Sievers M-series performance specifications

1. purpose

The purpose of this report was to verify the performance characteristics of the Sievers* M-Series TOC Analyzers. Performance was quantified by measuring the accuracy, precision, linearity, limit of detection, and limit of quantification. The Sievers M9 TOC Analyzers used in this study included one laboratory, two portable, and five online Sievers M9® units.

2. background information and calculations

2.1 Accuracy

The accuracy performance specification results are presented here as percent recoveries[1,2]. The averages of 10 replicates of sucrose standards were determined at the following concentrations: 250 ppb, 500 ppb, 1 ppm, 5 ppm, 10 ppm, 25 ppm, and 50 ppm.

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

$$\% \text{ Recovery} = \left(\frac{\text{Measured Standard Concentration}}{\text{Expected Standard Concentration}} \right) \text{X } 100\%$$

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

2.2 Precision

The precision performance specification data are presented as a % relative standard deviation (%RSD).
The standard deviation of 10 replicates 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

$$\text{Relative Standard Deviation (\%RSD)} = \frac{\text{(Standard Deviation)}}{\text{(Measured TOC Concentration)}} \text{ X } 100\%$$

A %RSD value close to 0% indicates a high degree of precision for the analyzer [1-3].

2.3 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[4,5]. A response efficiency of 100% indicates that the instrument recovered both compounds equally.

Response Efficiency is calculated using the following equation:

$$\text{Response Efficiency} = \frac{(Rss-RW)}{(Rs-RW)} \text{ X } 100\%$$

Where Rss is the measured concentration of 500 ppb 1,4-benzoquinone (BQ), Rs is the measured concentration of 500 ppb sucrose, and RW is the concentration of the reagent water blank. For USP/EP System Suitability, the acceptance criterion is a Response Efficiency between 85% and 115%[5].

2.4 Limit of Detection/Limit of Quantification

The limit of detection (LOD) is defined as the minimum concentration of TOC that can be reliably detected by the analyzer [1,2]. It is calculated by the following:

LOD = 3s

Where:

s = standard deviation of 10 replicates of online DI water

The limit of quantification (LOQ) is defined as the lowest concentration of TOC that can be determined quantitatively with an acceptable uncertainty [1,2]. It is calculated via the equation:

LOQ = 10s

2.5 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 measured by calculating a correlation coefficient (R2), slope of a regression line, and y-intercept. R2 values close to 1.0 represent a high degree of correlation.

3. experimental test plan

3.1 Sucrose and BQ Standards

This study was divided into two separate parts in order to quantify performance specifications using various calibrations on three different instruments. One laboratory Sievers M9 unit and two portable Sievers M9 units were used in this study. Using the different calibrations, a wide range of sucrose standards were run to encompass the full operating range of the analyzers and quantify differences (if any) between calibrations. Standard solutions of sucrose were produced at the following concentrations: 25 ppb, 50 ppb, 100 ppb, 200 ppb, 250 ppb, 500 ppb, 1 ppm, 5 ppm, 10 ppm, 25 ppm, and 50 ppm. For accuracy and precision performance specifications, the standards in the concentration range of 250 ppb to 50 ppm were used. For linearity, all 11 standards were used.

To determine system suitability and response efficiency, 500 ppb BQ standards were analyzed. These BQ standards and the associated reagent water blanks were part of the System Suitability Standards Set made at SUEZ. The table below outlines the order in which the samples were run on each instrument, the acid and oxidizer flow rates, and the number of repetitions.

TOC Concentration	Testing for	Acid (µl/min)	Oxidizer (µl/min)	Repetitions
Reagent Water	All	0.5	0	10/0
500 ppb	Acc/Prec	0.5	0	10/0
Rw for BQ	System Suitability	0.5	0	10/0
500 ppb BQ	System Suitability	0.5	0	10/0
25 ppb	Linearity	0.5	0	10/0
50 ppb	Linearity	0.5	0	10/0
100 ppb	Linearity	0.5	0	10/0
200 ppb	Linearity	0.5	0	10/0
250 ppb	Linearity/Acc/Prec	0.5	0	10/0
500 ppb	Linearity/Acc/Prec	0.5	0	10/0
1 ppm	Linearity/Acc/Prec	1.0	0.1	10/0
5 ppm	Linearity/Acc/Prec	1.0	1.2	10/0
10 ppm	Linearity/Acc/Prec	1.0	1.6	10/0
25 ppm	Linearity/Acc/Prec	1.0	3.4	10/0
50 ppm	Linearity/Acc/Prec	1.0	6.8	10/0

3.2 All Analyzers with 1 ppm Calibration

The three analyzers were each calibrated using a 1 ppm single-point calibration using KHP and Na_2CO_3 as outlined in Sievers protocols[6]. Once the analyzers were calibrated at 1 ppm and verified at 500 ppb, all of the sucrose and BQ standards were analyzed as described above.

3.3 Analyzers with Three Different Calibrations

After the completion of all samples using the 1 ppm calibration, the three analyzers were recalibrated as follows:

- Lab 0039: Multi-Point Calibration
  (250 ppb, 1 ppm, 5 ppm, 10 ppm, 25 ppm, 50 ppm TOC as KHP, and 10 ppm IC as Na_2CO_3)
- Portable 0042: 50 ppm Single-Point Calibration
- Portable 0043: 10 ppm Single-Point Calibration

New aliquots of the same sucrose and BQ standards were then run on each instrument with these new calibrations.

4. test equipment used

- Sievers M9 Laboratory TOC Analyzer Serial Number: 1312 0039
- Sievers M9 Portable TOC Analyzer Serial Number: 14010042
- Sievers M9 Portable TOC Analyzer Serial Number: 14010043
- Sievers Autosampler Serial Number: 10040214
- Sievers Autosampler Serial Number: 13020003
- Sievers Autosampler Serial Number: 09040005
- DataPro2 Software

5. calibration and verification

Please refer to sections 3.2 and 3.3.

6. results and discussion

All results presented here are for 10 replicates of each sucrose standard (250 ppb-50 ppm) with no rejects. There was one statistical outlier on the 25 ppm sucrose standard on Lab 0039 using the 1 ppm calibration, which was determined using a Grubb's statistical test for outliers[1-3] at the 99% confidence level. This data point was discarded.

6.1 Precision

Lab 0039

Calibration	Standard Concentration	Standard Deviation	%RSD
1 ppm Cal	250 ppb	2.2 ppb	0.9%
1 ppm Cal	500 ppb	2.7 ppb	0.5%
1 ppm Cal	1 ppm	6.7 ppb	0.6 %
1 ppm Cal	5 ppm	19.3 ppb	0.4 %
1 ppm Cal	10 ppm	78.9 ppb	0.8 %
1 ppm Cal	25 ppm	122 ppb	0.5 %
1 ppm Cal	50 ppm	362 ppb	0.7 %

Calibration	Standard Concentration	Standard Deviation	%RSD
Multi-Point Cal	250 ppb	1.9 ppb	0.8%
Multi-Point Cal	500 ppb	3.3 ppb	0.7 %
Multi-Point Cal	1 ppm	4.8 ppb	0.5 %
Multi-Point Cal	5 ppm	15.2 ppb	0.3%
Multi-Point Cal	10 ppm	70 ppb	0.7%
Multi-Point Cal	25 ppm	151 ppb	0.6 %
Multi-Point Cal	50 ppm	360 ppb	0.7 %

Portable 0042

Calibration	Standard Concentration	Standard Deviation	%RSD
1 ppm Cal	250 ppb	2.0 ppb	0.8 %
1 ppm Cal	500 ppb	3.9 ppb	0.8 %
1 ppm Cal	1 ppm	9.5 ppb	0.9 %
1 ppm Cal	5 ppm	18.4 ppb	0.4 %
1 ppm Cal	10 ppm	48.3 ppb	0.5 %
1 ppm Cal	25 ppm	91.9 ppb	0.4 %
1 ppm Cal	50 ppm	399 ppb	0.8 %

Calibration	Standard Concentration	Standard Deviation	%RSD
50 ppm Cal	250 ppb	4.7 ppb	1.0%
50 ppm Cal	500 ppb	4.0 ppb	0.7%
50 ppm Cal	1 ppm	7.4 ppb	0.7 %
50 ppm Cal	5 ppm	19.0 ppb	0.4 %
50 ppm Cal	10 ppm	42.2 ppb	0.4 %
50 ppm Cal	25 ppm	67.5 ppb	0.3 %
50 ppm Cal	50 ppm	323 ppb	0.6 %

Portable 0043

Calibration	Standard Concentration	Standard Deviation	%RSD
1 ppm Cal	250 ppb	2.0 ppb	0.8 %
1 ppm Cal	500 ppb	2.3 ppb	0.4%
1 ppm Cal	1 ppm	6.7 ppb	0.6 %
1 ppm Cal	5 ppm	30.3 ppb	0.6 %
1 ppm Cal	10 ppm	63.2 ppb	0.6 %
1 ppm Cal	25 ppm	70 ppb	0.3 %
1 ppm Cal	50 ppm	271 ppb	0.5 %

Calibration	Standard Concentration	Standard Deviation	%RSD
10 ppm Cal	250 ppb	1.8 ppb	0.7%
10 ppm Cal	500 ppb	2.3 ppb	0.4%
10 ppm Cal	1 ppm	8.4 ppb	0.8%
10 ppm Cal	5 ppm	20.2 ppb	0.4%
10 ppm Cal	10 ppm	85.0 ppb	0.8%
10 ppm Cal	25 ppm	78.9 ppb	0.3%
10 ppm Cal	50 ppm	272 ppb	0.6%

6.1.2 Precision Statistics

Using a two-tailed Student's t-test, it was assessed whether or not instrument precision (as %RSD) was statistically different depending on the calibration or depending on the individual unit [1,2]. At the 99% confidence level, there is no statistical difference ($p>0.01$) between the precision of the instruments regardless of calibration nor was there a statistically significant difference between the precision of each individual analyzer. The following table outlines the p-value results of the Student's t-tests for the precision of each analyzer

Instrument	Average %RSD 1 ppm cal	Standard Deviation	Average % RSD Alternate Cal	Standard Deviation	P-Value (student's t-test)
Lab 0039	0.62%	0.17%	0.60% (Multi-Point cal)	0.16%	0.85
Portable 0042	0.64%	0.23%	0.60% (50 ppm cal)	0.25%	0.62
Portable 0043	0.57%	0.15%	0.58% (10 ppm cal)	0.21%	0.95
All Units	0.61%	0.18%	0.58% (All alternate cals)	0.20%	0.68

6.1.3 Precision Performance Specification

Based on the data reported here, the precision performance specification for the Sievers M-Series TOC Analyzers is ⩽1%.

6.2 Accuracy

6.2.1 Percent Recoveries

TOC Concentration	%Recovery Lab 0039 1 ppm Calibration	% Recovery Lab 0039 Multi-Point Calibration	% Recovery Portable 0042 1 ppm Calibration	% Recovery Portable 0042 50 ppm Calibration	% Recovery Portable 0043 1 ppm Calibration	% Recovery Portable 0043 10 ppm Calibration
250 ppb	98.6%	98.0%	100.1%	104.7%	99.1%	99.6%
500 ppb	99.3%	97.8%	99.5%	104.2%	99.5%	99.4%
1 ppm	100.9%	99.5%	99.6%	104.6%	100.4%	100.8%
5 ppm	100.6%	99.9%	99.0%	103.7%	100.5%	100.4%
10 ppm	102.1%	99.2%	99.2%	103.1%	100.2%	99.2%
25 ppm	100.7%	98.8%	96.5%	101.6%	98.5%	98.5%
50 ppm	99.5%	97.1%	95.4%	100.1%	96.9%	96.4%

6.2.2 Accuracy Performance Specification

The results presented here demonstrate a high degree of accuracy of the Sievers M9 Analyzers regardless of the calibration. Several recommendations on the optimal calibration for particular sample concentrations include the following:

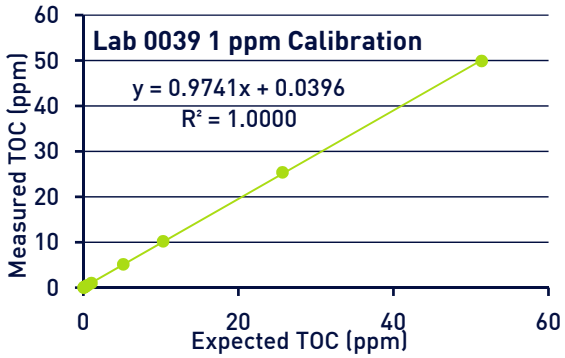
1) The 1 ppm calibration produced recoveries of 98.6% to 100.9% on all three instruments in the 250 ppb to 5 ppm range. On two of the instruments, using the 1 ppm calibration produced recoveries of 99.2% and 100.2% at the 10 ppm concentration indicating that using this calibration is still sufficient even at concentrations 10 times higher than the single calibration point.
2) The Multi-Point Calibration provided excellent results (98.8% to 99.5%) in the 1 ppm to 25 ppm TOC concentration range. Customers regularly running samples in this range can use this type of calibration if desired, though a single-point 10 ppm calibration produces equivalent recoveries. Below 1 ppm and above 25 ppm, the recoveries were lower by 2.0% to 2.9% using the multi-point calibration.
3) The 50 ppm single-point calibration provided the best results only at 50 ppm. A slightly lower calibration slope was likely produced using this type of calibration than the other calibration types leading to higher percent recoveries on all of the lower TOC concentrations (101.6% to 104.7%).
4) The 10 ppm calibration had excellent recoveries (98.5% to 100.8%) in the range of 250 ppb to 25 ppm. Recovery was slightly lower (96.4%) at 50 ppm, but that TOC concentration was five times higher than the single calibration point, so the results are not unexpected. On Portable 0043 – the unit that had both the 1 ppm and the 10 ppm calibrations – there was no statistical difference between the percent recoveries using either calibration in the 250 ppb to 50 ppm range ($p>0.01$).
5) As a general guideline, measurements on the Sievers M9 Analyzers should be either at or below the calibration point.

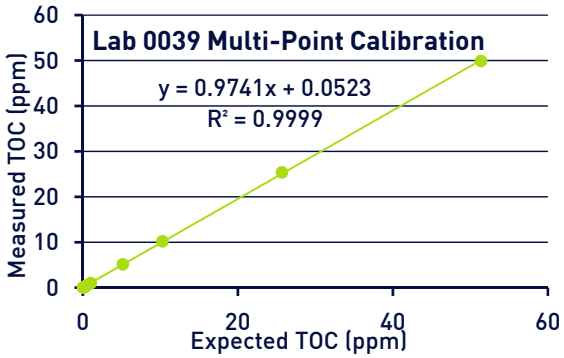
Based on the recoveries discussed above, the accuracy performance specification of the Sievers M-Series TOC Analyzers are ±2% when using the appropriate calibration based on the TOC range of the samples.

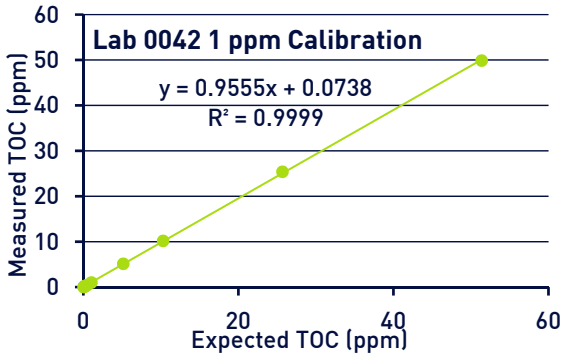
6.3 Linearity

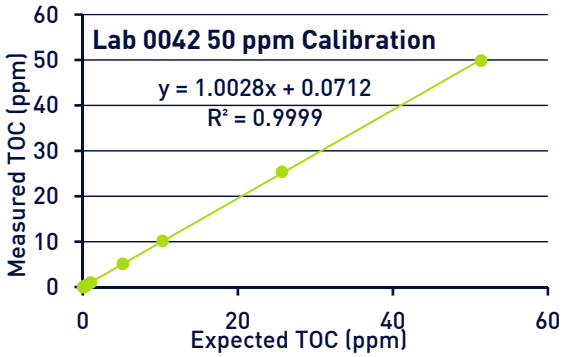
To demonstrate linearity, least-squares regression lines for a wide range of TOC concentrations were plotted (25 ppb to 50 ppm). Results of these regressions as well as the correlation coefficients (R2) are reported in this section of the results. These results are separated into two subsections with one demonstrating linearity of the full instrument range (up to 50 ppm) and the other showing linearity of the instrument across lower TOC concentrations (25 ppb – 1 ppm). Each of these subsections includes linearity plots for the different calibrations on each instrument.

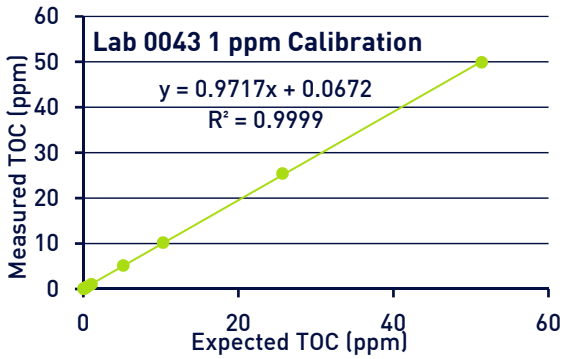
6.3.1 Linearity Across the Full Instrument Range (up to 50 ppm)

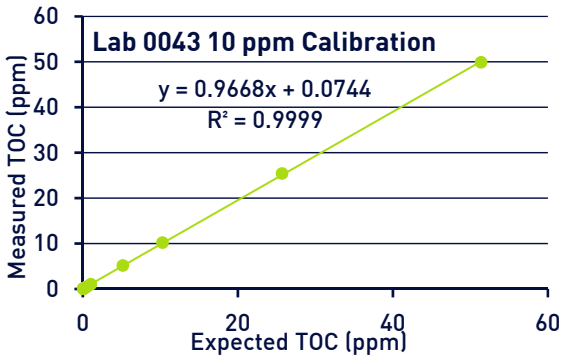




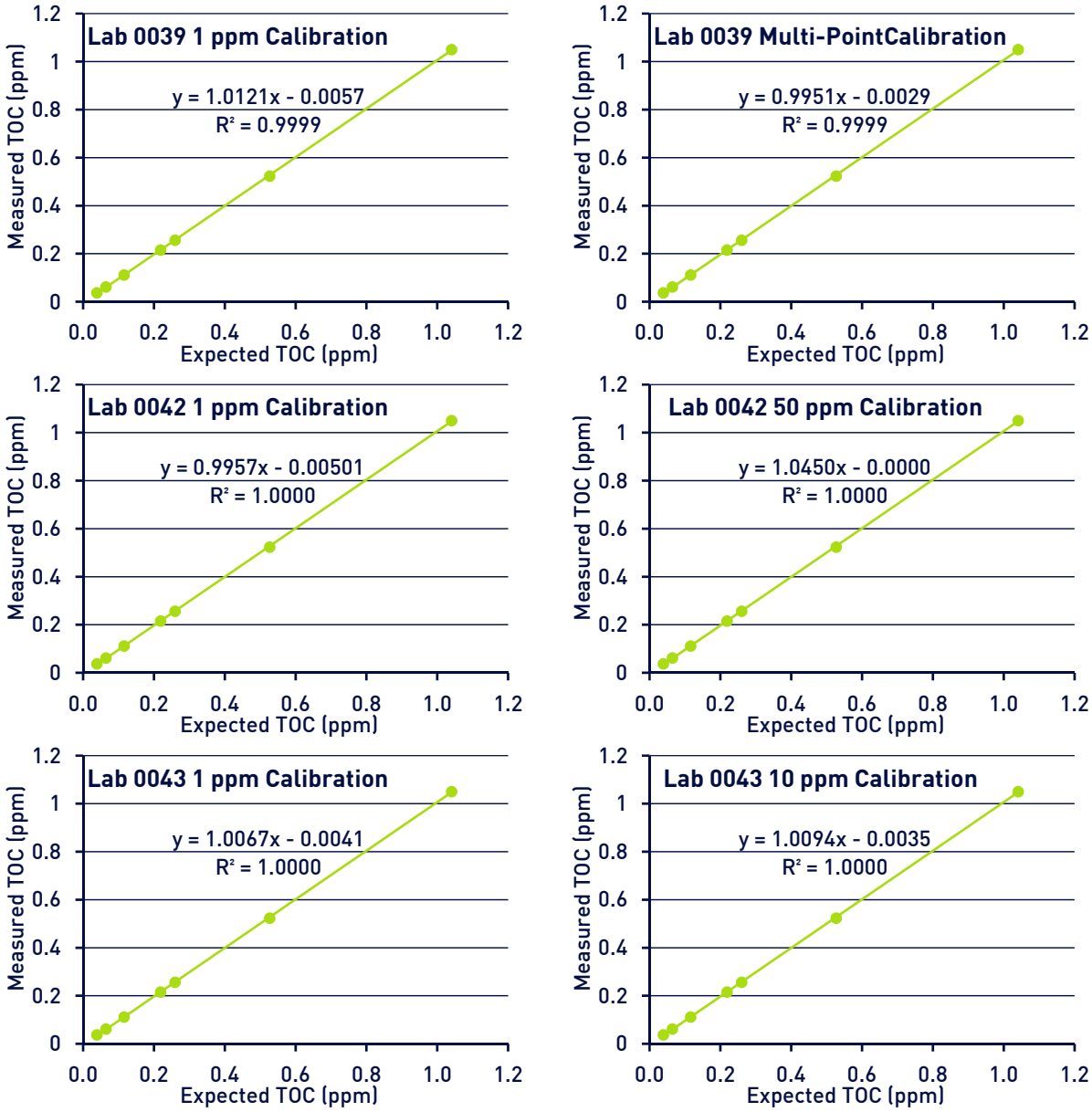








6.3.2 Linearity Across Low TOC Concentrations (up to 1 ppm)



6.3.3 Linearity Performance Specification

All three instruments demonstrated highly linear responses (R2 ⩾ 0.9999) across the full range of the instrument as well as at low TOC levels with the four different calibration options.

6.4 System Suitability

Instrument	Calibration	Response Efficiency
Lab 0039	1 ppm	100.9%
Lab 0039	Multi-Point	99.7%
Portable 0042	1 ppm	100.2%
Portable 0042	50 ppm	99.6%
Portable 0043	1 ppm	100.6%
Portable 0043	10 ppm	99.3 %

System suitability results from this experiment (99.3% to 100.9% response efficiency) demonstrate the excellent response efficiency of the Sievers M9 Analyzers for all calibration types. These response efficiencies are well within the acceptable USP/EP System Suitability range of 85% to 115%[5].

6.5 LOD/LOQ

To determine the LOD and LOQ of the Sievers M-Series Analyzers, 10 replicates of DI water on five Sievers M9[e] On-Line units were used. These units had serial numbers: 50, 51, 52, 54, and 59. In order to eliminate variability in TOC measurements due to water system changes, the Sievers M9[e] units were run for 24 hours. The 10 replicates for the LOD and LOQ calculations were selected during the most stable hour-long time span of the water system. The table below outlines the standard deviation for these 10 reps on each instrument, the average standard deviation, as well as the LOD and LOQ.

Sievers M9[e] Serial Number	Standard Deviation (10 reps)
50	0.003
51	0.010
52	0.012
54	0.009
59	0.008
Average	0.0084
LOD	0.03
LOQ	0.08

Based on the standard deviations of ten replicates for each of these units, the LOD and LOQ for the Sievers M-Series Analyzers are:

LOD = 0.03 ppb and LOQ = 0.08 ppb

7. conclusions

In summary, the performance specifications for the Sievers M-Series TOC Analyzers have been experimentally verified as follows:

Accuracy	±2% (250 ppb to 50 ppm)
Precision	≤1% (250 ppb to 50 ppm)
Linearity	R2≥0.9999 (25 ppb to 50 ppm)
LOD	0.03 ppb
LOQ	0.08 ppb

References

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5. USP <643> Total Organic Carbon.
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