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Integrating Total Organic Carbon (TOC) Analysis into Chemical Characterization for Toxicological Risk Assessment: A Case Study Evaluating the Relationship Between TOC and Gravimetric Residues

Stephanie R. Kearing, M.S.; Cassandra J. Meakin, Ph.D., DABT; Lindsey K. Borton, M.P.H., DABT

ISO 10993-17 recommends the use of conservative, quantitative exposure data for the purposes of toxicological risk assessment. ISO 10993-18 Section 6.3 identifies total organic carbon (TOC) analysis and non-volatile residue (NVR) determination (*via* gravimetric analysis) as acceptable methods for quantifying organic extractables from medical devices. While both techniques are non-specific and primarily used to demonstrate exhaustive extraction, few studies have systematically compared their relative performance or explored their utility in informing exposure assessment in toxicological risk assessments.

In this case study, test articles (titanium alloy orthopedic plates and screws) were exhaustively extracted under five conditions. For this orthopedic system, the materials of construction are well characterized. These devices provide a unique opportunity to assess whether TOC-derived total organic carbon values can be used to estimate total extractables and inform toxicological risk assessments by applying TOC results to known manufacturing process chemicals.

Three organic solvent extractions (non-polar, mid-polar, and polar solvents) were performed for 72 hours with agitation at 50°C, representing exhaustive extraction conditions for a long-term implant device per ISO 10993-18. Two aqueous extractions were performed to evaluate TOC compatibility:

1) Twenty-four hours with agitation at 50°C; and
2) Thirty minutes with sonication at room temperature.

Gravimetric (NVR) analysis was performed on all extractions and TOC analysis was performed on all aqueous extracts. A separate spiking study was conducted using compounds of varying volatility and solubility to evaluate the classes of analytes detectable by TOC.

Across all extractions, the highest total residue by NVR was obtained from the 72-hour aqueous extraction (340 µg). The highest TOC residue was measured in the 30-minute sonicated water extraction (141 µg). At first, this study suggests NVR is the more efficient means of quantifying gross residue. However, TOC measurements only quantify carbon-containing chemicals. When adjusted to account for non-carbon elements based on the device's extractables profile, the estimated total extractables increased to approximately 324 µg, which more closely matches the NVR results. These findings indicate that TOC can serve as a viable alternative to NVR.

TOC can quantify the gross residues in aqueous extractions of metallic devices, as well as NVR for the purposes of an exposure assessment. When the contact chemicals of a medical device are known, TOC values can serve as the quantitative exposure value for each chemical constituent for the purposes of toxicological risk assessment. The use of TOC as the exposure value for each contact chemical results in a highly conservative exposure estimation.

In conclusion, TOC analysis can be effectively leveraged as a conservative exposure value for toxicological risk assessment of metallic devices. When adjusted for non-carbon composition, TOC provides a conservative estimate of total extractables and offers an efficient means to evaluate manufacturing residuals in support of biological safety assessments.