December 2004
Establishing Adequate Solubility for TOC Analysis

A common objection to the use of TOC (Total Organic Carbon) analysis for analysis of trace residues in cleaning validation protocols is "My active is not water soluble." This may or may not be an appropriate objection. The key to the use of TOC for trace analysis in cleaning validation protocols is whether the target residue, such as the active, is water soluble at the *acceptance limit in the analyzed sample*. In other words, if the acceptance limit of the active in a swab desorption sample is 5 ppm, then the key question to ask is whether that active is soluble in the range of 5 ppm. In may cases the reported solubility used is solubility for formulation purposes. While that may be helpful for assurance of the appropriateness of using TOC for substances which are listed as soluble or slightly soluble, it *cannot* be used to reject the use of TOC for residue analysis purposes.

The key to confirming the use of TOC for substances that are listed as very slightly soluble or even insoluble in water is to perform a simple study to confirm appropriateness. What such a study involves is placing the substance in water such that the target concentration would be achieved if the material were fully water soluble at that concentration, and then comparing the measured TOC to the theoretical TOC at full solubility. There are several ways to perform such a study.

Option 1: Weigh 1 mg (1000 µg) of the active substance in an EPA (precleaned) vial. Add 40 mL of low TOC water (the theoretical concentration is thus 25 ppm). Cap the vial and sonicate for a given time (5 or 10 minutes). At the end of sonication, measure the TOC in the sample. Subtracting out the TOC from a suitable blank should result in a value for TOC due to the 1 mg of active substance. Compare the measured TOC in the sample to the "theoretical" TOC of the active substance (calculated from its formula, for example). An agreement of ±15% should be adequate to confirm water solubility for this purpose. Note that in the example, the actual TOC of the sample (assuming water solubility and assuming about 50% carbon in the active) will be in the range of 12.5 ppm C. If you can't accurately weight out 1 mg, then you might try a larger EPA vial and place 2.5 mg active substance in 100 mL water for sonication. Another (less desirable) alternative is to dissolve the active in a suitable volatile organic solvent to prepare a 10% w/w solution, and than add 10 mg of the solution to EPA vial. Allow the solvent to evaporate completely! Adequate drying is the key to make sure the organic solvent is not staying in the residue so as to interfere with the TOC analysis. This might require drying under different conditions.

Option 2: Perform a spiked coupon recovery study. First, spike the coupon at the surface area residue limit. For example, if the surface area limit is 4 µg/cm^2, if the swabbed area is 10 cm X 10 cm, and if the amount of water used for swab desorption is 40 mL, then a stainless steel coupon could be spiked with 400 µg (0.4 mg) of active substance. The concentration of active substance in the desorbed swab sample should be 10 ppm at 100% solubility and 100% recovery. In this case, you want to be a little more generous in terms of what constitutes acceptable water solubility. The reason for this is that the measured percent recovery is really due to both the *water solubility* and the *swab recovery*. Therefore, it is probably best to say that adequate water solubility is demonstrated by a swab recovery percentage at or above the minimum recovery percentage specified in your recovery policy/procedure. For example, if the minimum acceptable recovery is 50%, then a recovery of 50% at the spiked acceptance limit is adequate to determine water solubility. Note that because both factors are involved, you may want to consider spiking at twice the surface acceptance limit. If recovery

is 50% or more, this will give you even more assurance that the active substance is soluble at the surface acceptance limit.

There may be other methods that could also be used, such as exhaustive extraction in Option 1. That is, sonicate with one 20 mL portion of water, decant and measure the TOC in that portion. Then extract the *same spiked vial* with another 20 mL portion of water. If the second extraction is essentially the same as the blank, then one possible conclusion is that all the spiked material was dissolved in the first extraction. (Of course, one other possible conclusion is just that all the spiked material was entirely removed, but not entirely dissolved, in the first extraction.) A direct exhaustive extraction procedure may also be suitable for demonstrating adequate solubility for residues on medical device implants.

The purpose of this Cleaning Memo is neither to recommend nor discourage the use of TOC as an analytical method for cleaning validation. The purpose is to suggest alternatives for demonstrating by simple laboratory methods whether the residue being measured has adequate water solubility to be measured by TOC in a given validation protocol.