

# Sievers\* M500 TOC Performance Specifications

## TEST REPORT

### Purpose

The purpose of this report was to verify the total organic carbon (TOC) performance characteristics of the Sievers M500 TOC Analyzer. Performance was quantified by measuring the accuracy, precision, linearity, system suitability, limit of detection, and limit of quantification. Thirteen Sievers M500 TOC Analyzers were used in this study.

### Background Information and Calculations

#### 1. Accuracy

The accuracy performance specification results are presented here as percent recoveries<sup>1,2</sup>. The averages of three replicates of potassium hydrogen phthalate (KHP) standards were determined at the following concentrations: 250 ppb, 500 ppb, 750 ppb, 1 ppm, 1.25 ppm and 2.5 ppm.

The percent recovery for each standard was calculated using the following equation:

$$\% \text{ Recovery} = (\text{Measured Standard Concentration} / \text{Expected Standard Concentration}) \times 100\%$$

Percent recoveries close to 100% indicate a high degree of accuracy for the analyzer.

#### 2. Precision

The precision performance specification data are presented as a % relative standard deviation (%RSD). The standard deviation and %RSD are calculated as follows:

$$\text{Standard Deviation} = \sqrt{\frac{n \sum x^2 - (\sum x)^2}{n(n-1)}}$$

where:

x = Each result  
n = Number of measurements

$$\text{Relative Standard Deviation (\%RSD)} = (\text{Standard Deviation} / \text{Measured Concentration}) \times 100\%$$

A %RSD value close to 0% indicates a high degree of precision for the analyzer<sup>1,2,3</sup>.

### 3. Linearity

Linearity is defined as the ability of the TOC analyzer to generate data that are directly proportional to the concentration of multiple TOC standards across the dynamic range of the instrument. Linearity is determined by performing a linear regression and calculating the square of the correlation coefficient ( $R^2$ ). The square of the correlation coefficient is calculated using the following equation:

$$R^2 = \left( \frac{\sum(x - \bar{x})(y - \bar{y})}{\sqrt{\sum(x - \bar{x})^2 \sum(y - \bar{y})^2}} \right)^2$$

where:

- x = Each expected TOC result
- $\bar{x}$  = Average expected TOC result
- y = Each measured TOC result
- $\bar{y}$  = Average measured TOC result

$R^2$  values close to 1.0 represent a high degree of correlation.

### 4. System Suitability

System suitability is a test commonly performed in the pharmaceutical industry to confirm the instrument's ability to recover both an easy and a difficult-to-oxidize compound<sup>4,5</sup>. A response efficiency of 100% indicates that the instrument recovered both compounds equally.

Response Efficiency is calculated using the following equation:

$$\text{Response Efficiency} = (R_{ss} - R_w) / (R_s - R_w) \times 100\%$$

where:

- $R_{ss}$  = Measured concentration of a 500 ppb 1,4-benzoquinone (BQ) standard
- $R_s$  = Measured concentration of a 500 ppb sucrose standard
- $R_w$  = Measured concentration of the reagent water control

For USP/EP System Suitability, the acceptance criterion is a response efficiency between 85% and 115%<sup>5</sup>.

### 5. Limit of Detection/Limit of Quantitation

The limit of detection (LOD) is defined as the minimum concentration of TOC that can be reliably detected by the analyzer<sup>1,2</sup>. It is calculated by the following equation<sup>4</sup>:

$$\text{LOD} = 3.3 \sigma / S$$

where:

- $\sigma$  = Standard deviation of the response
- S = Slope of the calibration curve

The limit of quantification (LOQ) is defined as the lowest concentration of TOC that can be determined quantitatively with an acceptable uncertainty<sup>1,2</sup>. It is calculated by the following equation<sup>4</sup>:

$$\text{LOQ} = 10 \sigma / S$$

where:

- $\sigma$  = Standard deviation of the response
- S = Slope of the calibration curve

### Experimental Test Plan

#### 1. Accuracy & Precision Measurement

To evaluate the accuracy and precision of the instrument response across the operating range, standard solutions of KHP were produced at the following concentrations: 250 ppb, 500 ppb, 750 ppb, 1 ppm, 1.25 ppm, and 2.5 ppm. With the exception of the 2.5 ppm standard, all the standards are part of the Sievers 5-point Linearity set made the Sievers System Suitability. For each standard, four replicates were made with the first replicate rejected. This testing was performed on ten Sievers M500 instruments.

#### 2. Linearity

To evaluate the linearity of the instrument response, a linear regression was applied to the TOC results from accuracy and precision measurements above.

#### 3. System Suitability

To determine the instrument response efficiency,  $R_w$  control, 500 ppb sucrose and 500 ppb BQ standards were analyzed. These standards are part of the System Suitability Standards Set. For each standard, four replicates were made with the first replicate rejected. This testing was performed on ten Sievers M500 instruments.

#### 4. LOD/LOQ

To determine the LOD and LOQ, five Sievers M500 units with the standard iOS were configured to be Sievers M500e units. Additionally, three more Sievers M500e units were tested prior to shipment to semiconductor sites for Beta testing. In total, testing was performed on eight M500e units. Each unit was installed on a stable UPW system with a TOC concentration of 3 ppb or less. The units were allowed to rinse down overnight and then run online for at least 24 hours. For the most stable six-hour period, a 10 point moving standard deviation was calculated for the TOC measurements. The maximum standard deviation was determined and used as the basis for the LOD and LOQ calculations.

### Test Equipment Used

Sievers M500 TOC Analyzer: 0001, Super iOS  
Sievers M500 TOC Analyzer: 0002, Super iOS  
Sievers M500 TOC Analyzer: 0003, iOS  
Sievers M500 TOC Analyzer: 0004, iOS  
Sievers M500 TOC Analyzer: 0005, iOS  
Sievers M500 TOC Analyzer: 0006, iOS  
Sievers M500 TOC Analyzer: 0007, iOS  
Sievers M500 TOC Analyzer: 0008, Super iOS  
Sievers M500 TOC Analyzer: 0009, Super iOS  
Sievers M500 TOC Analyzer: 0010, Super iOS  
Sievers M500 TOC Analyzer: 0018, iOS  
Sievers M500 TOC Analyzer: 0020, iOS  
Sievers M500 TOC Analyzer: 0030, iOS

## Calibration and Verification

Each instrument was calibrated using the TOC Single Point Calibration protocol<sup>6</sup> which utilizes a 1.5 ppm KHP standard. Each instrument was verified using the Accuracy & Precision Verification protocol<sup>6</sup> which utilizes a 500 ppb sucrose standard.

When configured as M500e units for LOD and LOQ testing, each instrument was calibrated using the Low-Level TOC Single Point calibration protocol<sup>6</sup> which utilizes a 250 ppb KHP standard. Each instrument was verified using the Low-Level Accuracy & Precision Verification protocol<sup>6</sup> which utilizes a 100 ppb isopropyl alcohol (IPA) standard.

## Results and Discussion

All results presented here are for four replicates of each KHP standard with one rejection.

### 1. Accuracy

#### 1.1. Percent Recovery Results

Serial Number	250 ppb TOC % Recovery	500 ppb TOC % Recovery	750 ppb TOC % Recovery	1.0 ppm TOC % Recovery	1.25 ppm TOC % Recovery	2.5 ppm TOC % Recovery
0001	101.6	102.2	102.0	100.2	101.4	99.5
0002	104.2	99.7	100.6	99.1	99.6	100.0
0003	99.7	99.3	100.2	99.7	99.6	100.6
0004	100.0	99.6	100.3	99.9	100.2	99.8
0005	99.7	99.3	99.9	99.6	99.2	100.6
0006	99.9	100.1	100.1	100.1	100.1	100.2
0007	99.3	99.2	99.4	99.4	99.3	100.5
0008	100.6	101.5	100.6	100.0	99.9	100.4
0009	100.5	100.4	100.7	98.8	99.0	100.2
0010	100.6	98.8	101.0	99.2	99.0	100.2

#### 1.1.1. Accuracy Performance Specification

The results presented here demonstrate that Sievers M500 TOC Analyzers recover TOC with a high degree of accuracy. The recovery results ranged from 98.8% to 104.2%.

Based on the recovery results shown above, the TOC accuracy performance specification for the Sievers M500 TOC Analyzer is  $\pm 5\%$ .

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### 2. Precision

#### 2.1. Precision Results

Standard Concentration	Unit 0001		Unit 0002		Unit 0003	
	Standard Deviation (ppb)	% RSD	Standard Deviation (ppb)	% RSD	Standard Deviation (ppb)	% RSD
250 ppb	1.73	0.6	0.58	0.2	1.00	0.4
500 ppb	1.53	0.3	2.00	0.4	0.00	0.0
750 ppb	2.00	0.3	0.58	0.1	0.58	0.1
1.0 ppm	3.79	0.4	0.58	0.1	1.00	0.1
1.25 ppm	3.79	0.3	1.15	0.1	0.58	0.1
2.5 ppm	25.0	1.0	15.3	0.6	15.4	0.6

Standard Concentration	Unit 0004		Unit 0005		Unit 0006	
	Standard Deviation (ppb)	% RSD	Standard Deviation (ppb)	% RSD	Standard Deviation (ppb)	% RSD
250 ppb	0.58	0.2	0.00	0.0	0.58	0.2
500 ppb	1.73	0.3	1.00	0.2	0.58	0.1
750 ppb	1.15	0.2	1.53	0.2	2.65	0.4
1.0 ppm	0.58	0.1	2.08	0.2	1.53	0.2
1.25 ppm	0.58	0.1	11.0	0.9	4.36	0.3
2.5 ppm	5.04	0.2	9.02	0.4	5.51	0.2

Standard Concentration	Unit 0007		Unit 0008		Unit 0009	
	Standard Deviation (ppb)	% RSD	Standard Deviation (ppb)	% RSD	Standard Deviation (ppb)	% RSD
250 ppb	1.53	0.6	0.00	0.0	2.31	0.9
500 ppb	1.00	0.2	2.31	0.4	1.00	0.2
750 ppb	1.00	0.1	0.58	0.1	5.86	0.8
1.0 ppm	1.53	0.2	1.00	0.1	1.53	0.2
1.25 ppm	1.15	0.1	0.58	0.1	1.00	0.1
2.5 ppm	4.93	0.2	10.40	0.4	8.00	0.3

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Standard Concentration	Unit 0010	
	Standard Deviation (ppb)	% RSD
250 ppb	1.15	0.4
500 ppb	1.15	0.2
750 ppb	0.58	0.1
1.0 ppm	1.00	0.1
1.25 ppm	7.81	0.6
2.5 ppm	3.51	0.1

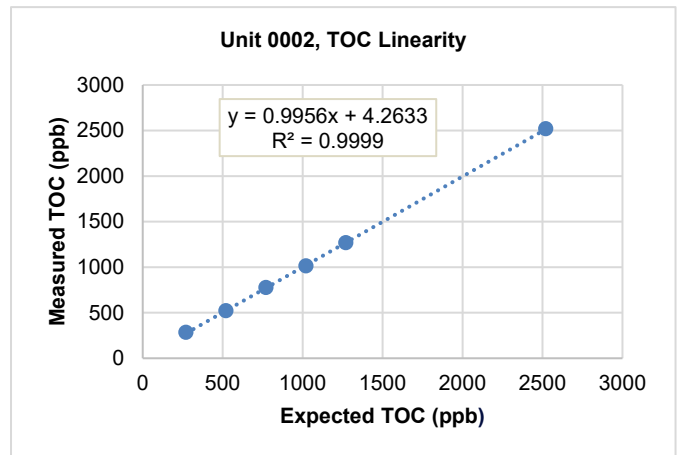
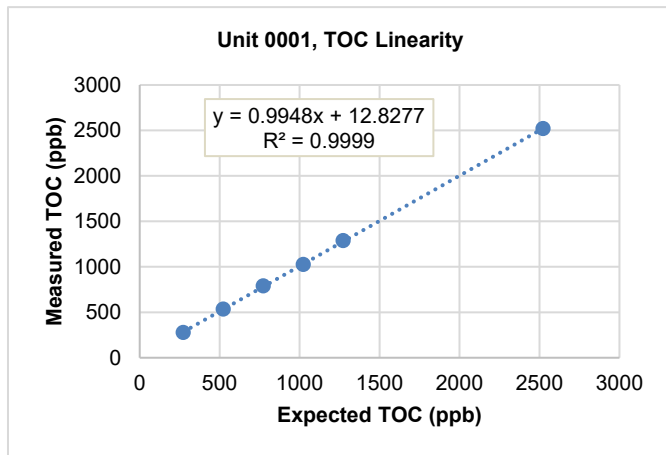
### 2.2. Precision Performance Specification

Based on the precision results shown above, the TOC precision performance specification for the Sievers M500 TOC Analyzer is  $\leq 1\%$ .

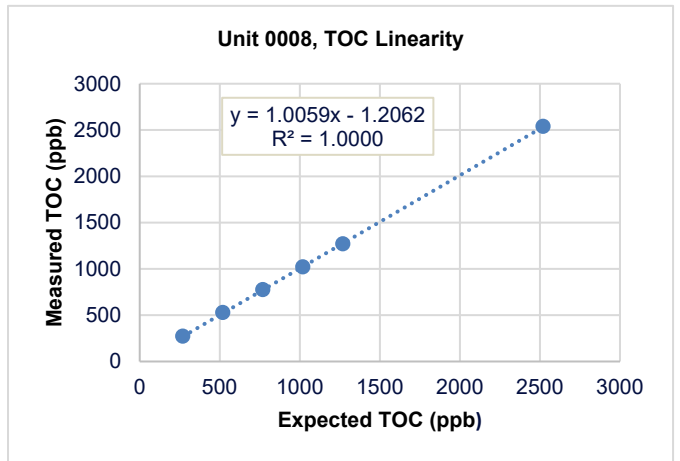
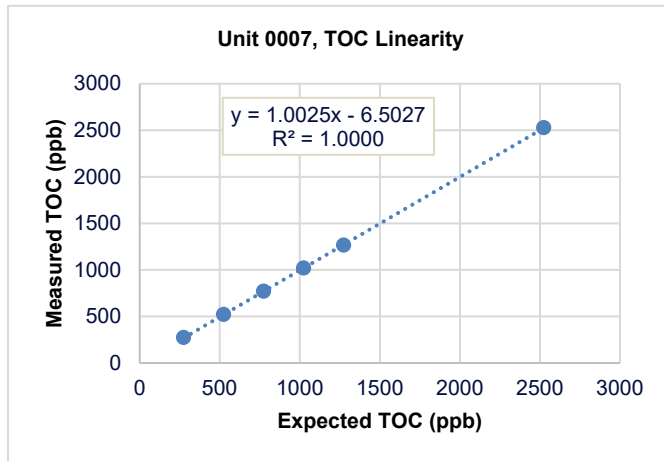
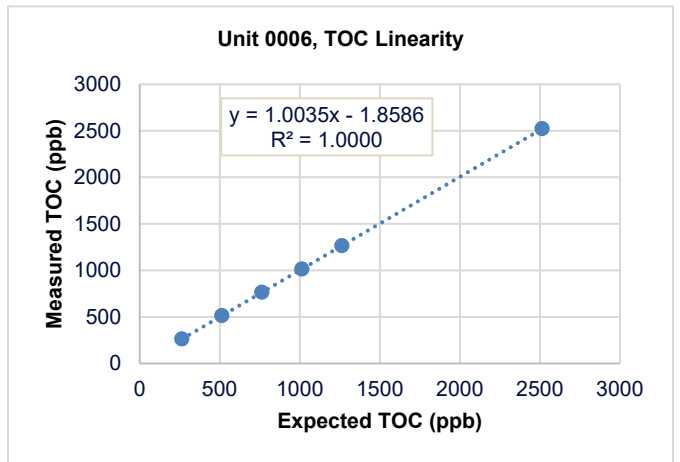
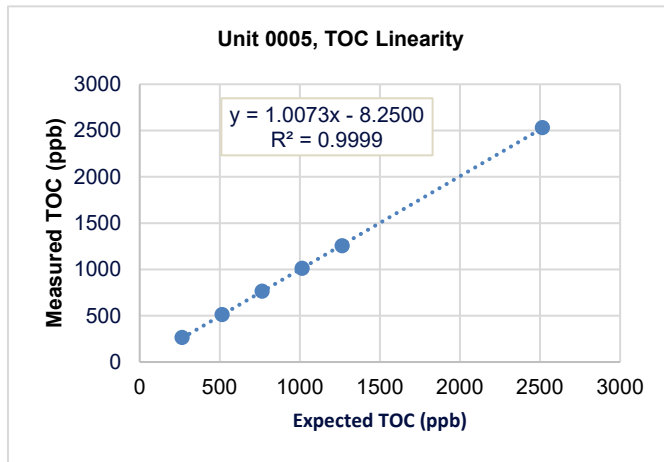
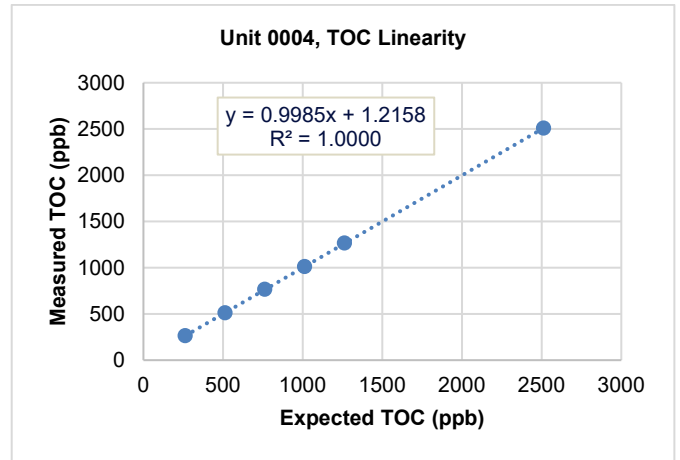
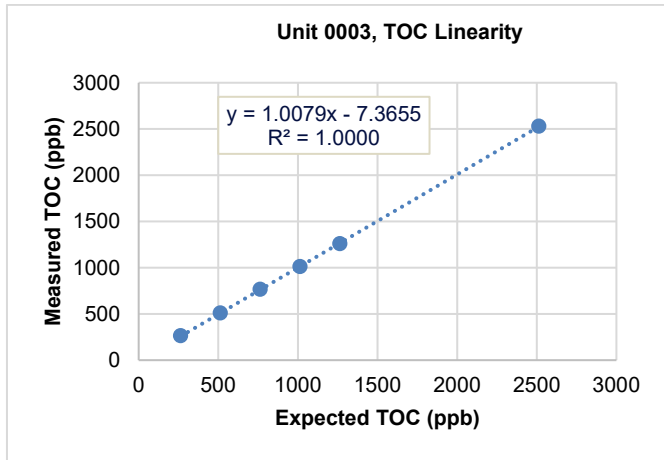
### 2.3. Linearity

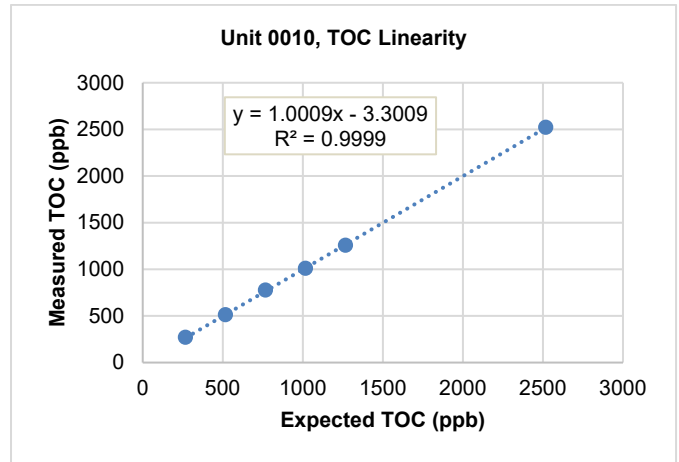
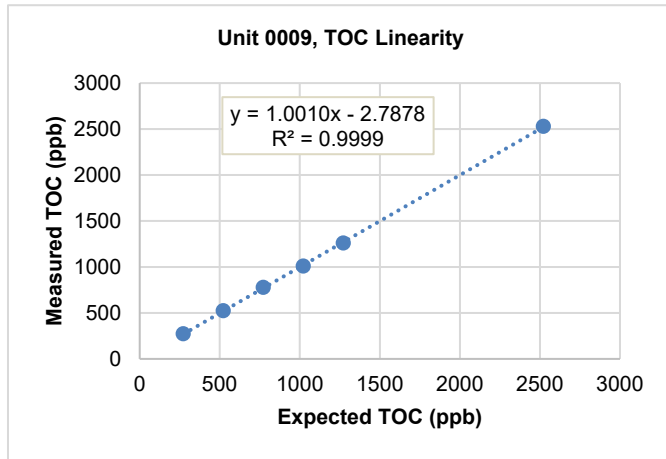
To demonstrate linearity, a least-squares regression was performed using the expected TOC and measured TOC data from each instrument. The linear regression equation as well as the square of the correlation coefficient ( $R^2$ ) are reported below for each instrument.

#### 2.3.1. Linearity Results



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### 2.3.2. Linearity Performance Specification

All ten instruments demonstrated a highly linear TOC response with square of the correlation coefficient ( $R^2$ ) values of 0.9999 or greater across the full range of the instrument.

## 2.4. System Suitability

### 2.4.1. System Suitability Results

Sievers M500 Serial Number	Response Efficiency
0001	103.0
0002	97.6
0003	99.2
0004	99.4
0005	100.0
0006	99.0
0007	98.2
0008	99.8
0009	97.2
0010	98.2

System suitability results from this experiment (97.2% to 103.0% response efficiency) demonstrate the excellent response efficiency of the Sievers M500 TOC Analyzer. These response efficiencies are well within the acceptable USP/EP System Suitability range of 85% to 115%<sup>5</sup>.



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### 2.5. LOD/LOQ

The table below lists the maximum standard deviation for each instrument observed over the most stable six-hour period, the overall average standard deviation, and the resulting LOD and LOQ.

#### 2.5.1. LOD/LOQ Results

Sievers M500e Serial Number	Maximum TOC Standard Deviation (ppb)
0003	0.008
0004	0.009
0005	0.010
0006	0.010
0007	0.009
0018	0.007
0020	0.009
0030	0.009
<b>Average</b>	<b>0.0090</b>
<b>LOD</b>	<b>0.03</b>
<b>LOQ</b>	<b>0.09</b>

#### 2.5.2. LOD/LOQ Performance Specification

Based on results presented above, the LOD and LOQ specifications for the Sievers M500 TOC Analyzer are 0.03 ppb and 0.09 ppb respectively.

### 3. Conclusions

In summary, the TOC performance specifications of the Sievers M500 TOC Analyzer have been experimentally verified as follows:

<b>Accuracy</b>	±5%
<b>Precision</b>	≤1%
<b>Linearity</b>	R2 ≥ 0.9999
<b>LOD</b>	0.03 ppb
<b>LOQ</b>	0.09 ppb

#### References

1. Barwick, V., S. Burke, R. Lawn, P. Roper, and R. Walker. (2001). Applications of Reference Materials in Analytical Chemistry. Cambridge: LGC Limited.
2. Ellison, S.R., V.J. Barwick, and T.J. Duguid Farrant. (2009). Practical Statistics for the Analytical Scientist. Cambridge: RSC Publishing.
3. Taylor, J.K. (1987). Quality Assurance of Chemical Measurements. Florida: CRC Press LLC.
4. ICH Harmonized Tripartite Guideline Validation of Analytical Procedures: Text and Methodology Q2(R1). (2005).
5. USP <643> Total Organic Carbon.
6. Sievers M500 TOC Analyzer Operation and Maintenance Manual.