

# Determination of urea in ultrapure water by IC-MS/MS

## Authors

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## Goal

To develop an ion chromatography-mass spectrometry (IC-MS) method to determine low concentrations of urea in ultrapure water (UPW)

## Introduction

Water used in the production of electronic devices, such as the components that make up computers and mobile phones, must be extremely pure. In particular, it must be free of ionic compounds. Typically, manufacturers aim to have the concentration of each ion below 1  $\mu$ g/L. Another water contaminant that manufacturers seek to minimize is urea, which has been shown to cause problems with semiconductor production.<sup>1</sup> While anions and cations are routinely measured in ultrapure water (UPW) by ion chromatography (IC), the determination of urea is more challenging due to its poor retention by ion-exchange phases and the lack of a suitable detection technique for low concentrations.

This application note describes a method to determine urea that meets these challenges. Urea is retained on a high-performance cation-exchange column and detected by mass spectrometry (MS). Triple-quadrupole MS is used for greater detection specificity and sensitivity. Chromatography is performed using a Thermo Scientific™ Dionex™ Integrion™ HPIC™ system with RFIC capabilities. This is a compact IC system that automatically generates the eluent needed for chromatography. Positive electrospray ionization was used prior to the detection of urea using a Thermo Scientific™ TSQ Quantiva™ triple quadrupole mass spectrometer. This application note describes the development and execution of this method for determining urea in UPW.

## Experimental

### Equipment

- Dionex Integrion HPIC system
- Thermo Scientific™ Dionex™ AS-AP Autosampler
- TSQ Quantiva Triple Quadrupole Mass Spectrometer
- Auxiliary 6-port switching valve for Dionex Integrion HPIC system (P/N 22153-62027) for column outlet – to divert to MS inlet or waste
- Thermo Scientific™ Chromeleon™ Chromatography Data System software 7.2 SR4 for IC control
- Thermo Scientific™ Xcalibur™/Thermo Scientific™ TraceFinder™ 4.1 software for MS control and data processing

### Reagents and standards

- Deionized (DI) water, Type I reagent grade, 18 MΩ·cm resistivity or better from Thermo Scientific™ Barnstead™ Easypure™ II system
- Urea (Sigma-Aldrich P/N U5128-1KG)

### Samples

Seven samples were provided by a semiconductor manufacturer. In this application note, these samples are designated samples 1 through 7.

### LC Conditions

Columns:	Thermo Scientific™ Dionex™ IonPac™ CS16-Fast-4µm, 2 mm × 150 mm (P/N 088601) Thermo Scientific Dionex IonPac CG16-Fast-4µm, 2 mm × 30 mm (P/N 088602)
Eluent:	1 mM Methanesulfonic acid (MSA)
Eluent Source:	Thermo Scientific™ Dionex™ EGC 500 MSA Eluent Generator Cartridge (P/N 075779) with a Thermo Scientific™ Dionex™ CR-CTC 600 Continuously Regenerated Cation Trap Column (P/N 088663)
Flow Rate:	0.2 mL/min
Inj. Loop Volume:	45 µL (full loop*)
Temperature:	40 °C
Detection:	MS (See below)
Run Time:	6 min
System Backpressure:	~2,250 psi

\*Loop prepared from 0.01 in. i.d. PEEK™ tubing

### MS Conditions

Ionization Method:	H-ESI (heated electrospray ionization)
Polarity:	Positive
Spray Voltage:	3,500 V
Vaporizer Temperature:	360 °C
Ion Transfer Tube Temperature:	350 °C
Sheath Gas Flow:	38 units
Aux Gas Flow:	12 units
Scan Mode:	Selective Reaction Monitoring (SRM)
Q1 & Q3 Resolution:	0.7 FWHM
Dwell Time:	0.015 s
CID Gas (Ar) Pressure:	1.5 mTorr
Chrom Filter:	8 s

**Table 1. Optimized SRM transitions.**

Compound Name	Retention Time (min)	Time Window (min)	Polarity	Precursor (m/z)	Product (m/z)	Collision Energy (V)	Dwell Time (ms)
Urea *	2.34	1.5	Positive	61.1	44	30	15
Urea-dimer	2.34	1.5	Positive	121	61	25	15

\*Transition used for quantitation of urea.

### Additional software used for MS analysis

Thermo Scientific™ TSQ Quantiva™ Tune 2.0 software was used for system tuning and calibration. The compound SRM optimization wizard was also used. Thermo Scientific™ TraceFinder™ 4.1 software was used for instrument method setup, sample sequence setup and submission, automatic detection and integration of SRM peaks, plotting of calibration curve (linear and 1/x weighting), ion ratio confirmation, and experiment report generation.

### Eluent preparation

The 1 mM MSA was prepared by the Dionex Integrion HPLC system eluent generator. The eluent generator also produced 50 mM MSA used to wash the system and column for 60 min after each day of analysis. It is possible to implement a 15 min wash at 50mM MSA into the gradient program when running samples containing higher cation concentrations. This facilitates washing of the column after each sample run. This wash solution is sent to waste and not to the electrospray interface.

### Preparation of standards

Prepare the 1,000 ppm stock solution by weighing 1 g of urea into a 1,000 mL volumetric flask and filling the flask to the mark with DI water. Shake the flask to thoroughly mix the stock solution.

To prepare 50 mL of 1 ppm intermediate standard solution, tare the balance with a 50 mL HDPP or HDPE bottle. Pipette 50 µL of the 1,000 ppm stock solution,

add DI water to 50.0 g total, cap, and shake the bottle to thoroughly mix the solution.

Prepare 50 mL solutions of working standards 1, 2, 3, 4, 5, 6, and 7 in a similar way, by pipetting 20, 25, 50, 100, 250, 500, and 1,000 µL of the intermediate standard into individual 50 mL labeled bottles. Dilute each one to 50.0 g total with DI water and thoroughly shake to mix the working standards. The final concentrations are shown in Table 2.

Table 2 shows the low concentration urea standards prepared in DI water to generate the calibration curve for sample analysis. Standards should be prepared on the day of analysis.

### Sample preparation

The samples were analyzed without preparation. After the initial analysis one sample was diluted 1:1 with DI water to have the measured amount of urea in the calibration range.

### System setup

The system setup is shown in Figure 1. A diverter valve is installed after the column so that the column can be washed without sending the effluent to the MS and without having to disconnect the column. To reduce the delay volume between the column and the MS, a short piece of 0.003 in. PEEK tubing was used. Ion source cleaning is basic maintenance for MS systems. Routine ion source cleaning is recommended weekly to prevent any salt clogging or corrosion effects.

**Table 2. Concentrations of calibration standards.**

	Concentration (µg/L)						
	Std 1	Std 2	Std 3	Std 4	Std 5	Std 6	Std 7
Urea	0.4	0.5	1.0	2.0	5.0	10.0	20.0

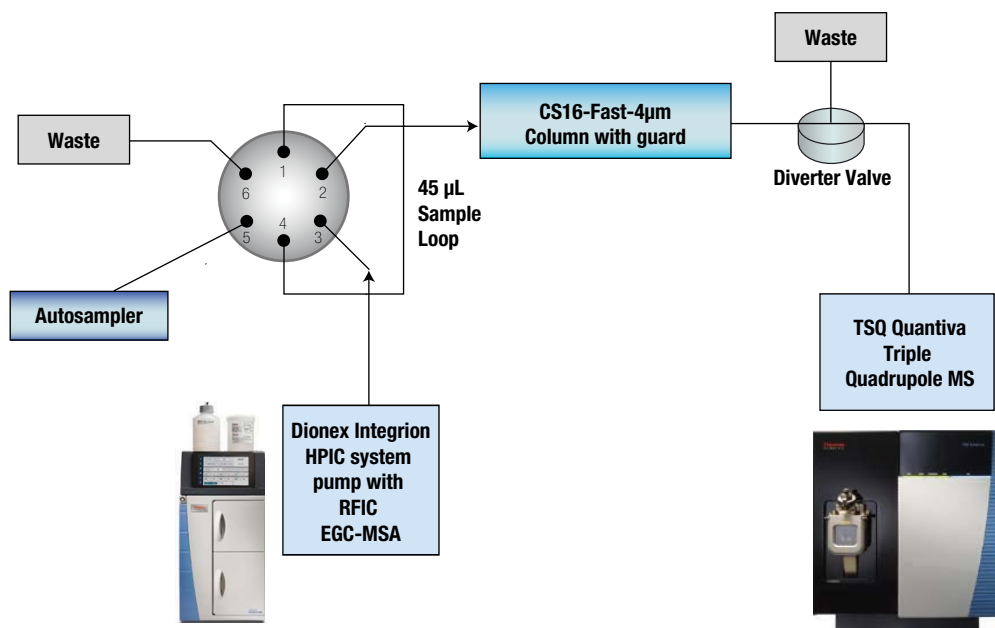


Figure 1. System configuration for IC-MS/MS urea analysis.

## Results and discussion

### Chromatography

Urea was retained just beyond the void volume of the Dionex IonPac CS16 4-µm column. The 2 mm format of this small-particle-size column was chosen to enhance sensitivity as well as reduce eluent usage and reduce waste. Figure 2 shows the IC-MS/MS chromatograms of one injection of each of the urea calibration standards. The 66.1 to 44  $m/z$  transition was used for detecting urea. Detecting urea by SRM reduces the possibility of interference from other early eluting compounds. The injection volume was optimized to produce the best peak shape and sensitivity. That study found an optimum injection volume of 45 µL. Acetonitrile is sometimes added after an IC separation to enhance MS sensitivity, but this was not required for this application. In fact, experiments using acetonitrile found that sensitivity was compromised due to formation of a urea-acetonitrile complex. This divided the urea between free urea and complexed urea.

### Calibration and minimum detection limit (MDL) determinations

Because the goal was to determine low concentrations of urea in UPW, we used a small range of low concentrations (0.4 to 20 µg/L) with more points at the lower end of the concentration range. Three injections of each standard were made. The results of the calibration

experiment showed a linear relationship between concentration and peak area response by least squares analysis (coefficient of determination ( $r^2$ ) of 0.9979) and by visual inspection of the plotted data (Figure 3).

The MDL was estimated by making seven injections a low concentration standard (0.4 µg/L). This study yielded a MDL of 0.14 µg/L using the formula:

$$MDL = 3.142 \times \text{average amount} \times \%RSD/100$$

(3.142 is the Student's  $t$  value for a 99% confidence level and a standard deviation estimate with  $n-1$  degrees of freedom for seven replicates.)

Figure 4 shows a chromatogram of one of the injections of the 0.4 µg/L standard.

### Interference study

To determine if common cations could interfere with the determination of urea in UPW, 5 µg/L urea was spiked into a water sample containing 25, 100, 125, 250, 125, and 250 µg/L of lithium, sodium, ammonium, potassium, magnesium, and calcium, respectively. While these concentrations are not high, they are higher than would be expected in UPW, and because urea is weakly bound to the column, it is very easy to displace it. Three injections of this sample yielded an 82.7% recovery, suggesting the method is appropriate for UPW.

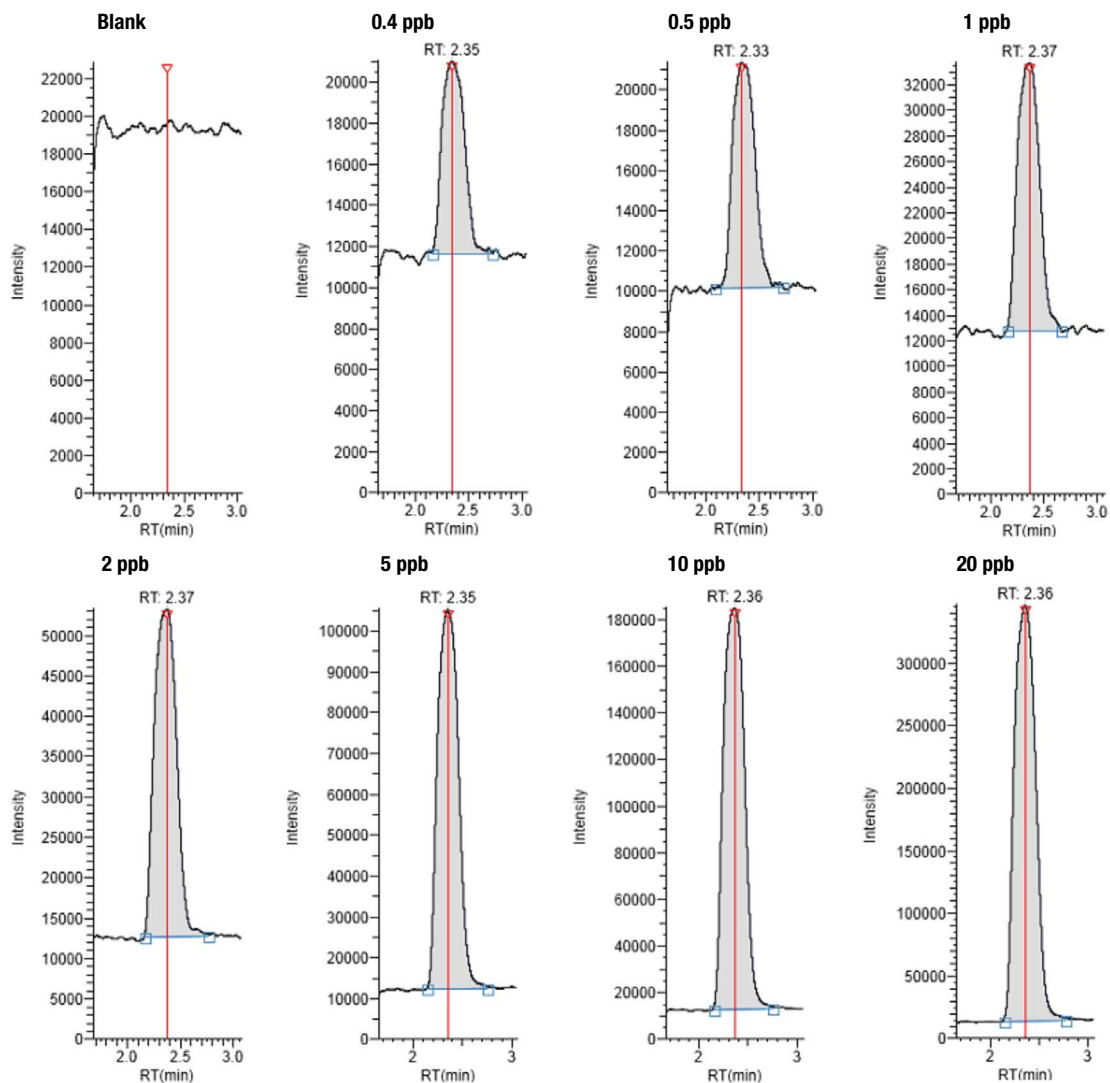


Figure 2. Urea calibration standards chromatograms.

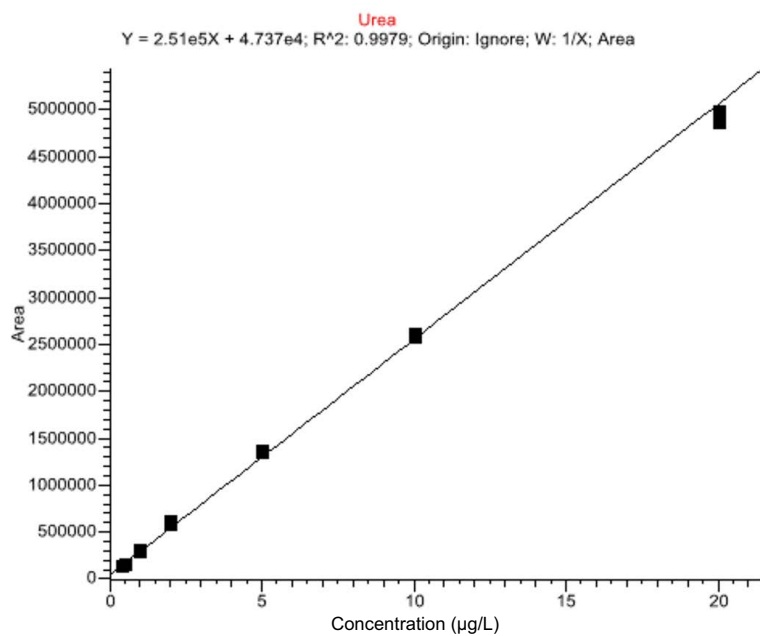


Figure 3. Urea calibration plot.

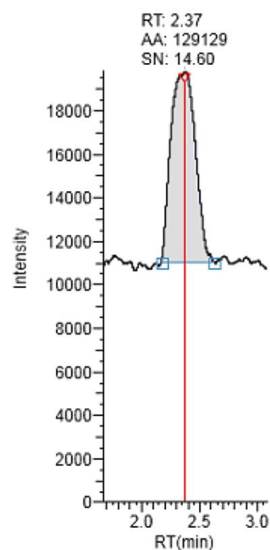


Figure 4. Chromatogram of a 0.4 µg/L urea standard.

## Sample analysis

Seven water samples from different parts of a semiconductor manufacturing process were provided by a customer (Figure 5). The results of our analysis are shown in Table 3. Sample #1 required dilution to have the urea concentration in the range of the calibration plot. Method stability during this analysis was checked by intermittently injecting 2 and 5 µg/L check standards. Each standard was injected three times during the

sample analysis. The 2 µg/L standard had a 98.6% recovery and the 5 µg/L had a 101% recovery. This suggests good method stability during this analysis.

To assess accuracy, samples #1, #2, and #6 were spiked with 5 and 10 µg/L urea and samples #2 and #6 were spiked with 2 µg/L urea. Each spiked sample was injected in triplicate. For these eight spiked sample preparations, the recovery ranged from 94.5% to 107%, suggesting that the determinations are accurate.

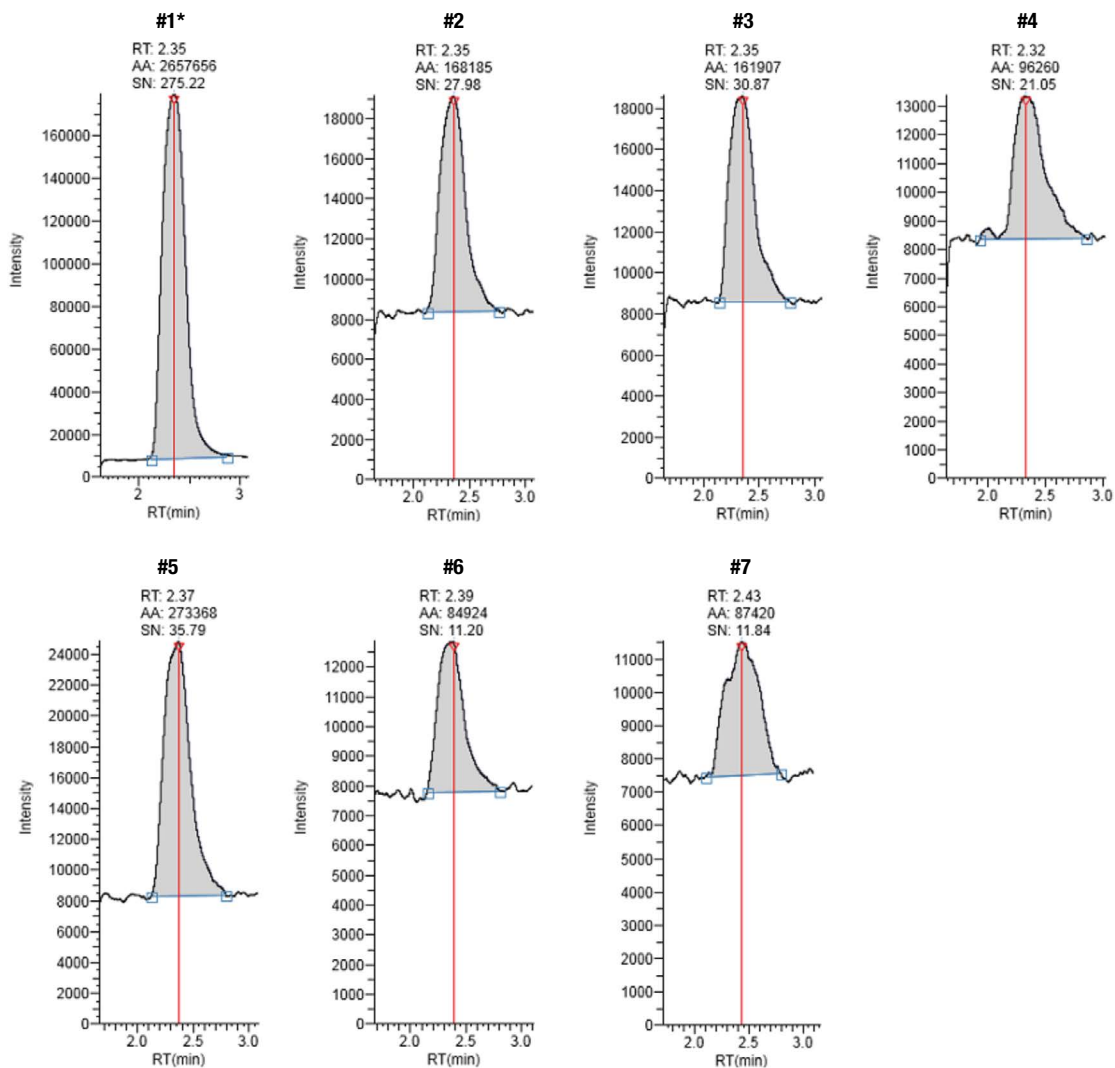


Figure 5. Sample chromatograms.

Table 3. Sample analysis.

	Amount (µg/L) #1*	Amount (µg/L) #2	Amount (µg/L) #3	Amount (µg/L) #4	Amount (µg/L) #5	Amount (µg/L) #6	Amount (µg/L) #7
Replicate 1	20.8	0.508	0.411	0.166	0.754	0.164	0.152
Replicate 2	19.5	0.481	0.456	0.172	0.815	0.150	0.162
Replicate 3	19.8	0.489	0.456	0.187	0.837	0.152	0.160
Average	20.1	0.493	0.441	0.175	0.802	0.155	0.158
<b>RSD</b>	3.28	2.81	5.89	6.18	5.36	4.88	3.35

\*Required a 1:1 dilution with DI water

## Conclusion

The IC-MS/MS method described in this application note can accurately determine low µg/L concentrations of urea in UPW, with a MDL of < 0.2 µg/L. Urea can be detrimental to the successful production of semiconductors. This method is easy to execute as the eluent is automatically prepared by the Dionex Integrion HPIC system with RFIC capability. The MS/MS detection provides both excellent sensitivity and confidence in peak identification.

## Reference

1. Godex, R. Measurement and Removal of Trace Levels of Urea in Semiconductor High-Purity Water. [Online] <http://www.astsciencecorp.com/files/file/GE%20TOC/IntelGodecHenleyEdit32.pdf> (accessed August 28, 2017).

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