

# Comparison of TOC Analyzers and Sensors for Pharmaceutical TOC Applications

## APPLICATION NOTE

### Background

In 2006, Jon S. Kauffman, PhD., Lancaster Laboratories, published results on the recovery of organic compounds likely to be present in pharmaceutical water systems using online TOC analyzers designed for pharmaceutical use<sup>1</sup>. The results of the study showed that different TOC measurement technologies, despite meeting the USP and EP suitability test, gave a wide range of recoveries for other organic compounds. The study concludes that “robust analytical TOC method validation is essential to the success of any online TOC system, particularly systems that release pharmaceutical-grade water in real time. Meeting USP <643> or EP 2.2.44 specifications may not eliminate risk.”

This application note repeats the percent recovery studies of the organic compounds used by Kauffman, and includes the Sievers\* CheckPoint Sensor.

### CheckPoint Design

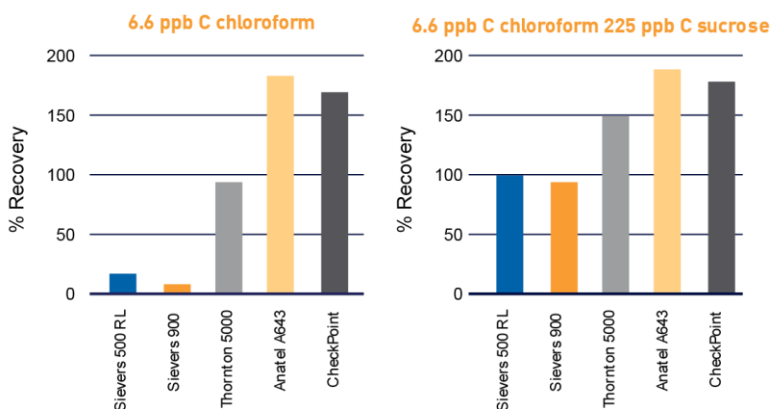
The CheckPoint is a fast-response, lightweight sensor that can be battery operated for truly portable measurements. The sensor design is similar to the direct conductometric (DC) detection with partial oxidation (DC/UV Rapid) analyzer in the Kauffman study. The CheckPoint consists of two conductivity cells, one before and one after a UV oxidation reactor. A peristaltic sample pump draws water from a sampler into the sensor at a flow rate of 0.5 mL/min. Like other continuous flow direct conductivity devices, the CheckPoint accomplishes varying degrees of oxidation depending on the specific compounds present.

**Table 1. TOC Instruments Used in the Study and their Methods of Detection and Oxidation**

TOC Instrument	Method
Sievers 500 RL	MC/UV
Sievers 900	MC/UV Persulfate
Thornton 5000TOC	DC/UV Rapid
Anatel A643	DC/UV
CheckPoint	DV/UV

### Measuring Devices in the Study

In addition to the CheckPoint, the other devices used in the original Lancaster Laboratories study were tested using an apparatus similar to that described in the 2006 paper. The instruments and their designations in the Kauffman paper included a Sievers 500 RL (MC/UV), a Sievers 900 (MC/UV-Persulfate), a Thornton 5000TOC (DC/UV Rapid), and an Anatel A643 (DC/UV) (**Table 1**).



**Figure 1. Percent Recovery for Injections of Chloroform and Chloroform Plus Sucrose on Different TOC Measurement Devices**

The analyzers and sensors were calibrated according to the manufacturers' instructions prior to the study. The organic compounds tested, measurement conditions (dissolved oxygen levels >3 ppm), and water conductivity (0.3  $\mu\text{S}/\text{cm}$  from  $\text{CO}_2$ ) were the same as used by Kauffman.

## Results

As in the Kauffman study, the direct conductometric sensors (A643, 5000TOC, and CheckPoint) gave very high recoveries for the chloroform and chloroform plus sucrose injections (**Figure 1**). The recoveries for the two membrane-based conductometric analyzers were much closer to 100%. The high recovery of chlorinated organic compounds with the direct conductometric sensors is due to the formation of hydrochloric acid in the oxidation reactor giving higher conductivity than from  $\text{CO}_2$  alone. This interference is not restricted to halogenated organic compounds.

**Figure 2** shows the recovery from the injection of 500 ppb C nicotinamide. Both the CheckPoint and the A643 give ~150% recovery for this nitrogen-containing compound due to the formation of nitric acid during oxidation. The 5000TOC gave low recovery for this compound, most likely due to incomplete oxidation. The membrane-based conductivity analyzers gave close to 100% recovery for this compound.

In contrast to erroneously high TOC measurements from the injections of chloroform, the direct conductometric sensors gave low or even negative recoveries for the conductive organic compounds, trimethyl amine and acetic acid (**Figure 3**). The concentrations tested produce a conductivity of ~0.3  $\mu\text{S}/\text{cm}$  from the ionization of the organic compound before oxidation. After oxidation, similar or even lower conductivity was measured with the 5000TOC, A643, and CheckPoint sensors, yielding low or even negative recoveries. The membrane-based conductivity analyzers gave recoveries closer to 100% for these samples.

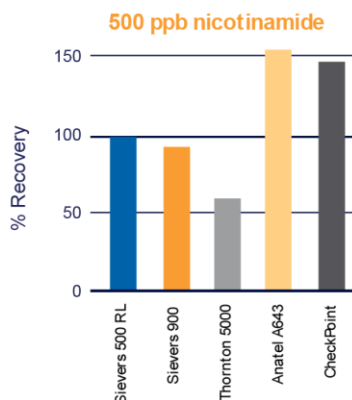


Figure 2. Percent Recovery for Nicotinamide

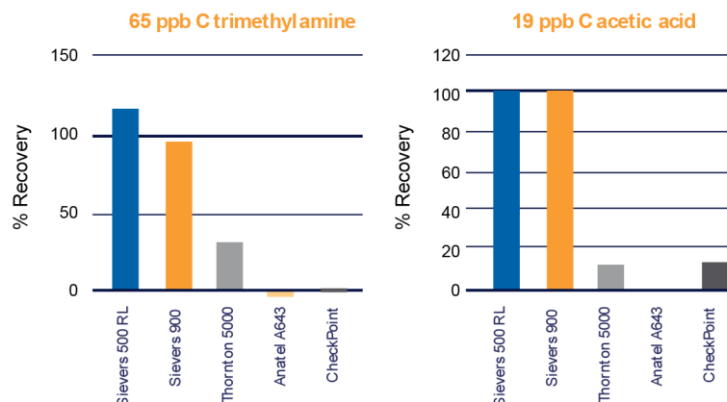


Figure 3. Percent Recovery for Conductive Organic Compounds

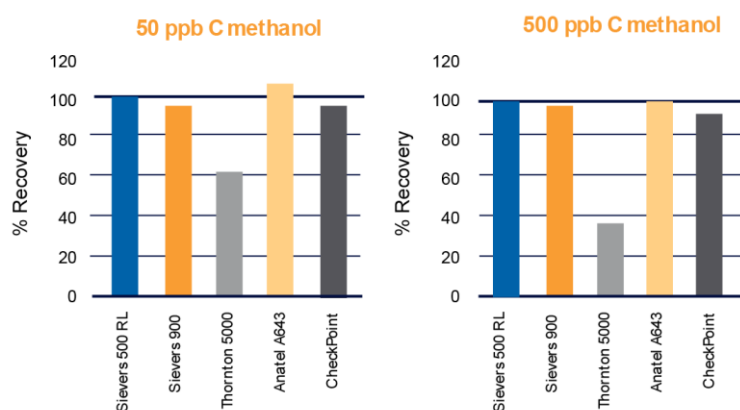


Figure 4. Recovery for Methanol at Two Concentrations Showing Non-linear Response of the A643

One surprise from the Kauffman study was the performance of the direct conductometric sensors for the injection of simple alcohols. As shown in **Figure 4**, the 5000TOC had low recovery for methanol at both 50 and 500 ppb. In contrast, the A643, the CheckPoint, and the membrane-based analyzers gave recoveries close to 100% at both concentrations. This non-linearity and low recovery for the 5000TOC appears to be compound-dependent, since a similar effect is not observed for injections of 2-propanol (**Figure 5**).

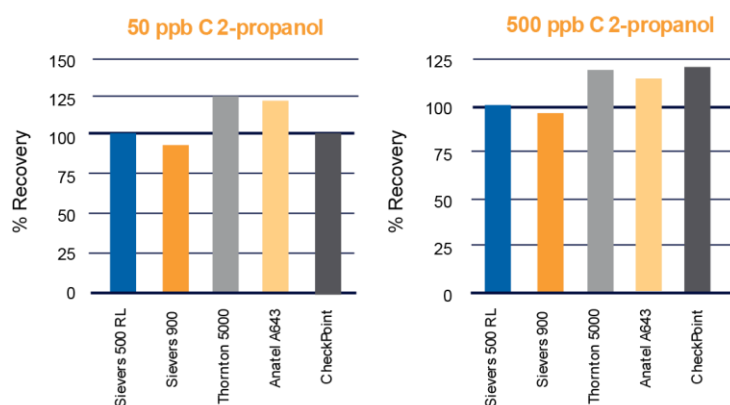
While the direct conductometric sensors gave erroneously high, low, and in the case of the 5000TOC, non-linear responses for the tested organic compounds, they passed the system suitability test as shown in **Figure 6**.

### Conclusion

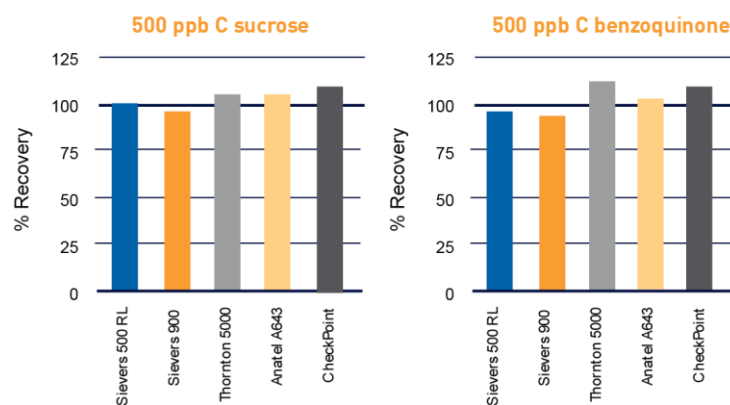
The CheckPoint, which employs direct conductometric measurement, gives results similar to the 5000TOC and A643 with both low and high recoveries depending on the types of organic compounds tested. The improved selectivity achieved with membrane-based conductometric analyzers provides better accuracy for TOC measurements and makes these instruments most appropriate for compendial applications, cleaning verification, process control, and regulatory reporting. Specifically, the Sievers 500 RL is ideally suited for real-time release of water, and the Sievers 900 for cleaning validation/verification. The true portability of the CheckPoint makes it a valuable tool for trending and general monitoring.

### Reference

1. "Kauffman, Jon S. PhD., "Validating On-line TOC Analyzers for Real-Time Release," Pharmaceutical Manufacturing, November/December 2006. (See the corrected version of this article at [http://www.pharmamanufacturing.com/Media/MediaManager/Validating\\_LancasterLabs\\_TOC.pdf](http://www.pharmamanufacturing.com/Media/MediaManager/Validating_LancasterLabs_TOC.pdf))



**Figure 5. Percent Recovery for 2-Propanol**



**Figure 6. Percent Recovery for 500 ppb and 500 ppb benzoquinone. All the models gave response efficiency between 85 and 115%.**