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October 17, 2018

Dr. Jennifer Orme-Zavaleta
EPA Science Advisor
United States Environmental Protection Agency
Ariel Rios Building (MD 4101M)
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

RE: Minimum Criteria for Selected Ion Monitoring (SIM) Methods

Dear Dr. Jennifer Orme-Zavaleta:

During the August 2014 face to face meeting, the Environmental Laboratory Advisory Board (ELAB or Board), a standing Federal Advisory Committee Act board that advises the U.S. Environmental Protection Agency (EPA or Agency), was asked by a public request to investigate issues related to Selected Ion Monitoring (SIM) gas chromatography/mass spectrometry (GC/MS) methods. ELAB submitted a letter proposing minimum SIM criteria on February 16, 2017, to which EPA provided detailed comments in a letter dated December 20, 2017. ELAB discussed EPA's comments and provided a revised set of minimum criteria in a letter dated May 16, 2018 , which addressed many of EPA's comments. EPA responded in a letter dated July 16, 2018 with some additional comments. EPA discussed EPA's comments and today we are submitting additional revisions that address EPA's comments. ELAB encourages EPA to use these minimum SIM criteria.

ELAB appreciates the opportunity to provide this information to the Agency in support of setting minimum criteria for SIM methods that will achieve harmonization between similar EPA methods and be achievable by many laboratories performing analyses in support of EPA regulations.

We look forward to working with EPA on this topic.

Respectfully,

Michael F. Delaney

Michael F. Delaney, Ph.D.
Chair, Environmental Laboratory Advisory Board

cc: ELAB Board
Thomas O'Farrell, ELAB Designated Federal Official

Attachment: *"Minimum Criteria for Selected Ion Monitoring (SIM) Methods"*

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Minimum Criteria for Selected Ion Monitoring (SIM) Methods
10/17/18

Background/Assumptions. Traditionally, identification and quantitation of trace organic constituents in environmental samples using Gas Chromatography/Mass Spectrometry (GC/MS) is accomplished using full-scan mode, in which all masses are monitored in each scan. This facilitates obtaining full mass spectra for compound identification as each organic compound elutes from the GC column. The sensitivity of GC/MS analyses can generally be increased by using Selected Ion Monitoring (SIM) in which a small number of masses are monitored for each target analyte. The masses that are monitored are carefully chosen to be significant contributors to the mass spectrum of the eluting target compounds. The set of masses is changed in timed sequence throughout the chromatographic run, to correlate with the characteristic ions of the analytes, surrogate standards and internal standards as they elute from the chromatographic column. Sensitivity is increased because more time is spent measuring the masses present in the eluting compounds, rather than measuring all masses.

Most full-scan GC/MS methods, including isotope dilution methods, may be conducted in SIM mode. Further, certain mass spectrometry systems are capable of running simultaneous SIM and full-scan acquisition. This document details the suggested minimum requirements for using SIM reliably. Without the benefit of a full mass spectrum in SIM mode, care must be taken to balance the chance of false negatives (not detecting a compound that is actually present) and false positives (detecting a compound that is actually absent). The minimum criteria presented here are considered a reasonable balance between false positives and false negatives because the criteria are tight enough to require strong analytical signals without being too restrictive. These minimum criteria must be met for SIM, even when combined with simultaneous full-scan acquisition.

These minimum criteria will likely need to be tailored to the specific data quality objectives (DQOs) of the project. SIM is primarily used to increase sensitivity; qualitative identification is secondary. Accurate quantitation and identification relies on the judgement of experienced analysts. Data qualifiers and written narration should be used to annotate results as needed.

This document is focused on high-resolution GC combined with low-resolution MS. It is not intended to, nor does it address, high-resolution MS, tandem MS (MS-MS or MS-MS-MS), or high-performance liquid chromatography (HPLC-MS).

We have used the imperative “must” for requirements, “should” for recommendations, and “may” for optional alternatives.

Definitions. Terminology may vary between various instrument manufacturers and MS types. These differences should not preclude a laboratory from configuring a SIM method that meets these minimum criteria. A SIM profile, or acquisition profile, is a list of retention time windows during the GC run. During each retention time window the MS moves from mass to mass, acquiring the detector signal at each mass for a specified “dwell time”, generally in milliseconds. (The MS monitors mass-to-charge ratios, m/z, but for simplicity “mass” is used in this document.) “Scan

descriptors" is the set of masses and dwell times. The "cycle time" is the amount of time it takes to cycle through the scan descriptors.

An example of a minimum definition of scan descriptors is shown here:

GROUP	START TIME (min)	Selected Ions	DWELL TIME (millisecond)
1	14.00	188, 190, 222, 224	175
2	18.92	256, 258, 289.90, 291.90	175

Minimum SIM Criteria. This minimum set of SIM criteria should be considered when operating a GC/MS in either SIM mode or simultaneous SIM and full-scan acquisition. This document focuses on SIM. Follow all additional procedures or criteria specified in the method. An Initial Demonstration of Capability (IDC) must be performed by the laboratory whenever SIM is used to show that its instrumentation, personnel, and implementation of the method meet quality control requirements specified in the method.

a. **Personnel.** The analysts who are going to perform the instrument analyses and process SIM data must perform the IDC specified in the method so they can demonstrate their ability to correctly generate results in the matrices of interest.

b. **Method Flexibility.** The flexibility to use SIM with a particular method varies depending on the associated regulation. The determination of whether SIM can be used with a specific method will be determined by each EPA program office. Verify that all QC acceptance criteria in the method are met.

c. **Type of MS.** Any type of MS can be used, provided it is allowed by the method and applicable regulations and meets the requirements found in this document.

d. **MS tuning criteria.** Method-required tuning criteria must be met. If tuning criteria are not required, use manufacturer's recommended tuning, or a consistent, defined tuning procedure that must be detailed in the SOP.

e. **Number of scans per peak.** Longer dwell times lead to better sensitivity, but also longer cycle times resulting in fewer scans across each chromatographic peak. A minimum of eight scans per chromatographic peak should be used, adjusting dwell times as required. This is considered sufficient to allow an accurate measurement of peak area. Verify this using the quantitation ion for the low-level standard. Simultaneous SIM and full scan acquisition may be used if all criteria in this document are met.

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f. **Number of scan descriptors.** The use of a large number of descriptors with longer dwell times can limit scans per peak. A minimum of one quantitation and two qualifying ions for each analyte should be used, unless fewer than three ions with intensity greater than 30% of the base peak are available. For compounds with fewer than three ions greater than 30% of the base peak, require lower abundance peaks to be present to confirm positive identifications. Consider using a high-mass abundant ion for quantitation since this should give better selectivity and/or sensitivity.

g. **SIM acquisition parameters.** The chromatogram may be divided into time windows, also known as segments or periods, with different acquisition parameters for each time window. This includes beginning and ending time of the window, masses to be monitored, dwell time for each mass (milliseconds), and scan time (seconds/scan). SIM time windows must be set to allow full baseline to baseline elution of peaks within the designated time window, including accounting for anticipated retention time drift. Analyze a mid- to high-concentration standard in full-scan mode. Select one primary quantitation ion (QI) and at least two confirmation ions. Verify that the QI is free from interferences due to an identical fragment ion in any overlapping peak(s). Selection of the QI should be based on the best compromise between the intensity of the signal for that ion and the likelihood and intensity of interferences. Interfering ions need to be considered as a major source of error when using SIM. The most intense ion might not be the best QI.

h. **Identification/identification verification criteria (e.g., ion ratios).** To confirm identification, follow all procedures in the method. Positive identification of an analyte in an unknown sample must include a detectable peak for each ion within the retention time window and an acceptable ion ratio between the quantitation ion and each confirmation ion, established using standards.

   The ratio of each of the two qualifying ions to the quantitation ion must be evaluated and should agree within ±20 percent (absolute) of the ratio established using standards. For example, if the base peak is used for quantitation (100%), and the ratio of the secondary ion in the standard is 45%, then the ratio of this ion in the sample must be between 25% and 65%.

   Interfering ions need to be considered as a major source of error when using SIM. Analyst judgment must be applied to the evaluation of ion ratios for complex matrices because the ratios can be affected by co-eluting compounds present in the sample matrix. Analysts should use qualifiers or narration, as allowed by the method or program, to distinguish between qualified and confirmed detections (*i.e.* near hits/near misses). Also, additional confirmations may be advisable, such as additional confirmatory ions or deuterated standards.

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