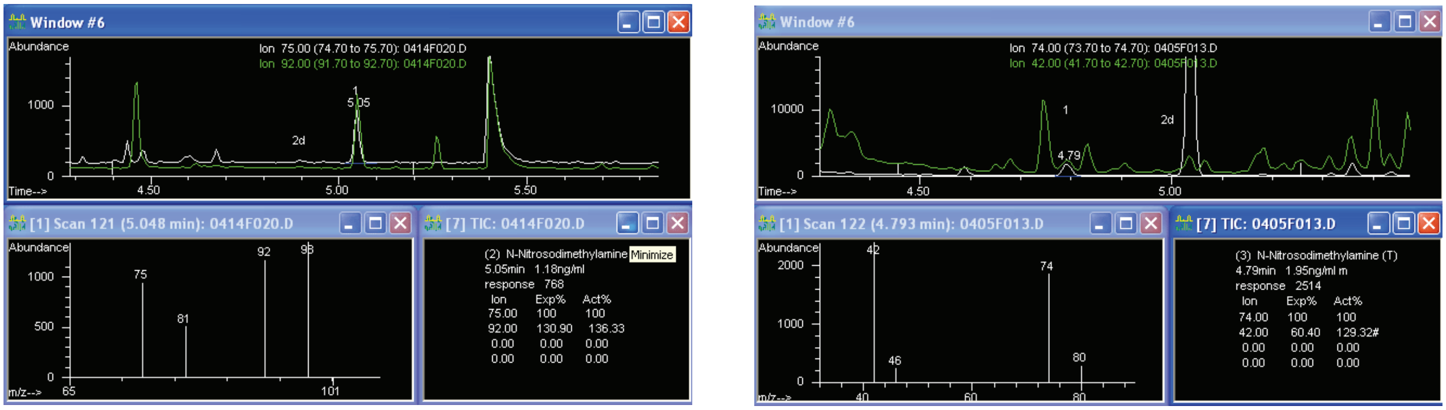
Figure 1b. EICPs of NDMA of a 0.5ng/ml calibration standard
Chemical Ionization



Results & Discussion

Positive chemical ionization using ammonia reagent gas has proved to be a very selective and sensitive approach to the analysis of NDMA. The use of LVI techniques have also contributed to increased sensitivity. The CI technique yields an approximate six fold increase in sensitivity over the electron impact ionization approach (Figure1). The selectivity of the CI technique is also apparent in matrix free calibration standards. The elevated baseline of the confirmation ion (m/z 42) in the EI spectrum illustrates the problem of maintaining proper isotope ratios. This problem is magnified in an extracted sample as shown in Figure 2.

Figure 2. Total Ion Chromatograms of 1.0ng/L NDMA in a Lab Fortified Sample



```
Ion  75.00 (74.70 to 75.70): 0414F020.D
Ion  92.00 (91.70 to 92.70): 0414F020.D
```

```
(2)  N-Nitrosodimethylamine
5.05min   1.18ng/ml
response   768
 Ion        Exp%      Act%
 75.00      100       100
 92.00      130.90     136.33
  0.00        0.00      0.00
  0.00        0.00      0.00
```

```
Ion  74.00 (73.70 to 74.70): 0405F013.D
Ion  42.00 (41.70 to 42.70): 0405F013.D
```

```
(3)  N-Nitrosodimethylamine (T)
4.79min   1.95ng/ml m
response   2514
 Ion        Exp%      Act%
 74.00      100       100
 42.00       60.40    129.32#
  0.00        0.00      0.00
  0.00        0.00      0.00
```

Analysis of the Method Detection Limit (MDL) study produced the following results in Table 1.

Table 1. Method Detection Limit (MDL) Summary

Analyte	Spike Level	Std. Dev.	MDL	%RSD Avg.	Avg. % Recovery
NDMA	1.0ng/L	0.018	0.055ng/L	1	153

Analysis of the Lab Control Samples produced the very good recoveries. Results are presented without isotope calculation to show extraction efficiency of EPA Method 3520C for NDMA (Table 2).

Table 2. Lab Control Sample Summary – Internal Standard Calculation

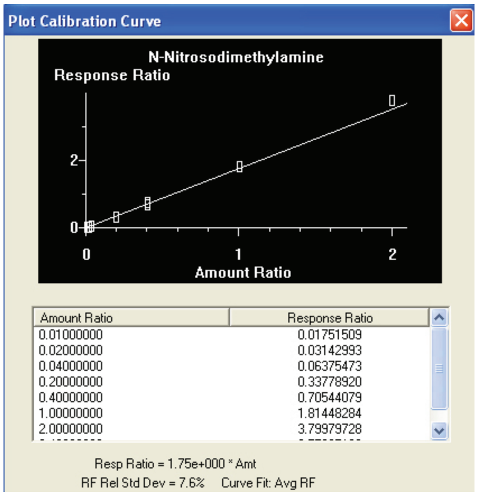
Analyte	Spike Level	LCS1	LCS2	Avg. Recovery	%RPD
NDMA	40ng/L	36.2ng/L	35.4ng/L	89.5	2.2

The linearity of NDMA across the calibration was also very good (Figure 3).

Conclusions

- EPA Method 3520C yields excellent extraction recoveries.
- Large Volume Injection with GC/MS using CI can easily obtain a reporting limit of 1.0ng/L.
- Selectivity of CI leads to lower background and increased response.
- NDMA by electron impact GC/MS is an inferior method that lacks the required selectivity for positive identification.

Figure3. Calibration Curve for NDMA



Amount Ratio	Response Ratio
0.01000000	0.01751509
0.02000000	0.03142993
0.04000000	0.06375473
0.20000000	0.33778920
0.40000000	0.70544079
1.00000000	1.81448284
2.00000000	3.79979728

Resp Ratio = 1.75e+000 * Amt
RF Rel Std Dev = 7.6%   Curve Fit: Avg RF

Future Work

Develop a solid phase extraction method to increase efficiencies in recovery and turn around time.

References

1. A.Eaton, M.Briggs, NDMA- Analytical Methods Options for a new Disinfection ByProduct?, Montgomery Watson Laboratories, Pasadena, CA
2. H.Prest, R.E.Herrmann, An approach to the determination of N-nitrosodimethylamine at part-per-quadrillion levels using positive chemical ionization and large volume injection.
3. Application note (23), Agilent Technologies, 2003.
4. EPA Method 8270C, Semivolatile Organic Compounds By Gas Chromatography/Mass Spectrometry (GC/MS), Test Methods for Evaluating Solid Waste Rev. 3, 1996.
5. EPA Method 3520C, Continuous Liquid-Liquid Extraction, Test Methods for Evaluating Solid Waste Rev. 3, 1996.

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